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Infertility and Recurrent Miscarriage: An Examination of Pregnancy Outcomes, Services and Patient Experience

Thesis presented by

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for degree of

Doctor of Philosophy

Research conducted at the INFANT Centre and the Pregnancy Loss Research Group,
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March 2024

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List of abbreviations

ACLA	anticardiolipin antibodies
ACOG	American College of Obstetricians and Gynaecologists
AFC	antral follicle count
AMH	anti-Mullerian hormone
ANA	anti-nuclear antibodies
aOR	adjusted odds ratio
APLA	antiphospholipid antibodies
APS	Antiphospholipid syndrome
Array-CGH	array-comparative genomic hybridisation
ART	assisted reproductive technology
ASRM	American Society of Reproductive Medicine
aβ2GPI	β2 glycoprotein I antibodies
BCL6	B-Cell CLL/lymphoma 6
BFS	British Fertility Society
BMI	body mass index
CI	confidence interval
CMS	Clinical midwifery specialist
CPG	Clinical Practice Guideline
CUMH	Cork University Maternity Hospital
DGGG	German Society of Gynaecology and Obstetrics
DOR	diminished ovarian reserve
ESGE	European Society for Gynaecological Endoscopy
ESHRE	European Society Human Reproduction and Embryology
EULAR	European Alliance of Associations for Rheumatology
FIGO	International Federation of Gynaecology and Obstetrics
FISH	fluorescent in situ hybridisation
FSH	follicle-stimulating hormone
FT3	free triiodothyronine
FT4	free thyroxine
FVL	factor V Leiden

Hba1c	glycated haemoglobin
HCG	human chorionic gonadotrophin
HFEA	Human Fertilisation and Embryology Authority
HIQA	Health Information Quality Authority
HIV	human immunodeficiency virus
HLA	human leukocyte antigens
HPRA	Health Products Regulatory Authority
HSE	Health Service Executive
HVS	high vaginal swab
ICSI	intracytoplasmic sperm injection
IVF	in vitro fertilisation
IVIG	intravenous immunoglobulin
KPI	key performance indicators
LA	lupus anticoagulant
LIT	lymphocyte immunotherapy
LWMH	low molecular weight heparin
MCC	maternal cell contamination
MD	mean difference
MLPA	Multiplex Ligation-dependent Probe Amplification
MTHFR	Methylenetetrahydrofolate reductase
NICE	National Institute for Health and Care Excellence
NK cells	natural killer cells
NWIHP	National Women and Infants Health Programme
ÖGGG	Austrian Society of Gynaecology and Obstetrics
OR	odds ratio
PCOS	polycystic ovarian syndrome
PGT-A	pre-implantation genetic testing for aneuploidy
PGT-M	preimplantation genetic testing for monogenic disorders
PGT-SR	preimplantation genetic testing for structural rearrangements
PICSI	physiological intracytoplasmic sperm injection
PIGD	pre-implantation genetic diagnosis
PIMS	Patient Information Management System

PT Gene	Prothrombin Gene
QF-PCR	quantitative fluorescence polymerase chain reaction
RCOG	Royal College of Obstetricians and Gynaecologists
RCT	randomised control trial
RE:CURRENT study	REcurrent miscarriage: evaluating CURRENT services
RIF	recurrent implantation failure
RM	recurrent miscarriage
ROI	Republic of Ireland
RPL	Recurrent Pregnancy Loss
RR	relative risk
RRR	Relative risk ratio
SCH	Subclinical hypothyroidism
SGGG	Swiss Society of Gynaecology and Obstetrics
SNP	single nucleotide polymorphism
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
Tgab	thyroglobulin antibodies
TNF-α	tumour necrosis factor alpha
TPOab -	thyroid peroxidase antibodies
TRUST Trial	The Randomised Uterine Septum Transection Trial
TSH	thyroid stimulating hormone
UK	United Kingdom
US	United States
WHO	World Health Organisation

Declaration

This is to certify that the work I am submitting is my own and has not been submitted for another degree, either at University College Cork or elsewhere. All external references and sources are clearly acknowledged and identified within the contents. I have read and understood the regulations of University College Cork concerning plagiarism and intellectual property.

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Research Outputs

The following manuscripts published or submitted for publication form the chapters in the current thesis.

Published Peer Review Articles:

Linehan L, Hennessy M, O'Donoghue K. Infertility and subsequent recurrent miscarriage: Current state of the literature and future considerations for practice and research. HRB Open Res. 2021;4:100.

Linehan L, Hennessy M, O'Donoghue K. Recurrent miscarriage and infertility: a national service evaluation. J Obstet Gynaecol (Lahore) [Internet]. 2023 [cited 2023 Nov 9];43(2). Available from: https://pubmed.ncbi.nlm.nih.gov/37529925/

Linehan L, Hennessy M, O'Donoghue K. An examination of care received by women with recurrent miscarriage and infertility against guideline-based key performance indicators. Eur J Obstet Gynecol Reprod Biol [Internet]. 2023 Mar 1 [cited 2023 Jan 16];282:17–23. Available from: http://www.ejog.org/article/S0301211523000027/fulltext

Linehan L, Hennessy M, Khalid A, Whelan J. National Clinical Practice Guideline Recurrent Miscarriage. Natl Women Infants Heal Program Inst Obstet Gynaecol [Internet]. 2023; Available from: https://www.hse.ie/eng/about/who/acute-hospitals-division/woman-infants/clinical-guidelines/https://www.rcpi.ie/faculties/obstetricians-and-gynaecologists/national-clinical-guidelines-in-obstetrics-and-gynaecology/

Hennessy M, Linehan L, Flannery C, Cotter R, O'Connell O, O'Donoghue K. A national evaluation of recurrent miscarriage care services. Ir Med J. 2023;116(No1):16.

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Articles currently under review:

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Published abstracts

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LA Linehan, I San Lazaro Campillo, M Hennessy, C Flannery, K O'Donoghue. Pregnancy outcomes following recurrent first-trimester miscarriage: a retrospective cohort study

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LA Linehan, I San Lazaro Campillo, M Hennessy, C Flannery, K O'Donoghue. Future pregnancy outcomes after recurrent first-trimester miscarriage. Abstract Published Fertility and Sterility 118(4):e182. DOI:10.1016/j.fertnstert.2022.08.521

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LA Linehan, M Hennessy, K O'Donoghue. An Examination of Care Received by Women With Recurrent Miscarriage And Infertility Against Guideline-Based Key Performance Indicators. Abstract Published BJOG An International Journal of Obstetrics & Gynaecology

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Escañuela Sánchez T, Linehan L, O'Donoghue K, Byrne M, Meaney S. Facilitators and barriers to seeking and engaging with antenatal care in high-income countries: A meta-synthesis of qualitative research. Health Soc Care Community. 2022 Nov;30(6):e3810–28.

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Research dissemination

Oral presentations:

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- Exploring Stakeholder Views and Experiences of Recurrent Miscarriage and Infertility Services and Supports in the Republic of Ireland. JOGS Annual Meeting, RCPI Nov 2023.
- Pro-AM Three Minute Thesis Competition: Recurrent Miscarriage and Infertility. UCC Bright Futures, April 2023 Winner Best Presentation.
- Recurrent miscarriage and Infertilty: A National Service Evaluation. SPHERE Meeting, RCSI, Dublin, March 2023.
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- Reproductive Outcomes Following First-Trimester Miscarriage: A Retrospective Cohort Study. Molecules to People, UCC, Sept 2022
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- Miscarriage and recurrent miscarriage: an evaluation of Irish and UK websites. RCOG World Congress, Sussex Place, London, June 2022
- Pregnancy Outcomes Following Recurrent First Trimester Miscarriage: A Retrospective Cohort Study. RCOG World Congress, Sussex Place, London, June 2022
- Developing guideline-based indicators for recurrent miscarriage care with a diverse stakeholder group. RCOG World Congress, Sussex Place, London, June 2022

- Incorporating professional and lived experience into the development of guideline-based care quality indicators: Practical insights from the RE:CURRENT Project. Health Services Research UK 15th Annual Conference, Sheffield, July 2022
- Pregnancy outcomes following recurrent first-trimester miscarriage: a retrospective cohort study. ESHRE Annual Meeting, Milan, Italy July 2022
- Future pregnancy outcomes after recurrent first-trimester miscarriage. ASRM Annual Meeting, Anaheim, California, US October 2022
- Recurrent miscarriage care in Ireland: Findings from a national service evaluation. BMFMS Annual Conference, Birmingham, UK Nov 2022
- Maternal characteristics and subsequent pregnancy outcomes following Recurrent Miscarriage. BMFMS Annual Conference, Birmingham, UK Nov 2022.
- An Examination of Care Received by Women With Recurrent Miscarriage And Infertility Against Guideline-Based Key Performance Indicators. BMFMS Annual Conference, Birmingham, UK Nov 2022
- Fertility and Reproductive Outcomes Following Recurrent Miscarriage: A Retrospective Cohort Study. Society of Maternal Fetal Medicine Annual Meeting, San Francisco, California, US February 2022
- Recurrent Miscarriage Care and Infertility: A National Service Evaluation. NPEC Annual Study Day, Dublin, Jan 2023.
- Stakeholder Views and Experiences of Recurrent Miscarriage and Infertility Services and Supports in the Republic of Ireland: A Qualitative Study. AEPU Annual Scientific Meeting. Telford, Nov 2023

Abstract

Background

Miscarriage and infertility are distinct reproductive health conditions which profoundly impact the lives of women and men affected. Although miscarriage is the most common complication of pregnancy affecting an estimated 23 million women globally a year, it remains poorly understood (1). There is a limited evidence base for investigation and treatments for miscarriage or recurrent miscarriage (RM), and approximately half of women/couples will have unexplained RM (2). Similarly, up to one in six couples are affected by infertility, this is an estimated 48.5 million people, with 30% having unexplained infertility (2,3). Miscarriage and infertility share a number of risk factors and are reciprocally associated, in addition to being associated with adverse pregnancy outcomes. The impacts of RM and infertility are also in parallel, with both experiences bearing psychological sequelae, economic burdens and isolation as a consequence of stigmatisation. Despite these commonalities, the dual experience of RM and infertility is not widely described in the literature or clinical practice guidelines and the optimal management of women/couples is unclear. RM and infertility are separately receiving greater attention from policy makers, nationally and internationally, therefore greater evidence is needed to inform policy and practice. Thus, the overall objective of this thesis is to examine the dual experience of RM and infertility and to add to the knowledge base on the current care issues, reproductive outcomes and lived experiences to inform improvements in care.

Methods

To meet this objective, a number of quantitative and qualitative studies were conducted. A narrative review of the literature was undertaken to determine what is known of the dual experience of RM and infertility and to identify the knowledge gaps (Chapter 2). A National Clinical Guideline was developed to provide evidence-based guidance for the management of RM in the Republic of Ireland (Chapter 3). A retrospective cohort study of women with three consecutive first-trimester miscarriages was undertaken to examine reproductive outcomes after RM, including women with a history of RM and infertility (Chapter 4). For this study descriptive and inferential statistics were utilised. A national

service evaluation was conducted using key performance indicators (KPIs) for RM to establish how care for women/couples with RM and infertility compares to international recommendations (Chapter 5). These KPIs were also employed in an audit of RM and infertility care in a tertiary referral maternity hospital to examine how care compared to international recommendations (chapter 6). A qualitative semi-structured interview study of women with lived experience of RM and infertility and healthcare professionals working in these areas was also undertaken, utilising reflexive thematic analysis (Chapter 8).

Results

The narrative review (Chapter 2) demonstrated that women with RM and infertility are not well studied in the wider literature and feature predominantly within sub-groups of investigations or treatments, and their experiences are underexplored within qualitative studies. These findings are reflected in the exclusion of women with RM and infertility in international Clinical Practice Guidelines, thus it is unclear how best to manage and support this complex cohort. The National Clinical Practice Guideline for the management of RM (Chapter 3) sets out evidence-based recommendations for the structure of care, supportive care, investigation and treatment of RM, including subsequent pregnancy management. The retrospective cohort study of 748 women with RM (Chapter 4) found a subsequent pregnancy rate of 77%, with a cumulative live-birth rate of 63%. The multinomial regression analysis demonstrated that maternal age, smoking and parental karyotype were associated with reproductive outcomes. Additionally, there was a lower live-birth rate in women age over 40 years (44%) or with a history of infertility (54%). The national service evaluation (Chapter 5) found that while care is largely in line with international clinical practice guidelines, there is variation in counselling, imaging and surgical treatments offered. Areas for education identified included fertility counselling and resources for information provision and supportive care. Importantly, clinical outcomes were seldom audited. The audit of care for 128 women with RM and infertility (Chapter 6) found that alongside good clinical practice there are several areas for improvement: Counselling regarding risk factors and treatments, availability of genetic counselling, access to ultrasound and cytogenetic investigation should be improved. The subsequent pregnancy rate was 70% with a live-birth rate of 63% and a preterm birth rate

of 11%, with 36% of women conceiving with assisted reproductive technologies. For the qualitative study (Chapter 7), 33 individuals were interviewed: 17 women with lived experience of RM and infertility and 16 healthcare professionals. Four themes were actively generated: “exploring all avenues”, “exhausting all resources”, “separateness” and “no woman is an island”, which captured this complex experience. The themes encompassed the challenges in seeking care and the many personal burdens of RM and infertility, which were compounded by stigmatisation, a lack of knowledge and awareness, the divisions within the healthcare system and the limited availability of supports.

Conclusions

This doctoral work has examined the dual experience of RM and infertility in the ROI and has provided meaningful insights into the difficulties within current service provision and the management of RM and infertility. This work has also provided guidance for evidence-based management for the care of women/couples with RM. It has made an important contribution to the literature in describing the reproductive outcomes for women following RM and RM and infertility. This thesis has also distinctly depicted the lived experiences of women with RM and infertility and also of relevant healthcare professionals. Through analysis of these findings, this thesis identified three overarching themes: 1) the dual experience of RM and infertility needs greater recognition; 2) there is a need for equity and balance in the care provided to women with RM and infertility; 3) information is central to improving care. Several recommendations for practice and policy are made. There is a need for greater education and training for healthcare professionals regarding reproductive health, which must be supplemented by increased availability of high-quality and accessible information resources for women and their families. Improvements in knowledge and awareness of RM and infertility must be accompanied by improved data collection to inform and develop services, identify inequities in care and better direct resources to improve access to RM and fertility care. There must be increased investment in supportive care for women/couples experiencing RM and infertility, with better acknowledgement of the life impacts of this experience on both partners. Recommendations from the Clinical Practice Guidelines for RM and for fertility must be appropriately resourced and implemented to facilitate standardisation of care,

alongside implementation of the Assisted Human Reproduction legislation to ensure better regulation within fertility services. Future research must prioritise the inclusion of women with a dual experience of RM and infertility in investigations, treatments, and outcome studies, thereby enriching the evidence base for management. Moreover, there is a need to explore factors contributing to delayed childbearing in Irish society and develop strategies to enhance and disseminate reproductive health knowledge effectively. Facilitators and barriers to accessing fertility and RM care across all levels of society must be examined to address the current inequities in care. Further patient and public involvement in research are also necessary to identify the optimal supportive care and resources for women/couples with RM and infertility. Addressing these issues can promote a more compassionate, informed, and equitable approach to reproductive healthcare for individuals dealing with RM and infertility in the Republic of Ireland.

Chapter 1 – Introduction

Chapter 1 – Introduction

1.1 Chapter overview

Miscarriage and infertility are separate reproductive health issues which impact hugely on the lives of women and men affected. Miscarriage and infertility are independently associated with adverse pregnancy outcomes (4,5), in addition to established psychological sequelae (6,7). Moreover, they share a number of risk factors, and are reciprocally associated with each other (8,9). Both conditions have been shown to have significant economic consequences at a personal and societal level (1,10). The stigma and misconceptions surrounding miscarriage and infertility also adversely affect the experiences of women/couples, leading to feelings of isolation and ability to seek supports (11,12).

Miscarriage is the most common complication of pregnancy, with approximately 23 million miscarriages occurring worldwide annually (1). Despite this, miscarriage is poorly understood and the causes and treatments for miscarriage and recurrent miscarriage (RM) are not well known (1). Additionally, even after investigations, up to 50% of women/couples will have unexplained RM (2). Infertility is known to affect one in six couples and a large global study estimated that 48.5 million couples were affected in 2010(3). However, as per miscarriage, up to 30% of couples will have unexplained infertility after standard investigations (2). The lack of easily identifiable explanations for either condition leaves women and couples with uncertainty about their reproductive health and reliant on empiric or unproven treatments (13,14). Both RM and infertility are known to be associated with subsequent adverse pregnancy outcomes such as preterm birth, growth restriction and other placental disorders (15).

This chapter will provide an overview of RM and infertility, outline the complexities of the investigation and treatment of these conditions, and highlight structure of care issues in the Republic of Ireland (ROI). The relevant definitions will be delineated (Section 1.2), as will related risk factors such as maternal age, body mass index and smoking (Section 1.3). Conditions associated with RM and/or infertility such as congenital uterine anomalies, thrombophilias and endometriosis will also be discussed, as well as their relevant investigations and treatments and the evidence underpinning them to illustrate why so few are recommended in current Clinical Guidelines (Section 1.4). The reproductive

outcomes after RM and infertility will be reviewed (Section 1.5). The lived experience of RM and infertility, separately and in combination, will also be explored (Section 1.6). The organisation of RM care and infertility care and the specific past and present challenges faced in the ROI will be outlined (Section 1.7). This chapter will conclude by highlighting the research gaps (Section 1.8) and outlining the structure of this thesis (Section 1.9).

Throughout this thesis, most publications, including my own works, refer to women and their male partners. I acknowledge that this may not be representative of how every person experiencing RM or infertility identifies their gender or their relationships. These terms were not used to exclude, or deny the rights of, transgender, gender diverse or non-binary individuals, but rather for cohesion of language and terminology, and in mindfulness of the harms of de-sexing language in women's healthcare (16,17).

1.2 Definitions

1.2.1 Miscarriage and Recurrent Miscarriage

A pregnancy loss (miscarriage) is defined as the spontaneous demise of a pregnancy before the fetus reaches viability (18). In Ireland, this term therefore includes all pregnancy losses from the time of conception until 24 weeks of gestation (19). Originally, recurrent miscarriage was defined as three consecutive miscarriages (20). However, definitions from the Royal College of Obstetricians and Gynaecologists (RCOG), American College of Obstetricians and Gynaecologists (ACOG), American Society of Reproductive Medicine (ASRM), European Society Human Reproduction and Embryology (ESHRE) have all varied over time, whereas the German Society of Gynaecology and Obstetrics (DGGG), the Austrian Society of Gynaecology and Obstetrics (ÖGGG) and the Swiss Society of Gynaecology and Obstetrics (SGGG) have retained their original definition of three miscarriages as shown in Table 1.1.

Table 1. 1: Summary of selected international RM definitions

Organisation	**RCOG**	**ACOG**	**ASRM**	**ESHRE**	**DGGG, ÖGGG and SGGG**
Previous Guidelines	Recurrent Miscarriage Green-top Guideline No. 17 (18)	Practice Bulletin no 24: Management of recurrent early pregnancy loss (22)	Evaluation and treatment of recurrent pregnancy loss: a committee opinion) (23)	Evidence-based guidelines for the investigation and medical treatment of recurrent miscarriage (24)	Recurrent Miscarriage: Diagnostic and therapeutic procedures. (25)
Year	2011	2001	2012	2006	2015
Definition	Three or more consecutive	Two or more consecutive	Two consecutive, clinical (ultrasound-diagnosed) pregnancy losses, three if epidemiological studies	Three or more consecutive	Three or more consecutive
Gestational Age	<13 weeks	<15 weeks	Not defined	“early” – not defined	<20 weeks

Updated Guidelines	Recurrent Miscarriage Green-top Guideline No. 17 (26)	Definitions of infertility and recurrent pregnancy loss: a committee opinion (27,28)	Definitions of infertility and recurrent pregnancy loss: a committee opinion (28)	Guideline on the management of Recurrent Pregnancy Loss (29)	Recurrent miscarriage: diagnostic and therapeutic procedures(30).
Year	2023	2018	2020	2023	2018
Definition	Three or more miscarriages, clinical discretion to investigate after two	Two or more consecutive	Two or more miscarriages	RPL: Two or more pregnancy losses RM: confirmed intrauterine pregnancy losses only	Three or more consecutive
Gestational Age	<13 weeks	<13 weeks	Not defined	Up to viability defined as 24 weeks. Specifies “recurrent early pregnancy loss” <10 weeks	<20 weeks

1.2.2 RM and Recurrent Pregnancy Loss (RPL)

The terms 'RM' and 'RPL' are often used interchangeably within the literature. However as evident from Table 1.1, RM generally refers to first-trimester miscarriage and RPL may include second-trimester losses up to viability. Furthermore, the RCOG, and to a lesser extent, the ACOG, have considered RM and second-trimester pregnancy loss separately (21,27,31,32). This distinction accounts for the variant aetiologies of first and second-trimester miscarriage. It recognises that second-trimester miscarriage is more aligned to stillbirth in pathology and that those experiencing second-trimester pregnancy loss are more likely to experience later second-trimester loss, preterm birth or stillbirth subsequently (33). In the absence of national clinical guidelines on RM or second-trimester miscarriage, clinicians in the ROI have followed RCOG guidance and thus RM in the ROI has generally referred to first-trimester miscarriage only (21,34). However, within this body of work, RM refers to two or more first-trimester miscarriages in line with the majority of guidelines in Table 1.1, unless defined otherwise.

1.2.3 Additional variances in definitions of RM

In addition to the variations in gestational age and number of pregnancy losses, other differences in the definitions of RM are present. ESHRE and the ASRM include biochemical pregnancy loss in their definitions, but ESHRE specifically excludes ectopic and molar pregnancy (35) . The ASRM guidance from 2012 stipulated that RPL merited investigation only where "pregnancy is defined as a clinical pregnancy documented by ultrasonography or histopathological examination", and that RM in epidemiological studies should be confined to three or more losses; this was not specifically renounced in their 2020 update (23,28). As pathologies such as thrombophilia appear to occur in similar rates among those experiencing consecutive and non- consecutive losses (36), the RCOG and ESHRE have also recommended abolishing this stipulation (32,35) .

1.2.4 Recurrent versus Sporadic miscarriage

Both the ASRM and RCOG emphasise that a distinction should be made between "sporadic" miscarriage and "true" or pathological RM when it comes to attributing a cause for RM and considering treatment (23,32). Sporadic miscarriage is attributed to random numeric chromosomal errors, such as polyploidy, monosomy or trisomy (23). As theorised by Rai and Regan, RM is identifiable as a distinct entity, rather than sequential sporadic

miscarriages, as it may occur with a normal fetal karyotype (particularly in women aged under 36), it has a higher incidence rate than would be expected by chance alone (1% vs 0.34%) and is related to past obstetric history (37). The population prevalence of women who have had one miscarriage is 10.8%, two miscarriages is 1.9%, and three or more miscarriages is 0.7% (1). The incidence of three repeated sporadic miscarriages (i.e., RM by chance) increases significantly with age, 0.13% at age 20-24 vs 13 % at age 45, i.e., a 100-fold increase (38). It follows that the incidence of two sporadic miscarriages by chance alone also increases with age: 1.21% at age 20 vs 26% at age 45 (32).

The 2021 Lancet series on miscarriage recognised that sporadic miscarriage is likely only diagnosed after investigation, concluded that such distinctions do not offer the best care for women and its authors therefore suggested a graded approach to care for all women experiencing miscarriage (14). This entails provision of miscarriage and preconceptual advice alongside risk factor screening following a first miscarriage (14). After a second miscarriage, women are offered a nurse or midwifery-led service, offering continuity of care, appropriate investigations, and ultrasound scanning for reassurance in a subsequent pregnancy (14). Following a third or subsequent miscarriage, women are offered a consultant-led service with full panel of investigations and interventions for RM(14). The 2023 RCOG guideline, while still distinguishing between RM and consecutive sporadic miscarriage, recommends ultimately that the Lancet Series model "should be encouraged as it appears to bridge the gap between sporadic and recurrent miscarriage care, encouraging a systematic graded approach rather than a fragmented one" (32).

1.2.5 Infertility

Infertility is defined by the World Health Organisation (WHO) as, "a disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected intercourse"(39). ESHRE has since expanded this to "a disease characterised by the failure to establish a clinical pregnancy after 12 months of regular, unprotected sexual intercourse or due to an impairment of a person's capacity to reproduce either as an individual or with his/her partner"(40). Using consistent algorithms and more applicable definitions of primary infertility (inability to have any live birth) and secondary infertility (inability to have an additional live birth), 48 million women world-

wide were estimated to be infertile in a 2010 global study across 190 countries (3). ESHRE has estimated that in Europe alone, 25 million couples — or one in six — are affected by infertility(41). As a result, women/couples are increasingly requiring assisted reproductive technologies (ART) to conceive. For example, in 2018, 1422 clinics offering ART services in 39 countries exceeded 1 million (1 007 598) treatment cycles in Europe for the first time (42). The number of treatment cycles per annum in Ireland has also grown; in the period from 2009 to 2020, the number of cycles increased from 7,589 in 2009, to a peak of 11,359 in 2018 (43). There were fewer treatment cycles in 2019 and 2020, with a total of 9,878 recorded in 2020 (the last year for which data are available). The 10.6% drop in the number of treatment cycles in 2020 may be the result of pandemic-related disruption (43).

1.2.6 Recurrent Implantation Failure

While this thesis will not explore recurrent implantation failure (RIF) in detail, it is important to mention as women experiencing RIF and RM often share investigations and treatments (44), and within the literature are found to be reported together within cohort studies (45–51). Moreover, the experience of infertility and subsequent pregnancy loss, such as RM after IVF (in vitro fertilisation) or RIF, is complex, and while RIF and RM are distinct entities, these groups may have shared lived experiences. Thus, RIF was considered in reviewing the literature across this thesis.

RIF is a specific phenomenon in couples undergoing fertility treatment. It is broadly defined as the absence of implantation after repeated embryo transfers (52). There has been a lack of international consensus on what defines RIF; the "Recurrent implantation failure in IVF: A Canadian Fertility and Andrology Society Clinical Practice Guideline" counted 13 international variations on the definition(52). Key inconsistencies include the number of failed embryo transfers; the number, stage and quality of embryo(s) transferred (cleavage stage, blastocyst and euploid status); as well as the definition of implantation (concentration of human chorionic gonadotrophin (HCG) and presence of a gestational sac)(52). An ESHRE Working Group on RIF concluded that RIF is a distinct scenario confined to women/couples undergoing ICSI (intracytoplasmic injection) or IVF of heterogeneous cause and prognosis, with a need for an individualised approach that is not based on numeric criteria such as number of embryos transferred (44). Thus, in the

ESHRE 2023 Good Practice Recommendations for RIF, RIF is defined as, “the scenario in which the transfer of embryos considered to be viable has failed to result in a positive pregnancy test sufficiently often in a specific patient to warrant consideration of further investigations and/or interventions” (44) .

1.3 Shared risk factors between RM and infertility

Although they are largely treated as separate entities, RM and infertility share many common risk factors. These include non-modifiable factors such as maternal age and ethnicity, and modifiable risk factors such as obesity, smoking, alcohol, caffeine, shift work and stress. As maternal age is closely related to aneuploidy and ovarian reserve, these are also discussed here within the non-modifiable group. These risk factors are presented in Table 1.2. The association between each risk factor and RM and infertility will be discussed in more detail below. The additional associated conditions are discussed in Section 1.4.

Table 1. 2: Overview of shared risk factors for RM and infertility

Shared Risk Factors	Associated Conditions

Non-modifiable
• Maternal age
• Aneuploidy
• Ovarian Reserve
• Ethnicity
Modifiable
• BMI
• Smoking
• Alcohol
• Caffeine
• Shift work
• Stress
	• Uterine anomalies
	  ○ congenital
	  ○ acquired
	• Genetic factors
	• Thrombophilias
	  ○ inherited
	  ○ acquired
	• Endocrine disorders
	  ○ Thyroid disease,
	  ○ polycystic ovarian syndrome
	  ○ diabetes
	  ○ hyperprolactinaemia
	• Infection
	• Endometriosis
	• Immunological
	• Male factors

1.3.1 Maternal age

Advanced maternal age, generally defined as 35 years and older, is associated with an increased risk of miscarriage, in addition to infertility, ectopic pregnancy, second-trimester miscarriage, stillbirth, and maternal morbidity (53–55)

Maternal age and fertility

It is well established that with advancing maternal age there is a gradual decline in female fertility, with the effects most pronounced after the middle of the third decade . This is due to a combination of a reduction in the number of oocytes, and a deterioration in oocyte quality (56). Studies using population registers of pregnant women in Denmark and Norway have demonstrated —in very large cohorts — that advanced maternal age is strongly associated with lower birth rates, maternal and fetal morbidity as well as miscarriage (53,55,57,58). Age alone has an independent negative effect on fecundity. A consistently higher miscarriage rate and lower pregnancy and live birth rate is observed in older women that persists despite the use of IVF and oocyte donation (59,60). This trend with maternal age is apparent across all European countries, even with advancements in IVF techniques (42). It is also evident that age is a greater predictor of pregnancy success than other markers of fertility such as follicle-stimulating hormone (FSH) and Anti-Mullerian Hormone (AMH) levels (61,62).

Maternal age and miscarriage

Specifically examining the effect of age on miscarriage risk, the risk of miscarriage has been shown to be approximately 12% for women aged 20-29 and this rises to 65% at the age of 45 and over (1). This increased incidence is directly related to an age-related increase in embryonic trisomy, particularly trisomies on chromosomes 13, 14, 15, 16, 18, 20, 21, and 22 (63). The risk of trisomy 16 — the most common cause of miscarriage — rises linearly from 20 to 40 years of age, whereas the risks of other trisomies rise after the age of 35 (64).

1.3.2 Aneuploidy

Aneuploidy, or numerical chromosomal abnormalities, are generally accepted to be the primary cause of sporadic miscarriage (65) . As explained above, the risk of aneuploidy is directly related to maternal age. Through pre-implantation genetic diagnosis (PIGD), it has been shown that there is an increase in aneuploidy with maternal age, even in those

embryos that looked developmentally and morphologically normal (66). Indeed, pre-implantation and sub-clinical pregnancy losses due to aneuploid embryos were postulated as explanations for infertility (67), although this has been refuted (68,69). However, aneuploidy is associated with poor oocyte quality and diminished ovarian reserve which are recognised causes of infertility (70).

In RM, cytogenetic analysis of pregnancy tissue demonstrated aneuploidy and a cause for miscarriage in 80% of cases (71). In a population who underwent IVF and who had a miscarriage and subsequent cytogenetics, the rates of aneuploidy were similar at 73% (72). However, in other examinations of pregnancy tissue in RM cohorts, the rate of aneuploidy in subsequent miscarriages appeared to be lower in women with more than two miscarriages than in women who experienced sporadic miscarriage and appeared to decrease further with successive miscarriages (73). This speaks to the theory mentioned in Section 1.2.4 put forward by Regan et al., that RM is a distinct pathology, not simply "bad luck", or just recurring sporadic miscarriage due to aneuploidy (37). However, cytogenetic testing of pregnancy tissue only partially reveals the potential role of aneuploidy in miscarriage as many pregnancy losses are sub-clinical or fail at the implantation stage (74).

1.3.3 Ovarian reserve

Ovarian reserve — the number of oocytes remaining in the ovary — can be indirectly measured using hormones such as early follicular phase inhibin B, FSH, and AMH, in addition to ultrasound assessment of AFC (75). Female infants are born with ~500,000 to 1 million oocytes, which gradually reduce in number over time, ultimately resulting in menopause (75).

Ovarian Reserve and Infertility

Women who have a reduced number of oocytes or diminished ovarian reserve (DOR) (measured according to AMH/FSH/inhibin B levels or antral follicle) may have infertility; the correlation between ovarian reserve and clinical outcomes is not clear(62). Prospective cohort studies have shown that measurements of all the above tests of ovarian reserve (76) and AMH alone (77) did not predict the reproductive potential of women with no prior history of infertility, that is, they were not reflective of oocyte quality. FSH levels were not more useful than age alone in predicting unassisted

conception in women with infertility (78), nor were they more useful than established fertility prediction models (79). AMH, which is increasingly being used as a "fertility test", is used to predict ovarian reserve (being a good marker of oocyte quantity) and is also useful in determining dosing in ovarian stimulation for fertility treatment and predicting stimulation response (62). However, while AMH can estimate oocyte quantity, in no situation does it indicate oocyte quality or likelihood of pregnancy success(62).

Ovarian Reserve and Miscarriage

Infertility with or without RM has been linked to DOR; the hypothesis being that women with low oocyte counts have a resultant reduced oocyte quality, with a greater risk of meiotic dysfunction and aneuploidy and subsequent failed implantation or miscarriage (80). However, women who have had an aneuploid pregnancy have so far not been proven to have a statistically significant DOR or earlier menopause than women with euploid pregnancy or pregnancy loss(81–83). Conversely, when examining ovarian reserve in women with RM, Shahine et al. noted that aneuploidy rates of blastocysts examined for pre-implantation genetic testing for aneuploidy (PGT-A) were highest in women with DOR defined as AMH <1ng/ml or FSH>10IU/ml on day 3 (84) . Katz-Jaffe et al. had similar findings, with a 66% rate of aneuploidy in the DOR group (defined as raised FSH or low AMH as above) compared to 51% in women with normal ovarian reserve ($p<0.05$) (85). A more recent study by Jaswa et al. found that while women with DOR had higher rates of aneuploidy in all age groups except 35-37 years, there was no difference in livebirth rates after PGT-A, independent of age (86).

Schumacher et al. found that women with severe DOR (AMH <0.4ng/ml) who had spontaneous conceptions miscarried at twice the rate as those with AMH ≥1ng/ml (hazard ratio, 2.3; 95% CI, 1.3, 4.3), even with adjustment for age, race, history of RM and obesity (87). A systematic review by Bunnewell et al. including 15 studies (n=3,082 women) showed that women with RPL (variably defined by the included studies as two or three miscarriages, less than 10 or 20 weeks) were more likely to have DOR compared with women who did not have RPL, as measured by low AMH levels (odds ratio (OR) 2.77; 95% confidence interval (CI) 1.41, 5.46) and low antral follicle count (OR 2.45; 95% CI 1.16, 5.19)(88). Women with unexplained RPL also seemed to have a higher incidence of DOR compared with women whose RPL had a known aetiology, as measured by low AMH levels

(OR 3.23; 95% CI 1.81, 5.76)(88). Wald et al. also noted DOR rates were higher in the unexplained RM cohort compared to women with an identified cause for RM (48% vs 29%, p = 0.005), and the DOR rate was increased in those under 38 years old with RM (22% vs. 12%, p = 0.04) (89).

Therefore, DOR in the form of low AMH and low antral follicle count (AFC) appears to have an association with aneuploid pregnancy and thus recurrent sporadic miscarriage, which should be considered when counselling couples and may have a role in the investigation of RM and infertility. A 2021 systematic review however was unable to draw any formal conclusions on any association between DOR (in the form of AFC or AMH measurements) and miscarriage due to the heterogeneity of studies (90). Thus, it remains the case that ovarian reserve is not indicative of oocyte quality or fecundity and age remains the best predictor of reproductive potential (62) .

1.3.4 Ethnicity

Ethnicity and infertility

Globally there are large variations in infertility rates. In a global study of infertility rates, it was shown that infertility prevalence was highest in South Asia, Sub-Saharan Africa, North Africa/Middle East, and Central/Eastern Europe and Central Asia (3). Primary infertility rates varied from 1.5% in Latin America and the Caribbean in 2010, to 2.6% in North Africa and the Middle East (3). A large study by the WHO on global and regional infertility prevalence estimates placed lifetime prevalence of infertility at 17.5% (95% CI 15.0, 20.3) (91). Prevalence rates varied globally from 10.7% in the WHO Eastern Mediterranean Region, 13.1% in African Region, 16.5% in European Region, 20% in the Americas to 23.2% in the Western Pacific Region (91). Period prevalence of infertility globally (12-month infertility) is estimated to be 12.6% (95% CI 10.7, 14.6)(91). This rate also varied, ranging from 10% in the Eastern Mediterranean Region to 16% in the African Region (91) .

Geographical location, while a separate issue, is closely linked to ethnicity and is consistently identified as a barrier to accessing artificial reproductive technologies(92) . This is due a variety of reasons ranging from the state or country that a person lives in, and the number and location of fertility clinics, to geographic isolation (92). This is demonstrable within wealthy nations, whereby apart from advancing age and increasing

body mass index (BMI), it has been found that infertility rates are comparable across various races/ethnicities, educational backgrounds, and household income brackets (93). Race and ethnicity have also been shown to affect outcomes following ART, such as lower live birth rates in Black, Hispanic, Asian and Middle Eastern/North African women, and lower clinical pregnancy rates in Black, Asian, Hispanic, American Indian/Alaska Native women (93). Additionally, Black women were shown to be more likely to have a preterm birth or a low-birth-weight baby after ART (93). Examining data from the United Kingdom, similar patterns were seen, with Black women presenting later for ART and also having lower live birth rates (94).

Ethnicity and Miscarriage

Ethnicity also impacts on miscarriage rates. A systematic review of race and IVF outcomes, which included five United States (US) registry-based studies, showed that Black, Hispanic, and Asian women had lower clinical pregnancy rates and/or live birth rates after IVF, compared with white women (95). A retrospective cohort study demonstrated a lower live birth rate after ART for Black, Asian, and Hispanic women, with the highest rate of miscarriage in Black women (95). Even when ART is not required, an increased risk of miscarriage persists for Black women. A prospective cohort study in the Unites States demonstrated that Black women had an increased risk of miscarriage compared with white women (adjusted hazard ratio = 1.57, 95% CI 1.27, 1.93) (96). When risk of loss before gestational week 10 was dichotomised at the median gestational age, there was little difference in miscarriage rates, but Black women had a greater risk thereafter compared with white women (adjusted hazard ratio = 1.93, 95% CI 1.48, 2.51) (96). Self-reported race is independently associated with risk of miscarriage, and the higher risk for Black women is concentrated in gestational weeks 10–20 (96). A retrospective cohort study of 196,040 women demonstrated that compared with white Europeans, the odds of a previous miscarriage were increased in Black African (adjusted odds ratio [aOR] 1.20; 95% CI 1.12, 1.29) and Black Caribbean women (aOR 1.31; 95% CI 1.21, 1.41) (97). Thus, women of colour are at greater risk of adverse pregnancy outcomes such as miscarriage, and this risk persists even with the use of ART.

1.3.5 Overweight and obesity

Obesity is a multifactorial disease that adversely affects lives worldwide and is increasingly at the centre of modern healthcare cost, policy, and intervention (98). Obesity is the result of several determinants that can be divided into upstream causes (policies by the government and economically driven factors), midstream causes (dependent on employment status, level of education), and downstream causes (behavioural factors)(99). The agreed WHO classification of overweight and obesity for adults is a BMI of 25 to <30 kg/m^2, and ≥30 kg/m^2 respectively (100); although increasingly the limitations of BMI in identifying/defining obesity are being acknowledged (101). Pregnant women with a BMI ≥30 is at greater risk of a variety of pregnancy-related complications compared with women with a BMI of 20 to 30, including pre-eclampsia and gestational diabetes(102).

Obesity and infertility

Obesity is known to have an impact on female fertility, both through anovulation and endometrial factors(103). Anovulation is thought to stem from the aromatisation of androgens in peripheral adipose tissue, with the subsequent high circulating oestrone levels leading to disruption of the hypothalamic-pituitary-gonadal axis (103). Additionally, insulin resistance and the subsequent hyperinsulinemia is purported to affect signalling pathways in ovulation(103,104). Thus, it is logical that obesity is associated with polycystic ovary syndrome (PCOS), the most common cause of anovulatory fertility, which is also associated with insulin resistance(104). Women with PCOS who have a higher BMI (>25) are more likely to experience miscarriage, which is discussed further below. This clinical association between implantation failure and obesity is attributed to inflammation caused by cytokine (especially adipokine) release, oxidative stress, genetic polymorphisms and epigenetics (99,103). Having a higher BMI may also affect ART success. The composition of follicular fluid is affected by increased adiposity and can lead to embryo fragmentation, poor blastomere score, and impaired folliculogenesis (103).

Higher BMI is associated with lower ovarian responsiveness to ovulation induction as evidenced by the need for higher doses of oral agents and gonadotropins and the lower number of oocytes retrieved during IVF (105). In addition, oocyte quality is impaired in both obese animal models and human clinical studies. In a linear manner, higher BMI is

correlated with lower implantation and clinical pregnancy rates and live birth rates when undergoing IVF/intracytoplasmic sperm injection treatment (105). This effect is most prominent in younger reproductive-aged women and is significantly attenuated with advancing reproductive age (105). However, the age-related decline in fertility has a greater impact than BMI on live birth rate at older ages, suggesting that delaying IVF for weight loss purposes may be detrimental for older women with overweight or obesity (106).

A 2023 systematic review of studies (other systematic reviews and randomised control trials) examining obesity and live birth rates (all using ART) in the last five years found that results were inconsistent in demonstrating an inverse correlation between BMI and live birth (103). Dietary and exercise interventions and pharmaceutical interventions have not been shown to have a consistent impact on live birth rates (103). Definitive high-quality evidence on newer drugs for pre-conceptual weight loss, such as semaglutide, in women trying to conceive either naturally or using ART is awaited (103). Although the evidence is unclear, many governing bodies have made recommendations regarding weight loss for women with obesity, including specific recommendations that women with a BMI over 30 should not be offered fertility treatment (99). Recently, the Health Service Executive (HSE) in Ireland has stipulated that upcoming publicly funded fertility treatment will only be available to women with a BMI of 18.5 to 30 (107). The ASRM however have stated, “On the basis of available evidence, there is no medical or ethical directive for adopting a society-wide BMI threshold for offering infertility treatment; rather, there is considerable evidence arguing against such a policy”. Additionally, they have stated, “Obesity should not be the sole criteria for denying a patient or couple access to infertility treatment”(105). Individual programs should be empowered to adopt program-specific BMI thresholds solely based on the ability to safely perform oocyte retrievals and other procedures within their clinical environment” (105). Negative attitudes towards people with obesity, also referred to as ‘weight stigma’, may contribute to restrictive practices in fertility treatment (108).

Obesity and male infertility

Male partner obesity is also associated with decreased fertility. Oligospermia and azoospermia have been observed in men with BMI >30 (99). Furthermore, the

combination of insulin resistance and increased peripheral conversion of androgens to oestrogens disrupts hypothalamic signalling. This inevitably affects the circulating level of testosterone, adversely affecting fertility (99).

Obesity and RM

A systematic review and subsequent meta-analysis (of two studies) has shown that women with a BMI < 18.5 and women with a BMI ≥ 25 have higher odds of RPL (different definitions included but grouped to mean two or more miscarriages) than the general population (OR 1.2; 95% CI 1.12, 1.28 and OR 1.21; 95% CI 1.06, 1.38, respectively) (109). In women with RPL having BMI ≥ 30 and BMI ≥ 25 has increased odds of further miscarriages (OR 1.77; 95% CI 1.25, 2.50 and OR 1.35; 95% CI 1.07, 1.72, respectively) (109). The quality of the evidence for these findings was low or very low, however. A separate meta-analysis had considered the same source data and in isolated analyses revealed that a correlation exists only between obesity (BMI >30 kg/m^2) and RPL (OR 1.75; 95% CI 1.24, 2.47; p = 0.001) (110). Nonetheless, there are studies which demonstrate that women with a BMI >30 are at greater risk of euploid miscarriage. An analysis from a well-characterised RPL database demonstrated that in pregnancy losses at <10 weeks' gestational age, women with obesity with RPL have a 58% chance of having a euploid loss compared with 37% in women without obesity (relative risk (RR)1.63; 95% CI 2.08, 2.47) (111). An analysis of pregnancy tissue indicated that women with obesity had a 46% euploid loss rate compared with 34% in women with a BMI <25 (OR 1.56; 95% CI 1.25, 1.95)(112) .

On review of the evidence, the ASRM concluded that various studies demonstrate a link between obesity and miscarriage risk, regardless of mode of conception (105). However, the adjusted ORs range between 1.2 and 1.9, suggesting that while a link exists, the association is modest and may be influenced by confounding factors (105).

1.3.6 Smoking

Smoking is an established modifiable risk factor for adverse pregnancy outcomes (113). These outcomes include, but are not limited to, preterm delivery, fetal growth restriction, placental abruption, placenta praevia, preterm premature rupture of membranes, and perinatal death (114).

Smoking and infertility

In addition to known risks during pregnancy, substantial harmful effects of cigarette smoke on fecundity and reproduction have become apparent. Smoking is associated with a prolonged time to conceive, ovarian follicular depletion, as well as negative effects on sperm parameters(114). In an observational study of over 12,000 women active smoking (daily smoking) was shown to be associated with failing to conceive after 6 or 12 months (OR 1.23; 95% CI 0.98, 1.49 for > 6 months, and OR 1.54; 95% CI 1.19, 2.01 for >12 months), as was passive smoking (OR 1.17; 95% CI 1.02, 1.37), compared with women with no exposure to tobacco smoke (OR 1.14; 95% CI 0.92, 1.42) (115).

Smoking and male fertility

Smoking has been shown to cause, not only a decrease in sperm motility, sperm concentration, and an increase in abnormal sperm morphology, but also genetic and epigenetic aberrations in spermatozoa. Both animal and human studies have highlighted the occurrence of sperm DNA-strand breaks (fragmentation), genome instability, genetic mutations, and the presence of aneuploids in the germline of animals and men exposed to tobacco smoke (116) . Heavy smoking (≥20 cigarettes/day) by men is independently associated with delayed conception (115).

In a meta-analysis of eight studies, paternal smoking of >10 cigarettes per day in the preconception period was found to be associated with an increased risk of first or second-trimester pregnancy loss, after adjustment for maternal smoking status (1–10 cigarettes per day, aOR 1.01; 95% CI, 0.97, 1.06; 11–19 cigarettes per day, 1.12; 95% CI 1.08, 1.16; ≥20 cigarettes per day, 1.23; 95% CI 1.17, 1.29) (117).

Smoking and ART

Smoking also appears to have a deleterious effect on ART outcomes. A systematic review and meta-analysis of 12 studies published in 1998 demonstrated an increased risk of infertility among smokers compared to non-smokers, (OR 1.60; 95% CI 1.34, 1.91), and subsequent meta-analysis of nine studies found an OR of 0.66 (95% CI 0.49, 0.88) for pregnancies per number of IVF-treated cycles in smokers versus non-smokers (118). More recent systematic reviews have reiterated these findings that women who smoke demonstrated significantly lower odds of live birth per cycle, significantly lower odds of clinical pregnancy per cycle and significantly higher odds of spontaneous

miscarriage(119,120) and significantly higher odds of ectopic pregnancy (OR 15.69; 95% CI 2.87, 85.76)(120).

Smoking and miscarriage

A systematic review demonstrated that any active smoking by women was associated with increased risk of miscarriage (Relative risk ratio (RRR) 1.23; 95% CI 1.16, 1.30; n = 50 studies) (121). The risk of miscarriage increased with the amount smoked (1% increase in relative risk per cigarette smoked per day)(121). Passive smoking increased the risk of miscarriage by 11% (121). Echoing the findings of Augood et al. above(118), significant negative fertility outcomes were detected in a meta-analysis of female smokers compared with non-smokers undergoing ART including decreases in: live birth rate per cycle (OR 0.52; 95% CI 0.37, 0.74), clinical pregnancy rate per cycle (OR 0.59; 95% CI 0.51, 0.68), number of retrieved oocytes (mean difference (MD) = −0.87; 95% CI –1.39, −0.25), and average fertilisation rate (MD = −4.80; 95% CI −8.49, −2.02), as well as a significantly increased miscarriage rate per pregnancy (OR = 2.48; 95% CI 1.79, 3.43) (122).

1.3.7 Alcohol

Alcohol has a clear negative impact on pregnancy and neonatal outcomes, including the fetal alcohol spectrum disorders. However, the relationship between alcohol and miscarriage and/or fertility is less clear.

Alcohol and infertility

A systematic review aiming to determine the effect of alcoholism on female fertility found it difficult to draw any clear association between “natural” fertility (i.e. spontaneous conception) and alcohol as there was a large degree of heterogeneity between studies with variation on the quantity of alcohol consumption studied and how exposure to alcohol was measured and assessed(123). However, the review did demonstrate a detrimental effect of alcohol on ART cycles (123). This has also been shown in a more recent systematic review whereby maternal alcohol consumption was negatively associated with pregnancy after IVF/ICSI treatment (OR 0.83; 95% CI 0.69, 1.01) (124). Compared with women who abstained, the chance of achieving a pregnancy after IVF/ICSI treatment decreased by 7% for women who consumed 84 g alcohol per week (six standard drinks in the United States) (OR 0.93, 95% CI 0.90, 0.98)(124).

Alcohol and male fertility

Paternal alcohol consumption was also negatively associated with partner's live birth after IVF/ICSI treatment (OR 0.88, 95% CI 0.79, 0.99) and the chance of partners achieving a live birth decreased by 9% for men who consumed 84 g alcohol per week (OR 0.91, 95% CI 0.88, 0.94)(124). A study focusing on the effects of male alcoholism showed an associated decrease in sperm concentration, motility and normal morphology (125).

Alcohol and miscarriage

Alcohol also increases the risk of miscarriage. A large Chinese study of 4.5 million women demonstrated that preconception alcohol consumption was associated with higher odds of miscarriage, and an increasing risk was found with paternal and maternal alcohol consumption (126). Compared with non-drinkers, the adjusted OR of miscarriage was 1.06 (95% CI 1.02, 1.10) and 1.59 (95% CI 1.15, 2.20) in maternal occasional drinkers and regular drinkers, respectivelyv(126). Compared with couples in which neither the male nor the female consumed alcohol, the adjusted OR for miscarriage among women was 1.09 (95% CI 1.07, 1.10), 1.13 (95% CI 1.06, 1.21) and 1.12 (95% CI 1.07, 1.17) in the couples in which only the female drank alcohol, only the male drank alcohol, and both drank alcohol, respectively(126). Conversely, the adjusted OR was 0.58 (95% CI 0.51, 0.65) in women with alcohol abstinence compared with alcohol drinkers (126). However, a systematic review of female lifestyle factors and pregnancy loss did not find an association between RM and alcohol consumption(109).

1.3.8 Caffeine

Caffeine is another substance which has been reported to be associated with RM and infertility.

Caffeine and infertility

The association between caffeine consumption and infertility is unclear. A systematic review and meta-analysis showed that low (≤100mg/day) (OR 0.95; 95% CI 0.78,1.16), medium (>200mg/day) (OR 1.14; 95% CI 0.69, 1.86) and high doses >400mg/day (OR 1.8; 95% CI 0.28, 12.22) of caffeine intake in women and men may not increase the risk of infertility (127). Notably, the quality of the evidence was all rated low. A systematic review examining any daily caffeine consumption on IVF/ICSI cycles showed women's and men's caffeine consumption was not significantly associated with the pregnancy rate (OR 0.97;

95% CI 0.85, 1.12; OR 0.93; 95% CI 0.75, 1.14; respectively) and the live birth rate (OR 0.98; 95% CI 0.89, 1.08; OR 0.98; 95% CI 0.86, 1.12; respectively) of IVF/ICSI (124). Examining male fertility alone, caffeine was associated with decreased normal sperm morphology but no other parameters; however, the lack of high-quality studies was noted (125).

Caffeine and miscarriage

The evidence for an increased risk of RM with caffeine consumption is conflicting, with observational studies reporting an increased risk of RM (128,129), miscarriage and other adverse outcomes such as preterm birth (130)and others reporting no association(131,132). The risk of RM has been shown to increase with higher doses of caffeine intake with those consuming >300mg/day at highest risk. In a meta-analysis of 15 studies, compared to women with no or low coffee consumption, the pooled RR for women with high coffee consumption was 1.65 (95 % CI 1.46, 1.87) in the caffeine-exposed group (132).

Thus, while high rates of caffeine consumption may carry a risk, due to heterogeneity of studies and a lack of high-quality studies, the effect of low caffeine consumption on infertility or RM risk is not clear.

1.3.9 Shift Work

Night shift work has been suggested to be a risk factor for miscarriage and infertility.

Shift work and infertility

Night shift work also appears to affect the female menstrual cycle and as a result can contribute to infertility and impacts on the success of ART (133–135). Specifically, recent studies have found altered levels of FSH, LH, and prolactin with sleep disturbance or circadian dysrhythmia (133). Disruption of circadian rhythms in the form of shift work, jet lag, and daylight savings time changes have been associated with poorer fertility in the form of failed embryo implantation, anovulation and amenorrhea and early pregnancy loss(134,135). Importantly, shift work also appeared to affect male partner fertility (136).

Shift work and miscarriage

Quenby et al found that working > 40 hours/week (OR 1.26; 95% CI 0·94–1.70) or working night shifts (OR 1·46; 95% CI 1.25, 1.71) was associated with miscarriage (1). Another

systematic review did not find an association between rotating shifts and miscarriage (OR, 1.05; 95% CI 0.85, 1.29, I^2 = 64%)(137). However, pregnant women who worked fixed night shifts had higher rates of miscarriage than women who worked regular day shifts (10 studies, n = 62,877; OR, 1.23; 95% CI 1.03, 1.47, I^2 = 33%)(137). Meanwhile, women who worked >40 hours per week had a 38% increase in the odds of miscarriage compared to women who did not (8 studies, n = 73,855; OR, 1.38; 95% CI 1.08, 1.77, I^2 = 73%) (137). It is important to note however that the above evidence was deemed low certainty as studies were at high risk of bias and imprecision.

1.3.10 Stress

Stress can be defined as a state of worry or mental tension caused by a difficult situation (138). Stress is a natural human response that prompts us to address challenges and threats in our lives (138). Psychological stress can include the experience of emotional trauma, social problems, concerns about money, marital/partnership disharmony, work pressure, significant change in personal circumstances as well as prior pregnancy loss (139).

Stress and infertility

Fertility treatment is an incredibly stressful experience, both physically and psychologically (140). A review of stress and infertility found a close relationship in women between fertility status, stress and quality of life with a resultant negative impact on reproductive function (141). The review also found that stress or poor quality of life is more likely to be reported in infertile rather than fertile women (141). Moreover, difficulty with conceiving propagates further stress and deteriorating quality of life (141).

Stress and miscarriage

Women with RM have been shown to have higher levels of stress, in addition to anxiety and depression (6,142). Whether stress is in itself a cause of RM has yet to be definitively proven, with some studies showing an association (143) and others failing to show that stress is a factor in pregnancy loss (144,145). A 2017 systematic review and meta-analysis of miscarriage and stress found that maternal psychological stress is significantly associated with an increased risk of miscarriage (overall pooled OR 1.42; 95% CI 1.19, 1.70, I^2 = 35.6%) (139). Sub-group analysis found that work stress was significantly associated with an increased risk of miscarriage (OR 1.27; 95% CI 1.10, 1.47; p = 0.001) (139). This is

in keeping with a survey of Irish women undergoing ART, which demonstrated that job-related stress was not associated with reduced conception rates but was shown to be associated with higher risk of miscarriage (146). A population-based case–control study also demonstrated that women who reported that their job was generally stressful and/or demanding had significantly higher odds of miscarriage than those who did not (OR 1.30; 95% CI 1.01, 1.68)(147).

1.4 Conditions associated with RM and infertility and their management

RM and infertility are associated with a number of medical conditions (specifically diabetes, polycystic ovarian syndrome, endometriosis, thyroid disorders, cancer treatments such as radiotherapy and chemotherapy) and uterine anomalies such as polyps, fibroids and uterine septae are also common to both groups (2). It should be acknowledged however, that after assessment for anatomical anomalies, endocrine anomalies, autoimmune disease, thrombophilia (for RM cohort only), infection (for infertility cohort only) and contributory male factors, up to 50% of those with RM, and 30% of those with infertility, will be left without explanation as to why they cannot achieve or maintain pregnancy (2). This implies that much has yet to be elucidated in this area and reflects the complex process of conception. In the absence of definitive causes, empiric treatments are also offered to women and couples with RM and infertility; these will also be discussed here.

1.4.1 *Congenital Uterine Anomalies*

Congenital uterine anomalies are formed when the two mullerian ducts, which are the embryological origins of the reproductive tract, fail to fuse and subsequently canalise as expected. Abnormal or absent duct development leads to an absent or unicornuate uterus (single-horned) (148). Failure of the ducts to fuse leads to a unification defect. Incomplete horizontal fusion results in either a partial unification defect (e.g. bicornuate (double-horned) uterus) or complete unification defect (uterine didelphys, “double uterus”) (148). Vertical fusion can also be affected (the descending mullerian duct and ascending urogenital sinus fuse and then canalise to form vaginal canal), causing an imperforate hymen or a transverse vaginal septum (148). If resorption or canalisation is incomplete, the result is a complete septate uterus, partial septate uterus or arcuate uterus, depending on how much resorption occurs (148).

A systematic review and meta-analysis found the prevalence of diagnosed uterine anomalies was 5.5% (95% CI 3.5, 8.5) in women with no history of RM or infertility, 8.0% (95% CI 5.3-12) in women with infertility, 13.3% (95% CI 8.9, 20.0) in women with a history of miscarriage, and 24.5% (95% CI, 18.3, 32.8) in women with miscarriage and infertility (149). The most common anomaly diagnosed in women without infertility and/or miscarriage was arcuate uterus, (the least severe form of canalisation failure); this was not more prevalent in women with miscarriage (149), and is not considered to be clinically significant in the latest ESHRE/European Society for Gynaecological Endoscopy (ESGE) classification (150). Canalisation anomalies, namely septate uterus, were significantly more common in women with a history of miscarriage (5.3%; 95% CI 1.7, 16.8, p=0.021) or miscarriage and infertility (15.4%; 95% CI 12.5, 19, p=0.001) (149). Unification anomalies such as bicornuate, unicornuate or didelphic uteri were also more prevalent in women with miscarriage (2.1%; 95% CI 1.4–3, p=0.001) or miscarriage and infertility (4.7%; 95% CI 2.9, 7.6, p=0.001) than in women without miscarriage and/or infertility (0.4%; 95% CI 0.2, 0.6) (149).

A systematic review and meta-analysis to determine the clinical implications of congenital uterine anomalies found that women with septate (RR 2.65; 95% CI 1.39, 5.06) and bicornuate uterus (RR 2.32; 95% CI 1.05, 5.13) had a significantly increased probability of first-trimester spontaneous miscarriage compared with women without congenital uterine anomalies (151). Chan et al. also examined the reproductive impact of congenital uterine anomalies in 3805 affected women and reported that those with canalisation defects, such as septate and partial septate uteri, appeared to have the poorest reproductive outcomes with a reduced conception rate (OR 0.86; 95% CI 0.77, 0.96) and increased risk of first-trimester miscarriage (OR 2.89; 95% CI 2.02, 4.14) (152). Chan et al. also found that women with a bicornuate and unicornuate uterus have an increased risk of first trimester miscarriage (OR 3.4; 95% CI 1.18, 9.76 and OR 2.15; 95% CI 1.03, 4.47 respectively), but do not appear to have reduced fertility (152).

1.4.2 Treatments for congenital uterine anomalies

Hysteroscopic uterine septum resection

This minimally invasive technique has been studied in women with infertility and miscarriage. A 2021 systematic review and meta-analysis of seven studies showed that

hysteroscopic septum resection was associated with a lower rate of miscarriage (OR 0.25, 95% CI 0.07, 0.88) compared with untreated women. No significant effect was seen on live birth, clinical pregnancy rate or preterm delivery (153). More recently, Carrera et al. updated this evidence to include the findings of the long-awaited TRUST (The Randomised Uterine Septum Transection) randomised control trial in their analyses alongside ten observational studies (154). The pooled OR for miscarriage was 0.45, (95% CI 0.22, 0.90). Again, no significant differences were found between the two groups in OR of clinical pregnancy, term live birth, or risk of caesarean delivery (154). The TRUST trial alone demonstrated no evidence of a difference in clinical pregnancy, ongoing pregnancy, pregnancy loss or preterm birth rates. but was limited by its small sample size, (n=80), and was not powered to evaluate any differential effect of septum resection in women with pregnancy loss before 24 weeks compared with those presenting with infertility, or according to the number of pregnancy losses (155).

Two other systematic reviews on hysteroscopic septum resection in women with histories of pregnancy loss or infertility have since been published (156,157). Both of these reviews only examined the observational studies available, excluding the TRUST trial for different reasons. Jiang et al. excluded the TRUST trial for not having adequate information on postoperative reproductive outcomes in women with recurrent miscarriage, primary infertility, or secondary infertility, separately, as well as having women with infertility and miscarriage unequally dispersed between the expectant and treatment groups and ultimately analysing them together (157). In their meta-analysis, women with recurrent miscarriage and a septate uterus, hysteroscopic septum resection was associated with an increased live birth rate compared to women without treatment (RR 1.77; 95% CI, 1.26, 2.49; p=0.001; I^2=0%), resulting in a postoperative live birth rate of 66% (95% CI 59, 72), and septum resection was associated with a reduced preterm birth rate (RR 0.15; 95% CI 0.04, 0.53; p=0.003; I^2=0%) and miscarriage rate (RR, 0.36; 95% CI 0.20, 0.66; p=0.0009; I^2=0%) (157). In women with a septate uterus and primary infertility, hysteroscopic septum resection was associated with an increased live birth rate (RR 4.12; 95% CI 1.19, 14.29; p=0.03; I^2=0%) and clinical pregnancy rate (RR 2.28; 95% CI 1.04, 4.98; p=0.04; I^2=0%)(157). The postoperative live birth rate was 37% (95% CI 30, 44), and the miscarriage rate of women with primary infertility was reduced (RR 0.19; 95% CI 0.06, 0.56; p=0.003) (157).

Noventa et al. also excluded the TRUST trial for including RM and infertility together; in this meta-analysis, the RM and infertility groups were considered separately (156). Women with septum resection were also compared to those without treatment, as well as examining the pre and post operative outcomes of women who underwent treatment. Examining three studies reporting data from women with infertility, the observed pregnancy rate was not different in women with a removed septum vs. controls (OR 1.66; 95% CI 0.48, 5.73; p=0.42; I^2 = 58%(156). Live birth rate was not different in women with septate uterus vs. controls (OR 2.03; 95% CI 0.42, 9.73; p=0.38; I^2 = 34%) (156). In four studies reporting pre- and post- operative data from women with infertility, live birth rate was higher after removal of the uterine septum (OR 20.06; 95% CI 2.53, 158.85; p=0.005; I^2 = 43%) (156). In six studies reporting data from women with RM, the live birth rate was not different in women who had the uterine septum removed vs. not removed (OR 2.96; 95% CI 0.96, 9.15; p=0.06; I^2 =78%) (156). In seven studies reporting data from women with RM, miscarriage was lower after removal of the uterine septum (OR 0.03; 95% CI 0.01, 0.06; p<0.0001; I^2 = 78%) (159). Live birth rate was higher after the removal of uterine septum (OR 49.58; 95% CI 29.93, 82.13; p<0.0001; I^2= 64%) (156).

Thus, across these different meta-analyses, there appears to be a trend for reducing miscarriage and increasing livebirth with hysteroscopic resection, enhanced with sub-group analyses of women with RM or infertility. However, there remains a dearth of high-quality evidence, and these effects are drawn from small numbers of medium to low-quality studies and should be interpreted with caution. Additionally, there remains no consensus on clinically significant uterine septum depth and criteria for surgical intervention. Therefore, the RCOG recommend surgery in this cohort should proceed with caution and ideally in the context of research, whereas ESHRE left a conditional recommendation citing that that TRUST trial was the only study to show no benefit (32,35). The National Institute for Health and Clinical Excellence (NICE) recommends that selection and treatment of women with septate uterus should be done by a multidisciplinary team including specialists in reproductive medicine, uterine imaging and hysteroscopic surgery (158).

Surgeries for other congenital uterine anomalies

Currently, abdominal or laparoscopic metroplasty for fusion or unification defects is generally not advisable owing to its potential association with significant intraoperative and postoperative complications and lack of evidence to support improved reproductive outcomes (148).

1.4.3 Acquired uterine anomalies

Fibroids

Fibroids or leiomyoma are benign tumours of smooth muscle cells (159). Fibroids are classified according to whether they are submucosal, intramural or subserosal. The International Federation of Gynaecology and Obstetrics (FIGO) classification further stratifies fibroids as outlined in Table 1.3.

Table 1. 3: FIGO classification of uterine fibroids.

Submucosal	0	Pedunculated intracavitary fibroid (i.e., submucosal fibroid without intramural extension)
	1	Submucosal fibroid with intramural extension < 50%
	2	Submucosal fibroid with intramural extension > 50%
Intramural	3	Intramural fibroid in contact with the endometrium but not extending into the uterine cavity or serous surface
	4	Intramural fibroid without contact with the endometrium and without extension into the uterine cavity or serous surface
Subserosal	5	Subserosal fibroid with intramural extension > 50% and < 50% subserosal
	6	Subserosal fibroid with intramural extension < 50% and > 50% subserosal
	7	Subserosal pedunculated fibroid
Other	8	Other types of fibroids (e.g., cervical, broad ligament, and parasitic fibroids)

Fibroids are associated with infertility, affecting implantation in several ways, even though high-quality epidemiological studies demonstrating this association are lacking (160,161). While the prevalence of fibroids in the general population is up to 40% in women of reproductive age, the prevalence of fibroids in RM populations is variable with rates of 0.5 to 10% quoted and the association between fibroid types and pregnancy loss is also variable (159,161). A large meta-analysis demonstrated no association between fibroids and miscarriage; however, it did not examine for differences between submucosal, intra-mural or subserosal fibroids (159). Submucosal fibroids (FIGO classification 0–2) are thought to contribute to RM through chronic endometrial inflammation, abnormal vascularisation, increased uterine contractibility, and abnormal local endocrine patterns (161). Submucosal fibroids have the strongest association with lower ongoing pregnancy rates and miscarriages (161). A systematic review and meta-analysis found that women with ≤6 cm non-cavity-distorting intramural fibroids had significantly lower live birth rates (OR: 0.48; 95% CI 0.36, 0.65; I^2=0; 3 studies, low-certainty evidence) compared with women with no fibroids(162) . A significant reduction in live birth rates was noted in fibroids ≤4 cm but not in the ≤2 cm subgroups(162).

A separate systematic review and meta-analysis found an association between fibroids and infertility (common OR 1.93; 95% CI 0.89, 4.18, p = 0.10) (160). Other reports also suggest a correlation exists between intramural fibroids and low fertility outcomes, but generally the relationship between fibroids and natural fertility was found to be poorly and inadequately investigated, with improper adjustment for confounders (160,161). Subserosal myomas are not associated with miscarriage and/or poor fertility outcomes(160,161).

Intrauterine Adhesions

Intrauterine adhesions refer to endometrial fibrosis with partial to complete obliteration of the uterine cavity and/or cervical canal (163). Any event that causes damage to the endometrium may lead to the development of intrauterine adhesions, resulting in menstrual disturbances, infertility and (potentially recurrent) pregnancy loss (163,164). Intrauterine adhesions are more prevalent among women having two or more miscarriages, with surgical management of miscarriage a likely risk factor (165). Women with identified and treated adhesions had fewer ongoing pregnancies and live births in

addition to a prolonged time to a live birth compared to women without adhesions(163). Additionally, women with hysteroscopically identified and treated mild intrauterine adhesions seem to have lower pregnancy and live birth rates compared to the general population (166).

Endometrial Polyps

The prevalence of endometrial polyps related to RM varies from 1.6% to 6% (161). Their association with infertility has long been suspected, and there appears to be a benefit in polyp resection for women with infertility, but studies are inconsistent(167). There is no clear evidence showing an association with RM (161).

1.4.4 Treatment for acquired uterine anomalies

Myomectomy for fibroids

There are no high-quality studies assessing myomectomy in women with RM and fibroids, and on this basis, the ESHRE guidelines do not recommend hysteroscopic removal of submucosal fibroids or the removal of cavity distorting intramural fibroids (35). The ESHRE guideline follows a Cochrane review on surgical treatment of fibroids for infertility, which concluded that it was uncertain if myomectomy improved clinical pregnancy rate for women with any type of fibroid (submucosal, intra-mural or subserosal)(168) . It was uncertain whether myomectomy for any of the described types of fibroids had any effect on the miscarriage rate, underpinned by very low-quality evidence (168). Conversely, Carbonnel et al. argue that this guidance goes against "common wisdom" when submucosal myomectomy for fibroids <3cms can be conducted in an office setting and can improve fertility outcomes and pregnancy loss (160,161,169). There is a need for high-quality studies to determine whether myomectomy is of benefit to women with RM or infertility and fibroids.

Resection of Intrauterine adhesions

Hysteroscopy remains the gold standard for identification of intra-uterine adhesions and hysteroscopic resection the primary treatment, but this has not been demonstrated to improve outcomes in RM populations (170). Resection seems to be of benefit, improving pregnancy and live birth rates, but appears to be of less benefit in those with more severe adhesions and pregnancy and live birth rates remain lower compared to the general population (166,171,172). The use of gels and hormonal treatments appear to improve

outcomes, but these have also not been demonstrated in specific fertility or RM populations to date (173).

Polypectomy

Although polypectomy is not recommended by ESHRE or ASRM to reduce miscarriage, it is shown to be of benefit in improving ART outcomes (161). Individualised treatment is prudent, given there are no universally accepted recommendations have been accepted to guide polyp management (161).

1.4.5 Genetic factors in RM and fertility

Aneuploidy

Fetal aneuploidy is the most commonly identified cause of sporadic and recurrent miscarriage, particularly in the first trimester (71). Chromosomal analysis offers an explanation for approximately 70% of women/couples with RM, although this figure may improve as newer techniques such as array-comparative genomic hybridisation (CGH) or single nucleotide polymorphism (SNP)-microarray identify greater numbers of chromosomal anomalies (174,175).

As mentioned previously in Section 1.3.2, fetal aneuploidy is strongly associated with maternal age (176). Chromosome anomalies in miscarriage specimens include trisomies, monosomies, polyploidies and structural anomalies. Trisomies are the most common numeric chromosome error, with Trisomy 16 and 22 being the most frequent, while Monosomy X is the most frequent sex chromosome error (177). Trisomies in particular are associated with maternal age >35 years (177,178), whereas unbalanced translocations are to be found more frequently in pregnancy tissue of younger women (aged <35) presenting with RM (179). In a meta-analysis of RM cohorts, aneuploidy was less likely with successive miscarriages (180), but this trend was only evident in women aged under 35, with higher aneuploidy rates persisting in women aged over 35 (72,73,178). Oocyte and embryo aneuploidy are primary causes of declining oocyte and embryo quality in women over 35 and are responsible for the diminished rates of pregnancy and livebirth (70).

Parental Chromosomal Anomalies

Parental chromosomal anomalies are also associated with RM. These can be classified into structural and numeric anomalies. Structural includes balanced reciprocal translocations, Robertsonian translocations, inversions, deletions and duplications, whereas numeric refers to anomalies such as trisomies or monosomies (181). Of these, parental balanced translocations are the most commonly identified in RM cohorts.

The prevalence of structural chromosomal anomalies was 5.3% for couples with two miscarriages and 6.6% with three, in a systematic review, with more recent studies reporting 4.4% and 3.7%, respectively (181–183). Chromosomal anomalies have been shown to be more common in the female partner and in younger couples (181). However, although miscarriage rates have been reported to be higher among couples with balanced translocations, livebirth rates are reassuring, with low reported rates of unbalanced chromosomal rearrangements in offspring (183–185).

The outcome of an inherited structural chromosomal rearrangement is dependent on the specific rearrangement. If a child receives an identical balanced reciprocal translocation from a parent, there are often no symptoms. If that translocation is unbalanced (part of one chromosome missing and an additional part of a chromosome present), it may lead to miscarriage or the birth of children with learning difficulties or physical disabilities (186). A Robertsonian translocation is where the short arms of certain chromosomes are lost and the long arms fuse together, and again this can be passed on to form an unbalanced translocation (186).

Other arrangements such as insertions, duplications, inversions or deletions can result in the addition or removal of genetic material, and the significance depends on the quantity of chromosomal material replicated, inserted, deleted or inverted and which chromosomes are affected (186). Both ESHRE and RCOG recommend timely referral to clinical genetics for a family with a structural re-arrangement to facilitate future pregnancy planning (32,35) .

1.4.6 Investigation of Genetic Factors

Testing of pregnancy tissue

While ESHRE has recommended array-CGH as the optimal test for cytogenetic testing, it must be borne in mind that their guideline encompasses first and second-trimester miscarriage, which have very different aetiologies. Array-CGH allows for high-resolution analysis of sequences mapped to specific regions and compared to test and control DNA (187). Array-CGH can be performed on fresh or paraffin-embedded tissue, allowing retrospective testing of miscarriage tissue saved from a prior dilation and curettage (187).

The ESHRE guideline suggests that array-CGH is superior as it has a reduced rate of maternal cell contamination (MCC) and does not require cell culture (35). However, this fails to take into consideration steps taken by (some) laboratories such as sorting, dissecting and cleaning each sample and regular auditing of ratios of identified normal female to male karyotype to ensure MCC is minimal (188). Culture failure due to fungal or bacterial contamination is an accepted risk in traditional karyotyping, however reflexive use of additional molecular technology using DNA can salvage genetic analysis, with reported success rates comparable to quantitative fluorescence polymerase chain reaction (QF)-PCR and assay regimens (189). These molecular tests can detect common aneuploidies and nine microdeletion syndromes in addition to alterations in the p and q arm of all chromosomes (189). Alternatively, a failed array may result in the complete loss of genetic material and repeat array is not always possible.

Another disadvantage is that array-CGH cannot detect balanced translocations, inversions, triploidy, tetraploidy, mosaicism or maternal cell contamination (187). SNPs are locations within non-coding regions of the genome where one nucleotide is highly variable between individuals. Using a SNP microarray, these nucleotide polymorphisms of the pregnancy tissue can be characterised and then compared to a maternal sample (187). This allows clinicians to identify maternal cell contamination, parental origin of aneuploidy and unbalanced chromosome segments and placental mosaicism. However, the SNP array is unable to detect balanced translocations, inversions or tetraploidy (187). Arrays are an evolving technology and will produce significant numbers of results where interpretation remains difficult, for example families with rare copy number variants whose significance may be uncertain until further examples are reported (190).

There are also specific benefits to traditional karyotype in the investigation of first-trimester miscarriage. Half of first-trimester miscarriage is caused by large chromosomal abnormalities, such as trisomy, which would be detected by karyotype (176,191). Karyotype analysis allows for cell-by-cell analysis which can identify abnormal male or female cell lines separate to that of a normal male/female allowing for the detection of mosaicism in addition to MCC (187). Karyotyping is crucial in identifying Robertsonian unbalanced translocations and determining the recurrence risk (192). Laboratories should perform QF-PCR prior to performing an array-CGH on pregnancy tissue in first-trimester miscarriage (190). This allows for early identification of molar pregnancy and trisomies 13, 18 and 21, which allows for deferral to karyotype if T13 or T21 is detected (193). Karyotype will detect an unbalanced Robertsonian translocation and importantly, the balanced carrier (192). The recurrence risk can be 100% for 13;13 and 21;21 Robertsonian carriers, which would be missed if array-CGH alone was performed (192).

Parental Genetic Testing

The format of the parental testing will vary according to whether a translocation or other anomaly is detected in pregnancy tissue. The testing may be performed by karyotyping (full or targeted), fluorescent in situ hybridisation (FISH), quantitative PCR, QF-PCR, Multiplex Ligation-dependent Probe Amplification (MLPA), or, rarely, microarray (194). More than one technique may be used as per the clinical geneticist (194).

1.4.7 Treatments for Genetic Factors

Preimplantation genetic testing for structural rearrangements

Women/couples identified as having a balanced translocation should meet with a clinical geneticist to discuss the significance of their particular translocation and the management of future pregnancies. The options include continuing to try to conceive naturally or to undergo IVF with preimplantation genetic testing (PGT) for structural rearrangements (PGT-SR) (32).

PGT is an embryo-selection technique developed to assess the chromosomal or genetic status of an oocyte or embryo prior to embryo transfer. PGT-SR is differentiated from PGT-A in that it is used to detect cases of unbalanced hereditary chromosomal anomalies, which are a result of one or both parents having a balanced chromosomal rearrangement (e.g. reciprocal translocations, Robertsonian translocations, and inversions)(195).

There is mixed evidence as to whether PGT-A or PGT-SR is more appropriate. PGT-SR does not demonstrate any significant increase in the livebirth rate between either group (183,195), however it appears to be of benefit to those with at least two pregnancy losses in sub-group analysis (196). Conversely, a systematic review and meta-analysis of six studies, all of which used the older FISH technique, revealed that this method of PGT was associated with an increased successful pregnancy outcome of translocation carriers (OR 8.58; 95% CI 1.40, 52.76) (197). A comparative study using next generation sequencing has shown higher rates of chromosomal abnormalities, including chromosomal unbalanced translocations and aneuploidy, in blastocysts from couples with chromosomal rearrangements compared to those without, especially from the female carriers (198).

Overall, the evidence is low-quality and insufficient in RM groups to suggest any deviation from the RCOG or ESHRE guidelines (32,35). High-quality randomised control trials (RCTs) are required in order to establish a definite benefit for IVF with PGT-SR for couples with a balanced translocation.

Pre-implantation genetic testing for aneuploidy for RM

Given the association between aneuploidy and RM, the selection of euploid embryos through PGT-A has been postulated as a way to reduce miscarriage rates and increase livebirth rates in women/couples with RM. However, the evidence for PGT-A in any form of IVF to date is conflicting, and there is a paucity of high-quality, adequately powered retrospective trials. A Cochrane review of PGT-A in IVF found insufficient evidence of any difference between IVF and IVF with PGT-A, and advised PGT-A with FISH is likely harmful (199).

Examining newer techniques of PGT-A and the resultant live birth rates, Sanders et al. conducted a large cohort study using the UK HFEA data (2,464 PGT-A cycles), which demonstrated an increased livebirth rate with PGT-A compared to non-PGT-A across all age groups (200). The Single Embryo Transfer of Euploid Embryo (STAR)S trial showed PGT-A did not improve overall pregnancy outcomes in all women, as analysed per embryo transfer or per intention to treat (201). There was a significant increase in ongoing pregnancy rate per embryo transfer with the use of PGT-A in the subgroup of women aged 35-40 years, but this was not significant when analysed by intention-to-treat (201).

In a large cohort study using clinical outcome reporting system data which examined over 12,000 IVF cycles including women with RPL, the use of PGT-A with frozen embryo transfer was associated with increased rates of live birth (48% vs 34%, $p < 0.001$) and rates of clinical pregnancy (59% vs 47%, $p < 0.001$) in women with three or more miscarriages (202). In addition, for women with RM use of PGT-A was associated with a significant decrease in the rate of spontaneous miscarriage (11 vs 13%, $p = 0.02$), and biochemical pregnancy (9.9% vs 11.5%, $p = 0.02$) (202). This was evident across all age groups, but in women with RM comparing IVF with PGT-A versus without PGT-A for live birth outcome, the odds of live birth were most significantly raised for ages 41–42, (aOR 2.62; 95% CI 1.94, 3.53), and for ages >42 years (aOR 3.80; 95% CI 2.52, 5.72) (202). Likewise, for risk of miscarriage the effect was greatest in older ages groups with OR 0.95 (95% CI 0.74, 1.21) for age <35 years, 0.58 (95% CI 0.32, 1.07) for ages >42 years (202). A smaller study examining PGT-A in a cohort of women with RM also observed a significant decrease of early pregnancy loss rates in the PGT-A group (18.1% vs 75%) and a significant increase in live birth rate per transfer (50% vs 12.5%) and live birth rate per woman (36% vs 12.5%) (203).

These results must be interpreted with caution, and women/couples with RM must be carefully counselled regarding the specific difficulties with PGT-A (195). There is much to be learned and perfected with regards to the technique, which is not standardised, and there is much heterogeneity among studies and between laboratories (195,204). There is a high rate of embryo loss, the potential for non-read or inconclusive results (with low chance of successful second biopsy), and the issue of mosaicism has not been definitively dealt with (195,204,205). The HFEA which governs IVF in the UK designates PGT-A a "code-red" add-on, i.e., it is not recommended (206).

1.4.8 Thrombophilia

The relationship between infertility and thrombophilia is not established. The latest guidelines on infertility — the British Fertility Guideline on the management of recurrent implantation failure, the ESHRE Guideline on unexplained infertility and the ASRM Guideline on the evaluation of women with infertility — do not recommend testing for inherited or acquired thrombophilias in women with a history of infertility (13,207,208).

Thrombophilia and RM

Thrombophilic disorders associated with RM can be acquired or inherited.

Acquired thrombophilia

Antiphospholipid syndrome (APS) is an acquired autoimmune condition defined as the association between antiphospholipid antibodies (APLAs) (lupus anticoagulant (LA), anticardiolipin antibodies (ACLAs, IgG and IgM), and β2 glycoprotein I antibodies (aβ2GPI, IgG and IgM)) and thrombosis (venous, arterial or microvascular) with pregnancy morbidity(209).

Pregnancy morbidity includes:

a) one or more deaths of a fetus (without any attributable congenital anomaly) after ten weeks' gestation
b) one or more preterm births of a neonate up to 34 weeks due to eclampsia/pre-eclampsia or placental insufficiency
c) three or more miscarriages less than ten weeks' gestation (209).

However, a retrospective cohort study published in 2013 found that the number of preceding miscarriages, type and sequence of previous pregnancies, and maternal age were not associated with APS in women with RM (36). There is no increased diagnostic yield for APS after three miscarriages rather than after two miscarriages and no increased diagnostic yield for APS after consecutive miscarriages rather than after non-consecutive miscarriages (36).Therefore, the ESHRE guideline development group took the decision to implement antiphospholipid antibody testing after two miscarriages(35).

Overall, antiphospholipid antibodies have been shown to have an association with RM, although the association is weak and appears stronger with second-trimester pregnancy loss (210–212). Testing for antiphospholipid antibodies in RM is in line with the British Haematology Society Guideline which states, "For women with recurrent or late pregnancy loss, screening for antiphospholipid antibodies can be considered as the results aid risk stratification and treatment decisions" (Evidence grade 2B) (213).

Inherited thrombophilia

There is conflicting evidence as to whether inherited thrombophilias such as factor V Leiden (FVL), prothrombin gene mutation, protein S, protein C, Anti-Thrombin or

Methylenetetrahydrofolate reductase (MTHFR) Mutation are associated with RPL, that is, first and second-trimester miscarriages.

FVL

An updated systematic review and meta-analysis has reviewed the associations between inherited thrombophilias and RPL, and whether the association varied according to first or second-trimester losses or two or three losses (214). Analysis of pooled data from 81 studies indicated a significant association between FVL mutation and RPL (OR 2.44; 95% CI 1.96, 3.03), for both heterozygous (OR 2.07; 95% CI 1.57, 2.72) and homozygous status (OR 2.76, 95% CI 1.34, 5.71) (214). Compared to the reference group, the risk of early RPL (OR 1.69; 95% CI 1.18, 2.41) and late RPL (OR 5.07; 95% CI 2.22, 11.57) were significantly higher among pregnant women with the FVL mutation (214).

Prothrombin gene

Analysis of pooled data from 64 studies indicated a significant association between the prothrombin gene mutation and RPL (OR 2.08; 95% CI 1.61, 2.68) (32). Nonetheless, there was no significant difference in the risk of first or second-trimester losses with the prothrombin gene mutation. A more recent study of 1155 women with RM in the UK found that inherited thrombophilias (FVL, prothrombin gene, anti-thrombin, protein S and C deficiencies) were equally prevalent in a RM population compared to the general population (215).

Protein S

A meta-analysis of ten studies indicated a significant association between deficiency of protein S and RPL (OR 3.45; 95% CI 1.15, 10.35) (214). However, considering the limited number of included studies and substantial between-study heterogeneity, the result should be interpreted with caution.

Anti-thrombin deficiency

Analysis of pooled data from seven studies showed no significant association between anti-thrombin deficiency and RPL (OR 0.83; 95% CI 0.29, 2.36) and analysis of pooled data from nine studies showed no significant association between Protein C deficiency and RPL (OR: 1.98; 95% CI 0.97, 4.04) (214). The authors note that in addition to heterogeneity of

studies, controlling of confounders was limited and thus these associations may be confounded by other risk factors for pregnancy loss.

MTHFR mutations

The MTHFR C677T mutation has been shown to be associated with RM in one systematic review (216), but not in others (217,218).

Inherited thrombophilia summary

Guidelines from the ACOG and the British Haematology Society recommend against testing for heritable thrombophilia in women with previous adverse pregnancy outcomes, including RM (213,219). This is in keeping with the ESHRE RPL guideline which limits inherited thrombophilia testing to those with additional risk factors (35). The 2023 RCOG guideline recommends limited inherited thrombophilia testing (FVL, Prothrombin gene and Protein S deficiency) in second-trimester miscarriage, but with the caveat that there is limited evidence that treatment improves outcomes (32).

1.4.9 Treatment of thrombophilia

Treatment of thrombophilia and infertility

There is no evidence to support treating infertility with either aspirin or low molecular weight heparin (LWMH) (13,220), with the exclusion of ovarian hyperstimulation syndrome (221). There is only low-quality to support the use of these medications even in the presence of thrombophilia (222,223).

Treatment of acquired thrombophilia

Low dose aspirin and LMWH are widely used to reduce the risk of RM in women with antiphospholipid syndrome (224). The American College of Rheumatology and the European Alliance of Associations for Rheumatology (EULAR) recommends that with a history of ≥ 3 recurrent spontaneous miscarriages < 10^{th} week of gestation and in those with a history of fetal loss (≥ 10th week of gestation), combination treatment with aspirin and LMWH at prophylactic dosage during pregnancy is provided (224,225). Updated systematic reviews in 2019 and 2021 examined antithrombotic therapy in women with RM and antiphospholipid syndrome have shown that livebirth rates were higher with aspirin and LMWH compared to aspirin alone, but the evidence is of low-quality (226,227). Meta-analysis of 12 RCTs by Lu et al. showed that live birth rate among women who

receive low-dose aspirin plus low molecular weight heparin therapy was higher than women who receive low-dose aspirin alone (RR 1.60; 95% CI 1.31, 1.94; $p < 0.00001$) (227). Meta-analysis also showed that women who receive low-dose aspirin plus unfractionated heparin therapy had a significantly higher live birth rate (RR 1.23; 95% CI 1.12, 1.36; $p < 0.0001$) (227). While there was little heterogeneity in these studies (I^2=44%), the included numbers are small in each analysis group, less than 400 (227). Hamulyák et al. analysed five trials including 1295 women which compared heparin plus aspirin with aspirin only (234). The pooled RR for live birth was 1.27 (95% CI 1.09, 1.49) in favour of heparin plus aspirin (226). There was significant heterogeneity between the subgroups of LMWH and unfractionated heparin (RR for LWMH plus aspirin versus aspirin 1.20; 95% CI 1.04, 1.38; RR for unfractionated heparin plus aspirin versus aspirin 1.74; 95% CI 1.28, 2.35; I^2 78.9%; $p = 0.03$) (226).

The EULAR "Recommendations for the Management of Antiphospholipid Syndrome in Adults" suggest the most common practice if the combination of aspirin and prophylactic dose heparin fails is to increase the dose of heparin to therapeutic dose, although no supporting evidence exists (224). Other treatment strategies may include the addition of hydroxychloroquine or low prednisolone doses in the first trimester (224). This recommendation stems from one observational study on the use of hydroxychloroquine, which compared the outcome of pregnancies treated by the addition of hydroxychloroquine to previous pregnancies with aspirin and/or LMWH, pregnancy losses decreased from 81% to 19% ($p<0.05$) (228). In 14 cases of refractory APS, the addition of hydroxychloroquine resulted in live born babies in 11/14 (78%) cases ($p<0.05$) (228). Similarly, prednisolone was given to women with refractory APS and among 23 pregnancies supplemented with prednisolone, 9 women had 14 live births (61%). Thus, this evidence is very weak to support the use of prednisolone or hydroxychloroquine (35,224), and the American College of Rheumatology does not recommend the use of prednisolone (225). Intravenous immunoglobulin (IVIG) is not associated with increased livebirths and there is insufficient evidence to recommend its use, although EULAR does state it can be used in very select cases (35,224).

Treatment of inherited thrombophilia in RM

Systematic reviews have failed to show any benefits from low-dose aspirin and LMWH for RM in those with inherited thrombophilia or unexplained RM (14,213,229). A 2022 systematic review of randomised control trials has shown that LMWH alone or in combination with low-dose aspirin have no influence on the miscarriage rate or occurrence of pre-eclampsia, and that LMWH alone has no influence on the livebirth rate (230). However, it is noted in all reviews that the quality of studies and randomised control trials are variable, with significant heterogeneity and that there is a need for high-quality randomised control trials (14,230). The Alife2 Trial which studied low-molecular-weight heparin for women with RM and inherited thrombophilia found that live birth rates were 116/162 (71.6%) in the LMWH group and 112/158 (70.9%) in the standard surveillance group (aOR 1.08; 95% CI 0.65, 1.78) absolute difference 0.7% (95% CI -9.2%, 10.6%)](231). Compared with standard surveillance, the use of LMWH did not result in higher live birth rates in women who had two or more pregnancy losses and confirmed inherited thrombophilia (231). Again, this trial had small numbers in each arm and was not powered to detect differences for the various inherited thrombophilias. Thus, the guidance from the British Haematology Society, and subsequently the RCOG and ESHRE, remains that routine use of LMWH in women with RM and inherited thrombophilia is not recommended (32,35,213).

1.4.10 Endocrine conditions associated with RM and infertility

Thyroid disease in RM

Hypothyroidism

In the Western world, thyroid hormone deficiency or hypothyroidism is usually caused by autoimmune thyroid disease or Hashimoto thyroiditis (232). Worldwide, iodine deficiency is the most common reason for hypothyroidism, and iatrogenic hypothyroidism following radioiodine therapy, or surgery for hyperthyroidism, are other important aetiological factors (232). Autoimmune hypothyroidism is caused by thyroid-specific antibodies against thyroid peroxidase (TPOabs), the enzyme involved in thyroid hormone synthesis, and against thyroglobulin (Tgabs), the backbone against which thyroid hormones are synthesised and stored (232). Due to the well-established adverse

outcomes linked with overt hyper- and hypothyroidism in pregnancy, and clear indications for treatment, the focus of research in thyroid disease and RM is whether RM is linked to sub-clinical hypothyroidism and the presence of thyroid antibodies.

Subclinical hypothyroidism (SCH)

SCH is a biochemical diagnosis defined by raised levels of serum thyroid stimulating hormone (TSH), above the accepted laboratory reference range, accompanied by normal concentrations of circulating thyroid hormones (free thyroxine (FT4) and free triiodothyronine (FT3) (232). Guidance from the American Thyroid Association in 2017 recommends that population- and trimester-specific references ranges for serum TSH should be defined by the local institute or laboratory and should represent the typical population for whom care is provided (233). If internal or transferable pregnancy specific TSH reference ranges are not available, an upper reference limit of 4.0 mIU/l may be used to define SCH (233) . SCH is usually asymptomatic and may represent the earliest stages of thyroid dysfunction, which can progress to overt hypothyroidism (OH) (228). There is debate as to what constitutes a raised TSH level, 4.0mIU/l is generally accepted, but in certain populations (e.g., women with thyroid antibodies and RM or infertility) this has been reduced to 2.5mIU/l (233). These variations have contributed to heterogeneity between studies, as well as in clinical practice. The RCOG has suggested, in their latest Scientific Impact Paper on SCH and antithyroid autoantibodies in women with infertility or RM, that upper-normal TSH level is 2.5-4.0mIU/l and that mild-moderate SCH encompasses TSH values above 4.0mIU/l up to 10.0mIU/l (228). A TSH value above 10.0mIU/l, even combined with normal free T4, is considered to represent OH (232).

A systematic review and meta-analysis estimated the prevalence of SCH to be 12.6% in RM populations (234). An Irish study found the rate to be 8.39% in a cohort of women with unexplained pregnancy loss of all gestations (235). Current evidence suggests no association between SCH and RPL when RPL was variably defined across the five studies with two or more consecutive and non-consecutive pregnancy losses up to 20 weeks (234). Just one of these studies, by Triggianese et al., suggested that there may be an association between SCH and consecutive RPL (236). Within the systematic review by Dong et al., the definition of SCH also varied with cut-offs of 2.5 and 4.0mIU/l (234). The RCOG Scientific Impact Paper concluded that mild-moderately raised levels of TSH (>4.0–

10.0 mIU/l) during pregnancy are associated with sporadic miscarriage, but insufficient evidence of this association exists for upper normal TSH levels (2.5–4.0 mIU/l) or for RM (232).

Thyroid auto-immunity in RM

Meta-analysis of 17 studies that provided data comparing the prevalence of thyroid autoimmunity (that is having thyroid peroxidase antibodies (TPOab) or anti-thyroglobulin antibodies) in a cohort of women with RPL (again variably defined across all studies in number/consecutive) to those without RPL revealed a statistically significant association between thyroid autoimmunity and RPL (OR 1.94; 95% CI, 1.43, 2.64) (234). Additional sensitivity analysis that excluded studies that did not have an entirely euthyroid cohort demonstrated that the association between thyroid antibodies and RPL remained statistically significant (234). Both ESHRE and RCOG recommend thyroid function and TPOab testing in their latest guidance for RM (32,35).

Thyroid disease in infertility

Overt hypothyroidism

Overt hyperthyroidism is associated with increased menstrual irregularities compared to euthyroid women and if left untreated, can contribute to pregnancy loss (237). Overt hypothyroidism also appears to be associated with infertility, with a greater impact on ovulation (237). Guidance from the American Thyroid Association supports the treatment of overt thyroid dysfunction in infertile women, with the goal of normalising thyroid function (233).

SCH and infertility

As with RM, data exploring the association between SCH and infertility are unclear, mostly owing to inconsistent definitions and a lack of adequate or appropriate control groups (232). The RCOG Scientific Impact Paper, the Guideline of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease during Pregnancy and the Postpartum, and a Best Practice Review were unable to determine a definitive association between SCH and infertility (232,233,237). However, prevalence data from over 19,000 women, found that women with infertility were more likely to have upper normal TSH levels compared with fertile women with a history of miscarriage, even after

adjusting for age, BMI, ethnicity and antibody status (238). The prevalence of SCH using an upper TSH concentration of 4.50 mIU/L was 2.4% (95% CI 2.1, 2.6) (238). Lowering the upper TSH to 2.50 mIU/L resulted in higher rates of SCH, 19.9% (95% CI 19.3, 20.5) (238). Multiple regression analyses showed increased odds of SCH (TSH > 4.50 mIU/L) with BMI ≥ 35.0 kg/m^2 (aOR1.71; 95% CI 1.13, 2.57; p = 0.01) and Asian ethnicity (aOR 1.76; 95% CI 1.31, 2.37; p < 0.001), and increased odds of SCH (TSH ≥ 2.50 mIU/L) with infertility (aOR 1.16; 95% CI 1.04, 1.29; p = 0.008) (238). Moreover, higher TSH concentrations have been shown to be a predictor of fertilisation failure in women undergoing IVF, which supports the important role of thyroid hormones in oocyte physiology (232).

Thyroid antibodies and infertility

The role of thyroid antibodies infertility is less clear. A meta-analysis of four studies found that unexplained infertility occurred more frequently in women who are euthyroid antibody-positive compared with women without antibodies (239). In the meta-analyses, the presence of thyroid antibodies was associated with an increased risk of unexplained infertility (OR 1.5; 95% CI 1.1, 2.0) (239). The RCOG Scientific Impact Paper, the American Thyroid Association Guideline and the Best Practice Review have not shown a clear impact of antibodies on IVF outcomes (232,233,237)but the presence of TPOabs appears to affect thyroid function during ART (232). The clinical recommendation from the RCOG Scientific Impact Paper is thus to either check TPOab status in women with infertility to determine whether thyroid function should be checked during ART and subsequent pregnancy or to undertake TFTs in women with infertility during pregnancy (232).

Treatment of thyroid disease in RM

Treatment with levothyroxine for women with RM and TPOab, whether euthyroid or with SCH, has been debated. It was hoped that two randomised trials would provide definitive evidence: the Tablet and T4Life trials. The Tablet Trial did not have sufficient power to analyse the RM subgroup alone, and the T4life trial (which was specifically examining women with two or more miscarriages) found that, compared with placebo, levothyroxine treatment did not result in higher live birth rates in euthyroid women who tested positive for TPOab (240,241). The T4life and Tablet trials were included alongside five other trials and eight cohort studies and analysed in a recent systematic review and meta-analysis by Yu et al., which examined outcomes in RPL populations with subclinical hypothyroidism

or thyroid autoimmunity (242). Levothyroxine supplementation was associated with a significant decrease in the miscarriage rate for women who were TPOab positive, (RR 0.59; 95% CI 0.44, 0.79; I^2=8.2%), but the authors did not observe statistical evidence of an association between levothyroxine supplementation and other maternal or neonatal outcomes, including pregnancy rate (RR 0.96; 95% CI 0.81, 1.14; I^2=0.0%) and live birth rate (RR 1.14; 95% CI 0.93, 1.39; I^2=42.1%) (242).

Yu et al. also found that in women with SCH without antibodies, analysis showed that levothyroxine therapy increased the rate of live births (RR 1.20; 95% CI 1.01, 1.42; I^2=0.0%) (242). Levothyroxine supplementation was associated with a decreased miscarriage rate in these women also (RR 0.65; 95% CI 0.44, 0.97; I^2=60.4%) (242). It is important to note that within the included studies there were varying definitions of SCH and dosages of levothyroxine; these must be addressed in order to make firm conclusions regarding treatment for women with subclinical hypothyroidism, particularly for TSH 2.5-4.0mIU/l, with and without thyroid autoimmunity and a history of RM.

Treatment of thyroid disease in infertility

Examining the use of levothyroxine in women with infertility, with and without ART, Unuane et al., concluded that there is little evidence to advise levothyroxine treatment at TSH levels between 2.5 and 4.0 mIU/L (237). Again, given the paucity of high-quality evidence and the heterogeneity of studies, the authors agreed with the RCOG recommendation that the cut-off value of 4.0 mIU/L for TSH as a reasonable intervention level for treatment of subclinical hypothyroidism in women with and without thyroid autoimmunity, even if undergoing ART (232,237).

Polycystic Ovarian Syndrome (PCOS)

PCOS is the most common endocrinopathy affecting reproductive-aged women, with impacts across the lifespan from adolescence to post-menopause (243). The updated 2023 International Evidence-based Guideline for the Assessment and Management of PCOS recommends that PCOS should be diagnosed using the 2018 International Evidence-based Guideline criteria (244) which built on the consensus-based 2003 Rotterdam criteria. This diagnosis requires the presence of two of the following:

i) clinical/biochemical hyperandrogenism;

ii) ovulatory dysfunction; and

iii) polycystic ovaries on ultrasound.

Alternatively anti-Mullerian hormone (AMH) can now be used instead of ultrasound (245).

PCOS and infertility

PCOS has a recognised substantial negative effect on fertility; indeed, the diagnosis of PCOS requires a degree of ovulatory dysfunction (244). Due to disturbances in follicular maturation, follicle growth often stops at a follicle size of 4–8 mm which prevents the development of a mature follicle and, therefore, ovulation (244). The pathophysiology of PCOS usually includes excess ovarian androgen production with an abnormal degree of insulin-resistance being a non-essential but common aggravating factor (246). Hyperinsulinaemia augments luteinising hormone stimulated androgen production (246). The precise mechanism of follicular arrest and anovulation is uncertain, but it is known that AMH – which is elevated in PCOS – plays a restrictive role in follicular development (246).

PCOS and RM

PCOS prevalence in women of reproductive age is between 10 to 13% (245), but has varied from 5 to 28% when cohorts have been organised according to ethnicity and whether BMI is <25 or ≥30 (247,248). A recent study has estimated the prevalence of PCOS in a single RM cohort to be 9.5%, with pooled prevalence from three retrospective cohort studies estimated at 14.3% (244).

Forty-three studies were included in the meta-analysis for the ESHRE Guideline on PCOS; 21 were prospective cohort studies and 22 were retrospective cohort studies, with 27 having a variable or unclear definition of miscarriage, and eight defining it as before 12 weeks (245). Thirty studies had high risk of bias, seven moderate risk of bias and the remaining six had low risk of bias. Miscarriage OR overall was 1.50 (95% CI; 1.20, 1.87) in pregnancies where women had PCOS compared to those who did not have PCOS (245). In pooled meta-analyses, even after sensitivity analyses and examining only high-quality studies, significantly higher odds of miscarriage, gestational diabetes, gestational hypertension, pre-eclampsia, preterm birth, and caesarean section, and also significantly

lower birthweight were observed in women with PCOS (245). This is in keeping with a previous meta-analysis which showed women with RM and PCOS were more likely to experience a further miscarriage and had a reduced chance for livebirth (244).

Treatment of PCOS

Treatment of PCOS in RM

Metformin is a biguanide which reduces hepatic glucose production by reducing hepatic gluconeogenesis as well as improving insulin sensitivity. The use of metformin to reduce RM risk is currently not recommended by ESHRE (35). This is largely in part due to low-quality indirect studies. A systematic review of four small low-quality studies showed no difference in miscarriage outcome with metformin, but a suggestion of potential benefit in livebirth outcome (14). The updated ESHRE Guideline on PCOS recommends that in women with PCOS undergoing IVF/ICSI, metformin may be used as an adjunct therapy as it has shown a reduction in the miscarriage rate per pregnancy (OR 0.3; 95% CI 0.18, 0.8), though again the quality of evidence is low (245).

Treatment of PCOS in infertility

The 2023 ESHRE Guideline on PCOS sets out a clear treatment for women with PCOS and infertility (245). Letrozole is the preferred first line pharmacological infertility therapy, with clomiphene in combination with metformin; gonadotrophins or ovarian surgery primarily having a role as second line therapy (245). IVF could be offered, potentially with in vitro maturation, as third line therapy, where other ovulation induction therapies have failed and in the absence of an absolute indication for IVF in women with PCOS and anovulatory infertility (245). Given the underlying risk for pregnancy complications in PCOS, single embryo transfer is preferred (245).

Diabetes

Diabetes is a chronic illness characterised by elevated levels of blood glucose and disturbed metabolism of fats and proteins. There are three major types of diabetes:

1. Type 1, in which the pancreas does not produce insulin;
2. Type 2 in which the body cells are resistant to the action of insulin that is being produced and over time the production of insulin progressively decreases; and

3. Gestational diabetes which occurs in pregnancy and can cause some complications during the pregnancy, and at birth and increases the risk of type 2 diabetes in the mother and obesity in the offspring (249).

Diabetes and infertility

Diabetes is associated with infertility, notably delayed puberty and menarche, menstrual cycle abnormalities, infertility, adverse pregnancy outcomes, and potentially early menopause (250). Historically, women with type 1 diabetes have frequently had amenorrhoea and infertility, due to central hypogonadism (250). Women with Type 1 diabetes may experience an earlier menopause, potentially due to autoimmunity (251). Type 2 diabetes is strongly linked with PCOS and its associated anovulatory infertility. Both conditions are associated with obesity, which also affects fertility (251). Poor glycaemic control and the presence of diabetic complications are associated with menstrual irregularities and lower fertility, however good glycaemic control has shown to improve fertility rates (251). Gestational diabetes is also associated with the use of ART. A systematic review and meta-analysis, which included 1,893,599 women, demonstrated a higher rate of gestational diabetes after ART regardless of whether the eligible studies included women with PCOS (RR 1.49; 95% CI 1.33, 1.66; I^2=75.0%) or not (RR 4.12; 95% CI 2.63, 6.45; I^2=0%), or whether this information was unclear (RR 1.46; 95% CI 1.22, 1.75, I^2=77.7%)(252).

Diabetes and RM

Women with well-controlled diabetes are not at increased risk for RM. Poorly controlled diabetes and a high glycated haemoglobin (HbA1c) is associated with fetal anomalies and RM (253). However, in a RM cohort clinically significant glucose levels were only found in 0.3% of women (254). Therefore, evaluation for diabetes in women with RM is likely better reserved for high risk or symptomatic women.

Prolactin in RM and infertility

Hyperprolactinaemia has a low prevalence in RM populations, with a single study demonstrating high prolactin in 1.2% of women tested (6/465) (255). There is insufficient evidence to suggest asymptomatic hyperprolactinaemia is associated with RM. There has

been conflicting evidence as to whether high or low normal levels of prolactin contribute to miscarriage, which requires further study (254,256).

Guidelines for infertility and RIF agree that prolactin is not recommended as part of routine infertility evaluation, but is indicated in the setting of galactorrhoea, oligomenorrhea, or amenorrhea (13,207,208).

Treatment of hyperprolactinaemia

Bromocriptine is recommended for use in the case of symptomatic hyperprolactinaemia in RM or infertility (35). A systematic review found that quinagolide was superior for reducing irregular menstruation, whereas bromocriptine was the best treatment for galactorrhoea, with cabergoline proven to be the safest drug (257). Optimal levels of prolactin and drug regimens during IVF are yet unclear, requiring further study (258).

1.4.11 *Infectious causes of RM and infertility*

Systemic infections with malaria, brucellosis, cytomegalovirus and human immunodeficiency virus, syphilis, dengue fever, influenza virus and of vaginal infection with bacterial vaginosis, are associated with increased risk of miscarriage (259). However, these associations are of variable strength. For example, syphilis is strongly associated with miscarriage as demonstrated by one case-control study in Brazil (OR 3.31; CI 2.20, 4.99; $p < 0.0001$) (260) and syphilis is included in antenatal screening programmes in the EU and United States (259). Conversely, a systematic review of brucellosis and miscarriage demonstrates conflicting miscarriage rates in women infected with brucellosis, ranging from 2.5-54%, suggesting higher quality studies are required to better delineate the association between brucellosis and miscarriage (261). The effects of Chlamydia trachomatis, Toxoplasma gondii, human papillomavirus, herpes simplex virus, parvovirus B19, Hepatitis B and polyomavirus BK infections remain controversial, as some studies indicate increased miscarriage risk and others show no increase in risk (259). Infectious screening in the form of high vaginal swab cultures in asymptomatic women is not recommended for RM (35).

There has been increased interest in the vaginal microbiome, with lactobacillus depletion linked to first-trimester miscarriage (262,263). Greater study is required to understand the role of infections and to determine what characteristics of the vaginal microbiome in women with RM may be significant.

Sexually transmitted infections such as chlamydia, gonorrhoea and mycoplasma are associated with pelvic inflammatory disease (264). Severe or repeated episodes of pelvic inflammatory disease are associated with tubal factor infertility, which accounts for 30% of female infertility (264).Screening for chlamydia, hepatitis B, C and Human Immunodeficiency Virus (HIV) is often part of standard protocols when investigating infertility or considering ART (13,208,265).

Chronic endometritis

Infection is also linked to chronic endometritis, which has also been linked to RM, infertility and RIF (266,267). Chronic endometritis is defined as localised inflammation of the endometrial mucosa characterised by the presence of oedema, increased stromal cell density, dissociated maturation of the stroma and epithelium, as well as the presence of a plasma cell infiltrate in the stroma (267). The diagnosis of chronic endometritis is based on hysteroscopy of the uterine cavity and endometrial biopsy, with plasma cells being identified histologically, while specific treatment is determined based on microbial culture (267). A systematic review and meta-analysis of seven studies of women with chronic endometritis found no difference in implantation rate, clinical pregnancy rate, miscarriage rate or livebirth rate between those women treated with broad spectrum antibiotics (of varying regimens) and women who were untreated (268). Two systematic reviews in 2022 have shown an association with chronic endometritis and miscarriage and reduced IVF success, with an improvement in ongoing pregnancy rates and livebirth rates following "cure" of chronic endometritis with antibiotic therapy (269,270). These reviews however solely include observational studies (269,270). Although the prevalence is high in infertility and diagnosis is using a relatively common procedure, this remains invasive, with additional risks of over-diagnosis and antimicrobial resistance, in the absence of certain aetiology, established treatment regimes, or randomised studies showing a clear benefit of treatment (267). Thus, current ESHRE guidance is that testing for chronic endometritis and endometrial scratching or biopsy (which are discussed in more detail below) are not recommended (35).

1.4.12 Endometriosis

Endometriosis is a chronic inflammatory disease defined as the presence of endometrium-like tissue outside the uterus (271). The exact prevalence of endometriosis

is unknown, but estimates range from 2 to 10% within the general female population but up to 50% in infertile women (272,273). Overall, evidence to predict endometriosis based on clinical symptoms alone is weak and incomplete (271). In a large retrospective analysis of the UK general practice research database concerning the prevalent symptoms within 3 years before the diagnosis of endometriosis (n=5540), women with subsequent diagnosis of endometriosis had higher proportion of abdominopelvic pain or heavy menstrual bleeding compared to women without endometriosis (73 vs. 20%) (274). Additionally, the following symptoms were found to be risk factors for endometriosis: abdominopelvic pain, dyspareunia with or without postcoital bleeding, a previous diagnosis of ovarian cyst, irritable bowel syndrome or pelvic inflammatory disease (274). Finally, the more symptoms were present, the higher the odds of being diagnosed with endometriosis were (1 symptom: OR 5.0; 95% CI 4.4, 5.7; 7 symptoms: OR 84.7; 95% CI 58.8, 121.8) (274). In specialist health care, severe dysmenorrhea was found to be predictive of a diagnosis of endometriosis in infertile women (275).

Endometriosis and infertility

Endometriosis is known to cause structural and functional abnormalities to the hypothalamic-pituitary-ovarian-endometrial axis and thus affects conception, endometrial receptivity and may contribute to embryonal loss (47,276). Alongside the association with infertility, endometriosis has been often, but not always, associated with poorer ART outcomes, including decreased yield of mature oocytes, lower implantation rates, and decreased pregnancy rates (277,278). However, despite the significant symptoms women experience with potential for anatomical distortion and decrease in fertility, endometriosis can take four to 11 years to diagnose (279). While endometriosis is recognised as a potential causative factor in fertility guidelines (13,208,280), it is not mentioned in the new ESHRE or RCOG guidelines on RM (32,35).

Endometriosis and miscarriage

Endometriosis is recognised as being associated with spontaneous miscarriage*, without a definitive link to RM.* A systematic review conducted by Maggiore et al. concluded that there was some evidence suggesting a possible association between endometriosis and spontaneous miscarriage, albeit tentatively, as many examined studies were retrospective (281). A more recent systematic review by Horton et al.—focusing on the

association of adenomyosis and endometriosis with fertility, obstetric, and neonatal outcomes of women through both assisted reproduction and natural conception, as well as the impact of endometriosis disease subtypes on different stages of the reproductive process—found an increased risk of miscarriage in both adenomyosis and endometriosis (OR 3.40; 95% CI 1.41, 8.65 and OR 1.30; 95% CI 1.25, 1.35, respectively) (282). A systematic review by Huang et al., published in 2020, examined miscarriage in women with endometriosis and included thirty-nine studies, (697,984 women, were included)(283). Miscarriage risk increased in women with endometriosis who spontaneously conceived (OR 1.81; 95% CI 1.44, 2.28, I^2=96%) compared with those without endometriosis, while women with endometriosis who underwent ART had a similar miscarriage risk, when compared to those with tubal infertility (OR 1.03; 95% CI 0.92, 1.14, I^2=0%)(283). Compared with those without adenomyosis, women with adenomyosis had an augmented miscarriage risk in ART (OR 2.81; 95% CI 1.44, 5.47, I^2=64%)(283). The heterogeneity and quality of studies included however, mean this analysis must be interpreted with caution.

A Danish nationwide historical cohort study with a nested case-control analysis identified a total of 29,563 women born between 1957 and 1997 in the national health registers, who had been diagnosed with endometriosis between 1977 and 2017; they included 295,630 women without endometriosis as controls (284). This study found slighter higher rates of miscarriage and RM in women with endometriosis; a total of 18.9%, 3.9%, and 2.1% of ever-pregnant women with endometriosis had 1, 2, and ≥ 3 pregnancy losses compared with 17.3%, 3.5%, and 1.5% of the women without endometriosis, corresponding to the odds ratios of 1.13 (95% CI 1.09, 1.17) for one loss, 1.18 (1.10, 1.26) for two losses, and 1.44 (1.31, 1.59) for three losses (284). When adjusted also for gravidity, the corresponding results were 1.37 (95% CI 1.32, 1.42), 1.75 (1.62, 1.89), and 2.57 (2.31, 2.85), respectively (284). Thus, endometriosis appears to confer an increased risk of miscarriage and RM, but high-quality studies are required to confirm this association.

Other experimental studies have focused on establishing the aetiology of miscarriage and infertility in women with endometriosis, which have considered theories such as a “toxic” pelvic environment with raised inflammatory factors, altered oocyte or embryonal quality

from inflammation or physical damage to the ovaries and fallopian tubes from endometrial pathology such as endometrioma (278,285,286). Fox et al. performed endometrial biopsies in women with RM (n=29) or unexplained infertility (n=53) and examined the levels of a postulated marker for endometriosis, nuclear protein B-Cell CLL/lymphoma 6 (BCL6), in endometrial samples. A subset of cases with abnormal BCL6 went to laparoscopy, and endometriosis was found in 9 out of 11 cases of RM and in 20 out of 21 cases of unexplained infertility (287). Freitag et al. demonstrated that women with RIF and endometriosis (n=67) were 1.3 times more likely to have chronic endometritis compared to controls without endometriosis, as demonstrated by raised plasma cell counts on endometrial biopsy (48). These biomarkers are currently being studied in unexplained infertility but remain in the realm of experimental research (288).

1.4.13 Immunological associations

There has been much interest in immunological factors such as peripheral and uterine natural killer (NK) cells, cytokines and human leukocyte antigens (HLA), and their potential role in RM and infertility.

Natural Killer Cells (NK)

NK cells are part of the innate immune system and may be classified according to their degree of CD 56+ expression (bright or dim) and their location (peripheral or uterine), with uterine NK typically being predominantly CD56+ bright (289). An updated systematic review and meta-analysis found that the CD56+ uterine NK level in women with RM was not elevated compared with controls, however in subgroup analysis of mid-luteal endometrial samples, women with RM had significantly higher levels of CD56+ uterine NK (standardised MD 0.49; 95% CI 0.08, 0.90; p=0.02; I^2=88%; 1100 women) (290). However, there was no difference in pregnancy outcome in women with RM stratified by uterine NK level, and no significant correlation between peripheral NK and uterine NK levels in women with RM (290). Overall, the findings indicated that measurements made on peripheral NK cells do not predict uterine NK level or activity. There was also significant heterogeneity between the studies, with differences in collection technique and reference ranges. Combined with the complexity of NK cell interactions, it is not yet possible to conclude if raised uterine NK cells are an association or consequence of RM (290).

A recent systematic review and meta-analysis of NK cell cytotoxicity in RM demonstrated a higher peripheral NK cells rate in women with RM during and outside of pregnancy compared to pregnant and non-pregnant controls (291). Again, while suggestive of an association, there was substantial heterogeneity regarding inclusion criteria and in techniques measuring peripheral NK cells. Thus, NK cell testing requires significant development before it is it be used in standard practice for either RM or RIF and is not recommended within updated ESHRE and RCOG Guidelines for RM (32,35).

HLA

HLA alleles and HLA sharing were found to be associated with RM in one systematic review, however the included studies had a high degree of selection and inclusion bias, thus must be interpreted with caution (292). HLA-C antibodies have been shown to be raised in women with RM (293) and to be higher in women who have previous miscarriage compared to a previous livebirth (294), but their association with RM has not been definitively proven (295).

Evidence is accumulating that reveals a tightly regulated system of HLA-F expression, and possibly also HLA-G and HLA-E, in the endometrium that is controlled by progesterone and under influence of gene variations, which may affect the success of implantation (296). Recent studies indicate that HLA-F and HLA-G are expressed in mid-secretory endometrium, HLA-G is expressed in the blastocyst and that HLA-F fluctuates during the menstrual cycle, being highest during the implantation window (296). It is postulated that interaction between HLA-G and HLA-F with specific receptors on uterine immune cells stimulate and facilitate embryo implantation and placentation by secretion of growth factors, cytokines and angiogenic factors (296).

There is a paucity of information on subsequent pregnancy outcomes in women with HLA sharing or antibodies and thus the significance of these associations for RM or infertility is yet to be determined.

Cytokines

Cytokines influence a broad range of physiological processes, including inflammatory responses to injurious stimuli, regulation of cellular proliferation, differentiation and cell death, and homeostasis after molecular perturbation via repair and remodelling processes (297). Several known cytokines, including interferons, interleukins, and growth

factors, are implicated in human diseases (297,298). It has been theorised those pro-inflammatory conditions, such as an increased ratio of inflammatory T-helper cell 1 cytokines (in particular tumour necrosis factor alpha (TNF-α)) to anti-inflammatory cytokines may contribute to RM (298). Generally, except for implantation and parturition, pregnancy is characterised by a T-helper cell 2 dominant cytokine pattern (299). T- cell dysregulation is also linked to unexplained infertility, RIF and pre-eclampsia (300).

A review of immunological testing in RM concluded that while some abnormal cytokine profiles are associated with RM, the intrinsic variations in cytokine levels makes reliable measurement and interpretation difficult (301). Moreover, cytokine polymorphism studies have found that no corresponding cytokine gene polymorphism has been strongly associated with RM (302–304). Greater study is required to determine the role of cytokines in RM and infertility and clinical practice.

Anti-Nuclear Antibodies (ANA)

Two meta-analyses have confirmed an association between RPL (defined as two miscarriages prior to viability) and ANA positivity (305,306). ANA positivity was associated with increased RPL risk, particularly with higher ANA titres (305). ANA was significantly associated with increased risk of female infertility either after the definite exclusion of individuals with autoimmune diseases or without exclusion (OR 1.99; 95% CI 1.29, 3.06, p = 0 .002), (OR 2.76; 95% CI 1.56, 4.88, *p* = 0.0005), respectively (307). The significance of these associations is not yet clear.

Anti-HY antibodies

Anti-HY antibodies are antibodies directed against male-specific minor histocompatibility (HY) antigens expressed on most or all nucleated male cells (35). A single observational study of 84 women implicated these antibodies in reduced livebirth after RM (308). An updated piece of work in this area involving 582 women with RPL found a history of a firstborn boy was significantly more frequent than in the Danish background population and was associated with significantly lower odds of a successful reproductive outcome in the first pregnancy after admission compared to a firstborn girl (OR 0.41; 95% CI 0.20, 0.83; p = 0.014) (309). The odds of a successful reproductive outcome were enhanced in women carrying ≥ 1 H-Y-restricting HLA class II alleles with a first-born girl compared to a firstborn boy (OR 3.33; 95% CI 1.40, 7.88; p = 0.005), while no difference in successful

reproductive outcome was seen in women with RPL not carrying these alleles (OR 1.20; 95% CI 0.33, 4.43; p = 0.781) (309). This work requires replication in other populations to further examine this association.

1.4.14 *Immune treatments*

Immune interventions have been proposed for the treatment of couples with RM and infertility and RIF of unknown aetiology or associated with immune disorders and include various treatments such as lymphocyte immunotherapy (LIT), intravenous immunoglobulin (IVIG), corticosteroids, intralipids, recombinant granulocyte colony-stimulating factor, and tumour necrosis factor inhibitor drugs.

A Cochrane review found paternal cell immunisation, third-party donor leukocytes, trophoblast membranes, and intravenous immunoglobulin provide no significant beneficial effect over placebo in improving the live birth rate (310). LIT consists of a lymphocyte concentrate (white blood cells) prepared from the peripheral blood of the partner or a third party to promote maternal immunomodulation that is meant to enable embryonic implantation (311). Thus, the donor selection process and the potential side effects/complications observed in LIT are similar to those of blood transfusion and the use of blood products (311). In addition to the risks related to blood transfusion such as transfusion reactions and transmission of viruses such as hepatitis, other systemic and local adverse reactions have been described, such as rashes and flu-like symptoms (311). A 2021 systematic review on LIT in RM and RIF found no high-quality evidence for the use of LIT, even though many of the studies examined found LIT to be of benefit in RM (311). Several factors account for this discrepancy, namely the methodological quality of studies, lack of consensus on laboratory controls, heterogeneity of the study populations, a lack of immune profiling or established parameters and the different treatment protocols (311).

Intralipid 20% is a sterile fat emulsion prepared for intravenous administration. It is made up of 20% soybean oil, 1.2% egg yolk phospholipids, 2.25% glycerin, and 76.5% water (312). Intralipid has only been suggested as a treatment for RM in women with elevated uterine NK cells, with a systematic review demonstrating that treatment of the target population (women with RPL or RIF) with intralipid led to an improvement in implantation rate, (OR 2.97; 95% CI 2.05, 4.29), pregnancy rate (OR 1.64, 95% CI 1.31, 2.04), and

livebirth rate (OR 2.36;1.75, 3.17), with a reduction in miscarriage (OR 0.2; 0.14, 0.30) (313). It must be noted however that although this data includes randomised control trials, these are small heterogenous studies, and it is not established which women benefit from such treatment or how to optimally diagnose an abnormal endometrial immune profile. Moreover, intralipid infusion is associated with anaphylactic type reactions, thrombophlebitis and acute pancreatitis (312).

In addition to improving outcomes for women with APS, hydroxychloroquine has been shown to be of benefit in women with RM and lupus erythematosus (314,315), as well as some types of placental inflammation (316). While it appears that hydroxychloroquine may be of benefit to women with RM with autoimmune disease (317), two randomised control trials are underway to determine if hydroxychloroquine improves pregnancy outcomes in women with RM without any autoimmune disease (318,319). One RCT of etanercept, a TNF-α inhibitor demonstrated increased livebirth rate and fewer miscarriages in the treatment group compared to placebo (320). However, this small study is inadequate to recommend such treatment.

A more recent quality assessment of systematic reviews and meta-analyses of immunotherapies has however noted an increase in quality over the last decade, as well as a trend towards benefit (321). The authors found that six out of 13 systematic reviews and meta-analyses of IVIG immunotherapy demonstrated improved treatment outcomes in women with RM, four out of six systematic reviews and meta-analyses of lymphocyte immunotherapy (n = 4/6, 66%) also showed benefit and all meta-analyses of corticosteroids (n = 3/3, 100%) and intralipids (n = 1/1, 100%) identified benefit in women with RM (321). Similarly, all IVIG systematic reviews (n = 4/4, 100%) and their meta-analyses of studies which evaluated women with immune-related RM such as abnormal levels of uterine NK or peripheral NK cells and/or activity, T-helper1/T-helper2 or T-helper17/regulatory T-call ratios, or the presence of autoimmune diseases, demonstrated benefit from the use of immunotherapy (321). It is crucial however, to consider that PRISMA Guidelines for systematic reviews and meta-analyses were published in 2009 to address several conceptual and practical advances in the science of systematic reviews and would have contributed to this quality improvement (322). Also, this systematic

review of immunotherapies did not scrutinise the methodological quality of the primary studies, and thus must be interpreted with the utmost caution (321).

There are considerable costs associated with immunotherapy and the potential for serious side effects, including transfusion reaction, anaphylactic shock and hepatitis, which demand caution and consideration before prescribing in this cohort (32,310). Therefore, the RCOG and ESHRE continue to not recommend immunotherapy in their latest guidelines (32,35). High-quality randomised control trials are much needed in this area.

1.4.15 Empiric treatments in RM

For women with unexplained RM, which can constitute 30-50% of couples with RM and/or infertility , a number of treatments are suggested and prescribed, often outside of current clinical guidance (34,323). In a UK-wide survey of early pregnancy units, Manning et al. identified that almost half of clinicians offered aspirin and LMWH to women without antiphospholipid antibodies and a quarter offered these medications and/or progesterone on women's request (323). In an Irish service evaluation of RM care in 2022, women with unexplained RM were also offered LMWH by 50% of participants and 17% would also use prednisolone, but progesterone was given by 80% of participants (34). This variation in prescribing practices merits further exploration as to why clinicians deviate from clinical guidance and the role that individual request has in the prescribing of empiric medications in RM. The evidence for and against the most common empiric medications is laid out below.

Aspirin and/ or LMWH

There is conflicting evidence regarding aspirin, LMWH or a combination as a treatment for RM. Several systematic reviews and meta-analyses have found no difference in livebirth rates or miscarriage rates (14,324,325) of which two included aspirin and LMWH (326,327). These are at odds with other systematic reviews of LMWH in unexplained RM that showed a reduction in miscarriages rates (328), a reduction in miscarriage rate and improvement in livebirth rate (329) or an improvement in ongoing pregnancies after 20 weeks (330). These differences likely stem from the variations in the preparation of LMWH used, differences in dosages and small sample sizes in the trials analysed. Large

multi-centre trials are required to establish if LMWH is of any benefit in RM as well as the optimal formulation and dose.

The EAGeR trial, a randomised control trial examining aspirin in women with one or two miscarriages (n=1078) showed pre-conception-initiated aspirin improved livebirth rates in those with raised C-Reactive protein (331). Further per-protocol analysis demonstrated that adhering to low-dose aspirin at least four days per week improved pregnancy outcomes (pregnancy rate, livebirth rate and fewer miscarriages) compared to placebo (332). A second randomised control trial demonstrated that low-dose aspirin did not improve livebirth rates in women with a history of RM (n = 400) (333).

While aspirin has not been proven to reduce miscarriage risk, it does have a role in reducing future placental dysfunction, pre-eclampsia and fetal growth restriction risk, particularly in women: aged over 35 years, who smoke and are undergoing ART (334–336). In low-risk nulliparous women, low-dose aspirin has been shown to improve fetal growth and reduced pre-term birth rates as well as pre-term pre-eclampsia (337,338), although there is no significant reduction in pre-eclampsia and gestational hypertension rates (338). Routine low-dose aspirin in low-risk nulliparous women has been shown to have a greater health gain and is more cost-effective than "screen and treat" approaches (339). Aspirin and LMWH have been subject to numerous RCTs and there is no significant evidence to suggest maternal or fetal harm from use in pregnancy (340–342).

In the absence of large multi-centre, randomised clinical trials of aspirin or LMWH in women with risk factors for placental dysfunction such as RM, the benefits of aspirin as demonstrated above, in addition to the risks posed to women with a history of RM, could justify administration of low-dose (75mg) aspirin in a future pregnancy. LMWH should be reserved for those with additional risk factors for venous thrombo-embolism or pregnancy loss, previous adverse pregnancy outcomes or for higher-order miscarriage after other therapies have been unsuccessful (35).

Prednisolone

A recent systematic review and meta-analysis suggested oral immunosuppressants such as prednisolone or cyclosporine A may be of benefit to women with unexplained RM (343). Oral administration of cyclosporine A or prednisolone increased live birth rate (OR 3.6; 95% CI 2.1, 6.15, $p < 0.001$) and ongoing pregnancy rate (OR 8.82, 95% CI 2.91, 26.75,

p = 0.0001) and also reduced miscarriage rate (OR 0.21, 95% CI 0.08, 0.52, p = 0.0007) (343). However, there was significant heterogeneity between studies, a moderate to severe risk of bias and dosing regimens were inconsistent .

Moreover, prednisolone has been suggested to be associated with adverse pregnancy outcomes such as oral cleft, fetal growth restriction, preeclampsia and gestational diabetes mellitus, and while a systematic review failed to demonstrate conclusive evidence of any such association, corticosteroids should only be prescribed when there is a clear indication for use and evidence of benefit for treating an underlying maternal condition (344). Similarly, cyclosporine A use during pregnancy appears to be associated with premature delivery and low birthweight infants (345). Comorbidities such as hypertension, pre-eclampsia and gestational diabetes mellitus are also reported at higher incidences than the general population (345). Thus, there is a need for greater evidence before prednisolone or cyclosporin A can be recommended in women with unexplained RM.

Progesterone

Progesterone is one of the most widely used empiric treatments for recurrent miscarriage (323). Progesterone and the orally-administered progestogen dydrogesterone upregulate the production of T-helper2 type cytokines and suppress the production of T-helper 1 and T-helper 17 cytokine production in vitro (299). This is particularly relevant to the fact that the T-helper 1 type cytokines TNF-α and interferon gamma and the T-helper 17 cytokine interelukin-17 have embryotoxic and anti-trophoblast activities (299). These cytokine-modulating capabilities of dydrogesterone may contribute to the demonstrated beneficial effects of dydrogesterone in recurrent spontaneous miscarriage and threatened miscarriage .

An updated systematic review and meta-analysis showed that following progesterone treatment, the miscarriage rate for women with recurrent miscarriage was reduced and livebirth rate was increased, but these results were not statistically significant (14). The livebirth rate was higher for the subgroup of women with a history of three or more miscarriages than the subgroup of women with a history of two or more miscarriages (14). The authors suggest that micronised vaginal progesterone treatment can therefore be considered for asymptomatic women with recurrent miscarriage and is likely to be more

effective in women with a high number of previous miscarriages, given that there are no safety concerns for the use of micronised progesterone or dydrogesterone (346,347).

1.4.16 *Male factors*

Male factor infertility accounts for up to 50% of infertility and is being recognised as contributory to RM. In general, the work-up of the male partner includes a full medical history and physical examination, semen analysis, genetic testing, which may include karyotyping and DNA fragmentation, as well as relevant imaging (348).

Semen analysis performed according to WHO guidelines is the gold standard investigation for male infertility (349). Abnormal semen parameters include:

- A low semen volume, also called hypospermia, defined as less than 1.4mls (95% CI 1.3, 1.5)
- Total sperm number whereby a low concentration of sperm, or oligospermia, is defined as less than 39 (95% CI 35, 40) (106 per ejaculate) or no sperm, also described as azoospermia
- Progressive motility should be evident in 30% of sperm (95% CI 29, 31), with no more than 1% with non-progressive motility and no more than 20% of sperm should be immotile. Reduced motility is also referred to as asthenazoospermia.
- At least 4% of sperm must have normal forms. The term for higher rates of abnormal forms is teratazoospermia (349).

Notably, none of the terms such as oligospermia, azoospermia etc. are used in the updated WHO guidance as the WHO wishes to move away from reference ranges to define infertility and promote more individualised care, as well as the growing knowledge regarding genetics (350). There is increasing recognition of the role of male factors beyond the semen analysis in RM and infertility and that traditional semen parameters have relatively poor predictive value for spermatozoa fertilizing capacity and reproductive outcomes (351). A recent review identified that male BMI and age contribute to unexplained RM (352). There are several case-control studies and a recent meta-analysis which demonstrate the rate of sperm aneuploidy in male partners of women with RM is higher, even where other semen parameters are within typical range (353,354). Sperm DNA fragmentation are breaks in the genome of spermatozoa (355) which have also been

shown to be present more frequently in male partners of women with RM (354,356–360). However, this association has not been extensively examined with regard to pregnancy outcomes. One systematic review and meta-analysis demonstrated a lower pregnancy rate, and higher miscarriage rate, for couples where high levels of sperm DNA fragmentation existed in IVF and in ICSI (361).

Semen quality and sperm DNA fragmentation may be affected by modifiable risk factors such as smoking, alcohol consumption, weight status and presence of a varicocoele, but the degree to which such interventions may improve sperm quality and reduce RM risk remains unclear (362).

Treatment of male factors

Male factor infertility may require in vitro fertilisation, including specialised techniques such as ICSI (where the sperm is directly injected into the oocyte) (363) and/or surgical sperm extraction techniques such as:

- Percutaneous epididymal sperm aspiration (PESA)
- Microsurgical epididymal sperm aspiration (MESA)
- Testicular sperm aspiration (TESA)
- Testicular sperm extraction (TESE) - single or multi-site
- Microscope-assisted testicular sperm extraction (MicroTESE) (364).

While there is an increasing body of evidence to suggest an association between sperm DNA damage and RM (360), greater evidence that sperm aneuploidy or DNA fragmentation significantly affects pregnancy outcomes is required to recommend routine testing. Evidence to support any subsequent interventions such as or including ART is also required.

A Cochrane review in 2019 found no evidence that sperm selection with hyaluronic acid had an effect on livebirth or clinical pregnancy rates but may reduce miscarriage (365). The HABSelect Trial demonstrated no difference in livebirth rate for those receiving ICSI or physiological ICSI (PICSI) (where sperm are selected according to how they bind to hyaluronic acid) (366), but secondary analysis suggests it may be of benefit for older couples (367). The HFEA has designated PICSI as a “code red” i.e., not recommended, add-on (368). To date, no conclusive evidence exists to justify PICSI for RM.

International guidelines for sperm DNA fragmentation offer low grade evidence for antioxidants and addressing lifestyle factors, in addition to medium grade evidence for varicocele repair, for men with high levels of sperm DNA fragmentation (355). Until a role for sperm DNA fragmentation testing is established in RM care however, antioxidants and varicocele repair are not recommended by EHSRE solely to prevent RM (35).

1.5 Pregnancy outcomes associated with RM and Infertility

In addition to any risk factors or associated conditions a woman/couple with RM and infertility may have that could influence a future pregnancy, it is also important to consider the inherent risks that a history of RM and/or infertility poses and the likelihood of future successful pregnancy.

1.5.1 Pregnancy outcomes after infertility

Livebirth rates

In considering the likelihood of successfully conceiving, a number of factors have been shown to be of particular relevance to women/couples with infertility. In a 2010 systematic review and meta-analysis looking for predictors of live birth in infertility, negative associations were found between pregnancy and female age (OR 0.95; 95% CI 0.94, 0.96), duration of infertility (OR 0.99; 95% CI 0.98, 1.00) and basal FSH (OR 0.94, 95% CI 0.88, 1.00) (369). A positive association was found with the number of oocytes collected (OR 1.04; 95% CI 1.02, 1.07) (369). The type of infertility and the fertilisation method were not shown to be significant. Since then, several clinical prediction models for IVF models predicting cumulative live birth over complete cycles have been developed in the UK and US using national-level data, each of which is intended for a particular point in the person's treatment, e.g., before the first complete cycle starts, at the first embryo transfer or before the start of the second complete cycle (370). Within the prediction models female age, the duration of infertility, female BMI and AMH are important pre-treatment predictors, while the number of eggs collected adds value when treatment level information is known (370). However, these models must be validated in other geographical locations before being suitable for widespread use.

Livebirth rates after IVF decrease with age: 30% of individual IVF cycles in women aged ≤35 years result in a livebirth, compared with 9% in those aged 40 years and 1% in those aged > 44 years(371). A 2023 systematic review and meta-analysis examined maternal

age and the success rates of ART after euploid embryo transfer (seven studies, n = 11,335 ART embryo transfers) and found age to have a significant negative impact even when the risk of aneuploidy was reduced (372). A higher ongoing pregnancy rate and livebirth rate (OR 1.29; 95% CI 1.07, 1.54; I^2 = 40%) in women aged <35 years than in women ≥35 was found, and this difference was sustained when comparing women aged <35 to women 35–37, 38–40, or 41–42 (372).

Oocyte or egg donation use has increased over the last four decades and can be used in women aged over 35, mostly over 40, with reduced oocyte quality (373). Reproductive outcomes in donor egg cycles are not linked to recipient age and more closely linked to oocyte quality and donor age and thus can help to improve livebirth rates in older women who have lower success rates with IVF (374). For example, the HFEA data from 2017 demonstrated that autologous oocyte ("own egg") IVF had a livebirth rate of 11% in women aged 40-42 and 4% in women aged 43-44, but that IVF with oocyte donation led to a livebirth rate of over 25% in women aged 40 and over (371).

Complications of pregnancy following infertility and ART

Infertility is also an independent risk factor for adverse pregnancy outcomes compared with women in the general population without fertility issues (5). Some complications were also present even in the absence of IVF such as preeclampsia, placental abruption, and placenta previa (5). Studies have shown that the use of ART was associated with an increased risk of obstetric complications such as pregnancy-induced hypertensive disorders, placental abnormalities, gestational diabetes, but also perinatal complications such as prematurity, low birth weight, small for gestational age and congenital anomalies (375). These side effects have been attributed to the increased incidence of multiple pregnancies, especially in older women (376). However, studies have shown that the risk of complications was maintained in the case of singleton pregnancies obtained after ART compared to the general population (377).

For women with age-related infertility embarking on IVF with and without oocyte donation, there are specific complications of pregnancy. As mentioned above, women aged over 35 are at an increased risk of gestational diabetes, pregnancy-induced hypertension, preeclampsia and antenatal issues like preterm labour and preterm, prelabour rupture of membranes, and the increased necessity for an operative delivery

(375). In a retrospective cohort analysis of over 36 million births in the Unites States, women aged 45 and older are at increased risk of severe morbidity, defined as stroke, embolism, eclampsia, and hysterectomy (378). Including blood transfusion, the risk for severe morbidity was 5.3% for women aged 45–54 years, 2.7% for women aged 40–44 years and 2.0% for women aged 35–39 years ($p < 0.01$) (378). Severe morbidity was more than three times higher (RR 3.33; 95% CI 3.03, 3.66) for women 45-54 years compared with women 25–29 years (378). Specifically looking at preeclampsia, a systematic review of 27 studies comprising of 7089 oocyte donation pregnancies, 1,139,540 naturally conceived pregnancies and 72,742 IVF pregnancies showed increased risk with oocyte donation (373). The risks of preeclampsia and severe preeclampsia was increased in oocyte pregnancies compared to naturally conceived pregnancies (pooled OR of all subgroups: 5.09; 95% CI 4.29, 6.04; I^2 = 19% and OR 7.42, 95% CI 4.64, 11.88; I^2 = 49%, respectively) and compared to IVF pregnancies (pooled OR of all subgroups: 2.97; 95% CI 2.49, 3.53; I^2 = 51% and OR 2.97; 95% CI 2.15, 4.11; I^2 = 0%, respectively) (373). A review of pregnancy outcomes following oocyte donation was unable to draw a firm conclusion on the risk of preeclampsia in double donation (donor oocyte and donor sperm) pregnancies due to conflicting evidence in the few studies available but theorised a higher risk (379).

In conclusion, maternal age has the greatest bearing on livebirth rates in women with infertility, except where oocyte donation is undertaken. Maternal age also contributes significantly to risks of complication in pregnancy after infertility, which are further increased by oocyte donation use. Pre-conceptual counselling and evaluation of cardiovascular risk factors is recommended in women considering ART (380).

1.5.2 Pregnancy outcomes after RM

Live birth rates

There are few cohorts in the literature examining livebirth rates in women with a history of RM. A prospective cohort study that examined the reproductive outcomes of 42 women in Ireland with a history of unexplained RM (defined as three consecutive first-trimester miscarriages) who received no treatment in subsequent pregnancy, reported a livebirth rate of 78.5% (33/42) (381). In their cohort of 431 women with RPL (defined as two losses before viability) investigated and treated according to ESHRE guidance, Ticconi

et al. reported a livebirth rate of 86% (382). In a randomised control trial examining the effects of enoxaparin alone versus a combination of aspirin, progesterone and prednisolone on pregnancy outcomes for women with RPL (again, two losses before viability), Fawzy et al. found a livebirth rate of just 48% in the women taking placebo compared to 81% in the enoxaparin group and 85% in the combined group (383). It is notable however that second-trimester miscarriage was included in their definition and that women who miscarried again did so at later gestations; 11.8 weeks in the enoxaparin group, 13.5 weeks in the combined group and 14.2 weeks in the placebo group (383). Ali et al. reported a livebirth rate of 75.7% overall in their cohort study of women with RPL (up to 24 weeks) (384). The live birth rate was further stratified according to primary (73.6%) vs. secondary (81.6%) and two miscarriages (73.9%) vs. three or more (79.7%)(384). However, women were also on a variety of treatments, including levothyroxine, progesterone, folic acid, human chorionic gonadotrophin, LMWH, aspirin, vitamin D, and psychotherapies which were not delineated in this study (384). The PROMISE trial which examined progesterone in women with unexplained RM (defined as three or more first trimester miscarriages) had a live birth rate in the progesterone group of 65.8% (262/398) and in the placebo group of 63.3% (271/428) (385).

Two Irish studies examined pregnancy outcomes in women who had attended a RM clinic. Greene et al. examined pregnancy outcomes after two consecutive first trimester miscarriages in 242 women with no living children and reported a subsequent pregnancy rate of 82.3% (242/294) of women, with 72.7% (176/242) achieving a live birth (386). In this cohort, 69.4% had unexplained RM and medications including aspirin (45.2%), progesterone (16%), LMWH (6.8%), levothyroxine (4.4%) and metformin (2.4%) were prescribed for future pregnancy alongside supportive care (386). Women prescribed any medication were more likely to achieve a live birth ($p = 0.016$). However, the prescription of aspirin ($p = 0.096$) or progesterone ($p = 0.069$) alone did not significantly affect pregnancy outcome (386). Fee et al. demonstrated a livebirth of 75.3% in a cohort of 299 women with three consecutive miscarriages. Outcomes were not analysed according to the results obtained or the treatments given, which included progesterone (58.2%,), levothyroxine (14.4%), aspirin (23.7%) and LMWH (14.0%) (387). Fertility treatment was not recorded in this study.

Thus, while it is evident that the majority of women will have a livebirth after RM, it is not clear whether this is affected by conditions associated with RM, the treatment of known causes or by empiric treatments and many published cohorts have included second-trimester losses which may have influenced results.

Complications of pregnancy associated with RM

Studies evaluating complications in pregnancies after RM are also few in number and conclusions affected by the inclusion of second-trimester miscarriages.

An Irish retrospective cohort study demonstrated that women with RM (n = 2,030) were more likely than women without RM (n = 28,023) to have a BMI ≥30, to have had assisted conception or a previous perinatal death (388). Recurrent miscarriage was associated with an increased incidence of preterm birth (37 weeks gestation, 8.1 versus 5.5%, aOR 1.54; 95% CI 1.29, 1.84), very preterm birth (32 weeks gestation, 2.2 versus 1.2%, aOR 1.80; 95% CI 1.28, 2.53), and perinatal death (1.2 versus 0.5%, aOR 2.66; 95% CI 1.70, 4.14) (388). Induction of labour and Caesarean section rates in subsequent pregnancies were also reported as increased in the RM group (388). However, miscarriages were only confirmed to have been three consecutive in the primary RM group and it is unclear if women attended a RM clinic and what investigations, treatments or supports were available to this cohort (388). Dempsey et al. found no significant adverse pregnancy outcomes, such as stillbirth, preterm birth or growth restriction in their cohort of 42 women, with one woman developing preeclampsia (381). Similarly, Fee et al. found the rate of preeclampsia was 2.2%, pregnancy-induced hypertension was 2.2%, fetal growth restriction was 5.3%, preterm birth ≤ 34 weeks was 1.8%, and preterm birth > 34 weeks < 37 weeks was 6.6%, which are in line with population studies (387).

Ausbeck et al. examined 235 women with a history of two miscarriages under 12 weeks gestation and found a significant increase in gestational diabetes compared to 17,435 women with history of one or no miscarriage (aOR: 1.69, 95% CI: 1.10, 2.59), but no increased risk of preterm birth (389). In a population-based cohort study examining the data of 619,875 women from the Swedish Medical Birth register, Gunnarsdottir et al. found increased rates of preeclampsia, stillbirth, small for gestational age weight, placental abruption and preterm birth but none of these outcomes achieved statistical significance and the gestational age of pregnancy losses was not defined (334).

In a systematic review examining pregnancy loss and preterm birth (n = 58,766 with a history of RPL) a trend toward higher odds of PTB was observed with the increasing number of pregnancy losses: 2 RPLs (pooled OR, 1.31; 95% CI, 1.09, 1.57; I^2 = 88.9%); ≥2 RPLs (pooled OR, 1.58; 95% CI, 1.27, 1.96; I^2 = 71.7%); and ≥3 RPLs (pooled OR, 1.81; 95% CI, 1.58, 2.07; I^2 = 73.6%) (390). Again, RPL included pregnancy losses up to 20 weeks gestation.

In their systematic review, Quenby et al. found associations between RM (defined as three miscarriages) and subsequent adverse pregnancy outcomes, including preeclampsia aOR 1.22 (95% CI 0.86, 1.73), placental abruption aOR 1.67 (95% CI 1.21, 2.30), placenta praevia aOR 2.81 (95% CI 0.87, 9.04), low birth weight aOR1.98 (95% CI 1.09, 3.58) and stillbirth 1.69 (1.17, 2.45) (1). The risk of preterm birth rose with each successive miscarriage, from aOR 1.17 (95% CI 1.05, 1.31) after one miscarriage to aOR 1.76 (95% CI 1.39, 2.22) (1). However, it was not clear which studies were included for each meta-analysis and if all definitions of RM were at least three consecutive first-trimester miscarriages (1). A prior systematic review by Chen et al. demonstrated similar findings with increased odds of antepartum haemorrhage (OR 2·38, 95% CI 1·98, 5·27), gestational diabetes (1·23, 1·02, 1·47), preterm delivery (1·73, 1·28, 2·07), small for gestational age (1·52, 1·19, 1·98), and perinatal death (2·30, 1·62, 4·97) (15). Again, definitions for RM in the studies included for meta-analysis was unclear.

Overall, it appears that RM is associated with adverse pregnancy outcomes, but the studies contain mixed cohorts, and the results are inconsistent, calling for greater research in this area.

Pregnancy outcomes after RM and Infertility

There are no published cohorts that examine the subsequent pregnancy outcomes of women with RM and a history of infertility. Several studies have examined pregnancy outcomes following fertility interventions such as PGT-A in women with a history of RM, but not infertility (202,391,392). These studies mainly focused on whether the intervention led to increased birth rates but did not examine other obstetric outcomes such as preterm birth. Thus, there is a clear gap in the literature as to what the subsequent reproductive outcomes are for women with a history of RM and infertility.

1.6 Lived experience of RM and Infertility

Considering all of the topics associated with RM and infertility covered above, it is clear that the experiences of RM and infertility, separately and in combination, are complex. It is evident that even where there are associated medical conditions, many ambiguities remain regarding the investigations and treatments in both scenarios. It is also evident that RM and infertility have an impact on subsequent pregnancy outcomes. Women and couples who are living with RM and infertility therefore encounter many difficult and stressful scenarios and decisions on their journey to have a family, as well as a wide range of emotions. These stresses percolate into all areas of women/couples' lives as they deal with the practical and emotional impacts of such diagnoses. This section will examine the lived experience of RM, infertility and the dual experience, specifically the psychological impact on both partners, which can be exacerbated by stigma, in addition to the economic implications.

1.6.1 The lived experience of RM

Psychological impact of RM

The psychological consequences of miscarriage involve both trauma and bereavement and the Lancet series review identified that anxiety, depression, and suicide are strongly associated with miscarriage (1). Meaney et al. demonstrated that experiencing a single miscarriage is psychologically impactful, with a need for support and that RM evokes concern regarding future fertility and reproductive health (393). Unsurprisingly, this is augmented by the experience of multiple miscarriages (394), but also the shocking nature of the diagnosis (393). Despite being the most common adverse outcome of pregnancy, miscarriage is widely unexpected, and women feel uninformed about its prevalence (393). This aligns with other studies which have demonstrated that public knowledge of miscarriage symptoms and treatment is poor and largely underestimated (395–397). As mentioned above, miscarriage and RM are associated with significant psychological morbidity (398), with several studies showing that women with lived experience of RM have higher scores on various anxiety and depression scales (398–401), as well as reduced quality of life scores (399). In some women the experience of miscarriage leads to the development of post-traumatic stress disorder and remains significant up to nine months later (400). Descriptions of grief following miscarriage are highly variable but tend to

match descriptions of grief used to characterise other types of significant personal losses (402).

As well as feeling unprepared for the diagnosis of miscarriage and uninformed about the subsequent management, women have found the experience of miscarriage itself to be distressing (393). The physical experience of miscarriage was frightening and potentially traumatising as women were unprepared for the physical experience of miscarriage and the degree of haemorrhage (393,403,404). Care received also affected women's experiences and contributed to disenfranchised grief, with poor communication from staff when breaking bad news, the use of insensitive language such as "products of conception", the lack of private space and the perceived lack of social support cited as factors (405). Women with RM also found there was a lack of sensitivity from staff regarding their increasing anxiety and fear around ever having a successful pregnancy (406). Negative interactions with healthcare staff added to distress and was perceived as a lack of support or empathy (407).

Women felt dismissed and frustrated when denied investigations due to not fulfilling criteria for investigation (usually three consecutive miscarriages) and this was exacerbated when suggested their losses were down to "bad luck" (408). The refusal to investigate was more frustrating when women felt they had risk factors for pregnancy loss, such as being over 35, and merited investigation sooner (393). Following their loss, women wanted information from care-providers on miscarriage risk and wanted a clear plan for their investigation and treatment, as well as supports for future pregnancy (406,409,410).

The male partner experience of RM

The psychological impact is not confined to the female partner following RM and there can be a considerable impact on the male partner, again extending to post-traumatic stress disorder (411). The grief of male partners is largely unrecognised and neglected, often seen as secondary to that of their female partners (412,413). Harty et al. identified that RM has a significant psychological impact on men and that it is the deeply emotional experience (412). Moreover, men are placed in the roles of protector and supporter, wherein their own needs are secondary and often neglected (412). Additionally, some men are unprepared to adequately support their partner in such a difficult life event and

use maladaptive coping skills such as “trivialisation and wishful thinking” or “avoidance”, which can exacerbate post-traumatic stress in female partners (411). Miscarriage also contributes to a change in sexual relationships, which can be of greater significance to male partners and is recognised as a risk factor for marital breakdown (414).

Stigma and miscarriage

Psychological distress can be augmented by the “a vast silence” or stigma surrounding miscarriage, with many women only hearing about other women’s experiences once they had disclosed their own miscarriage (12). This can be frustrating for women as they report feeling that the unnecessary secrecy surrounding miscarriage, and even pregnancy under 12 weeks, was responsible for their lack of awareness around the prevalence of miscarriage (12,393). This stigma also perpetuates their own psychological distress as women feel they cannot discuss miscarriage and their feelings around their loss (12). Women also feel that their family and friends do not know how to support them; people are commonly uncomfortable discussing the miscarriage or did not know how to acknowledge their loss (12). This leads to feelings of loneliness and isolation as women feel that miscarriage is something they cannot talk about freely (12). The stigma of miscarriage can also be exacerbated when seeking health care. Many of the risk factors for RM are also stigmatised, such as maternal age and obesity, and carry additional burdens of “self-responsibility”, which adds to self-blame (415,416).

Economic impact of miscarriage and RM

The Lancet Series on miscarriage recognised that there are short and long-term costs associated with miscarriage and RM, affecting individuals, health-care systems and wider society (1). Health-care costs include the direct costs of the management of miscarriage as well as preventative costs such as progesterone therapy (1). Direct costs for the individual included work absences and use of annual leave, but the review also identified reduced productivity following miscarriage as both a burden to women and a cost to society (1). There were no studies estimating the long-term costs associated with more protracted psychological morbidities following miscarriage such as depression. Nonetheless, taking into account these short-term costs of miscarriage, the economic cost of miscarriage in the UK was estimated to be £471million annually in 2021 (1).

In the ROI, the *Organisation of Working Time (Reproductive Health Related Leave) Bill 2021* has stalled in becoming legislation and thus women in Ireland remain without specific paid leave for miscarriage or fertility care (417). A cross-sectional study of 135 women in the ROI with RM was conducted using an anonymous web-based national survey which demonstrated that 66% (n = 47) of women took time off from work for investigations (n=71), 62% (n=38) for receiving results (n = 61), 77% (n = 75) for early reassurance scans in the next pregnancy (n = 97) and 18% (n = 24) for attending support services (n = 135) and 70% reported reduced productivity at work (418). Additionally, to receive RM care, women travelled a combined 32,109km to attend all RM care appointments, costing on average €20,300 for transport, parking and fuel (418). Other out-of-pocket expenses included further investigations, scans, and other services such as fertility services, averaging over €250,000 with additional costs for the minding of children/dependents while attending RM care appointments of €1,350 (418).

Pregnancy after RM

Qualitative work with couples experiencing RM has demonstrated that the first trimester of a subsequent pregnancy is a time of stress and anxiety, where women/couples experience a turmoil of emotions and hypervigilance (419). While women/couples employ their own coping strategies and divide the difficult period into personal milestones, they found that ultrasound was a valuable source of reassurance, albeit short-lived (419). Regular ultrasounds in this period have been shown to be an important part of supportive care for RM cohorts (420,421), and they are desired by women/couples (393,409,410). Previous studies of women with unexplained RM have demonstrated that supportive care alone is beneficial to outcomes in subsequent pregnancies (422,423). Couples also valued the environment of a dedicated early pregnancy clinic, away from busy emergency or antenatal areas (393). Empathy and compassion from staff were highlighted as additional sources of support in the first-trimester, especially when the anxiety this period poses to those experiencing RM was acknowledged (419). Staff knowledge and competence in RM care was particularly appreciated, as was continuity of care (393,409).

Overall, the psychological and physical impact of RM is substantial, and women and their partners have a need for psychological support during and after RM. This need continues into subsequent pregnancy, where practical and emotional supports are valued. However,

these needs must be highlighted to all healthcare staff working in maternity services and supportive care standardised through the development and implementation of evidence-based guidelines, and specific to the geography for this thesis, the development and implementation of an Irish Clinical Guideline for RM.

1.6.2 The lived experience of infertility

Psychological impact of infertility on women

Infertility is known to permeate many aspects of women's lives and is psychologically, socially and financially burdensome (424). Even before commencing treatment, repeated failed attempts to conceive and the acceptance of the need to pursue treatment are distressing and can lead to a sense of a "loss of control" and failure for the partner diagnosed as infertile (425). Women experience a wide range of emotions during treatment, and significant stress and challenges related to the painful, embarrassing, complex, and confusing treatments and side effects (424). Women undergoing infertility treatment are more prone to depression and experience it more frequently than male partners (426). In a systematic review exploring gender differences during fertility treatment, females had more negative experiences with infertility than males, including lower levels of identity, self-esteem, and physical health; and higher levels of depression, stress, anxiety, stigma, and shame (427). The psychological burden of infertility treatment is so onerous that it is the most common reason for stopping treatment (428).

Male partner experience of infertility

Compared to their fertile peers, men with infertility experience greater levels of anxiety and depression, although this appeared to be less than their female partners (7,427). A systematic review of qualitative literature on male factor infertility found that the experience is complex, with the desire for fatherhood running alongside difficult emotional experiences (429). Men experience infertility as a "life crisis" but put pressure on themselves to remain strong, despite facing stigma and often ridicule (429). Similar to miscarriage, there is also an impact on sexual and marital relationships (7), with reduced quality of life scores and marital satisfaction scores (430–432).

Stigma

Fertility also carries a distinct stigma, which proliferates feelings of shame and isolation (433). While fertility-related stigma can be heightened due to cultural or religious backgrounds (434), all women dealing with the stigma of infertility face increased psychological distress and decreased quality of life (433). Because of stigma, many couples with infertility choose not to share their experience with family and friends, isolating themselves from supports and often withdrawing socially (433). As with miscarriage, the lack of understanding and awareness can lead to unintentional insensitivity from others and distress for the woman/couple (433). As mentioned previously, male infertility carries a particular stigma that is associated with shame, fear of ridicule and a feeling of diminished masculinity (429).

Financial impact of infertility

The financial impact of infertility is significant. In their qualitative study on the lived experience of infertility, Ozturk et al. outlined the financial difficulties for women in the United States seeking fertility care (424). Financial costs were a major obstacle to treatment; all participants reported increased financial burden and stress related to these costs and difficulty affording treatment (424). Some women perceived the financial burden including dealing with insurance companies as more stressful than treatment itself, which they also generally identified as highly stressful (424). The cost of fertility treatment is significant, with one IVF cycle in Ireland costing between €4,100-5900 in 2017 (43). As mentioned with regard to miscarriage, there is currently no statutory leave available while undergoing fertility treatment (417). The extraordinary cost of fertility treatment has been cited as a contributory reason for ceasing fertility treatment, however, it was less impactful than the psychological or physical impact and maternal age (428).

In summary, infertility impacts almost every aspect of the lives of women/couples affected. The difficulties related to the experiences of infertility in Ireland are unexplored and thus the distinct needs of those seeking infertility care remain unidentified.

1.6.3 The lived experience of RM and infertility

Psychological impact of RM and infertility

The combined experience of RM and infertility is less well researched, but a small number of qualitative studies offer insights into the issues faced. Women who experience

miscarriage after fertility treatments experience many negative psychosocial manifestations of grief response including depression, anxiety, despair, frustration and anguish (435). In some cases, this even extends to suicidality (424). It has been suggested that the loss of a pregnancy after infertility is so immense as to be equivalent to the death of a child for these couples, representing the loss of their hopes of parenthood (436).

In a qualitative study of eight women experiencing RM and infertility, descriptive phenomenology was used to explore the meaning and the specific difficulties of the dual experience (437). However, this American study did not explore the experiences related to investigation and treatment or navigating the system/structure of care, focusing on the experience of pregnancy loss. They described the difficulty of returning to treatment after loss and the sense of having financial investment in each pregnancy (437). Women had a sense of running out of time and felt hopeless and tentative to hope to become pregnant again (437). Women also described feeling profoundly alone as others did not understand their experience and the absence of understanding from healthcare professionals and others with children (437). Using a nationally representative sample of American women (n = 2,894) from the National Survey of Fertility Barriers, Schwerdtfeger and Scheffler examined long-term psychological outcomes and reactions to pregnancy loss and infertility among mothers and involuntary childless women (436). Women who wished to have children but who have experienced pregnancy loss or infertility reported the lowest life satisfaction and highest levels of depression, which persisted despite a considerable period of time (seven years) passing since the loss or first year without a conception (436). However, women with the dual experience of pregnancy loss and involuntary childlessness reported the most fertility-related distress, alongside the highest depressive scores and also expressed more complicated emotions such as feeling "cheated by life" or "failures as women" (436).

While these studies identified the deep emotional experience for women, there were little insights into what effective supports women used or desired, aside from the need for time and sensitivity to their experience (437). Women valued talking to women who had undergone similar experiences and while support groups were suggested, women's experiences of attendance were not explored (437). The supports required by women in a subsequent pregnancy were not explored. While the psychological distress of

involuntary childlessness was recognised, again the supports required by women/couples were not explored (436). Thus, further qualitative work is needed to identify what supports are valued and helpful for women experiencing RM and infertility as they undergo treatment and experience miscarriage, but also as they embark on a subsequent pregnancy or withdraw from treatments.

While it is clear that RM and infertility, separately and in combination, have a profound impact on the lives of women and couples, several gaps remain in the literature. From an Irish perspective, there needs to be a greater examination of how the current system is experienced, by both staff and women/couples. Qualitative work could examine how the public and private division of RM and fertility services (discussed in Section 1.7) affects care provision, the difficulties that arise for healthcare providers and women/couples and how this care varies nationally. It could also explore how current supports and services are experienced by women and their healthcare providers, identifying strengths and deficits within the system. For women and couples who do not go on to have a pregnancy, it would be important to elicit the influences around the decision to stop trying and the supports required to improve awareness and care provision. Further qualitative work is also needed to explore in greater detail the experience of pregnancy after RM and infertility to capture the challenges faced or if the significance of their history was recognised within antenatal care services and what influence it had on obstetric decision making.

1.7 Organisation of RM and Fertility Care

1.7.1 International recommendations for RM care

Early pregnancy and miscarriage care

In recognition of the fact that the delivery and organisation of care impact on the experience of women and couples (410), ESHRE has issued specific guidance on the organisation of RM care (29). They suggest that couples with two or more pregnancy losses could be referred to a dedicated RPL (ESHRE definition is any two losses under 24 weeks) or RM clinic. A RPL clinic is an outpatient clinic that offers a non-acute service that is consultant-led with specialist investigations, support and if possible, treatment of couples with RPL (29).

In particular, ESHRE outline the following essential elements in the organisation of care:

- Staffing – this refers to obstetrics and gynaecology staff, ultrasonographers and psychological support staff
- First visit – this should allow time for a complete history
- Equipment/location – this refers to the appropriate scanning and laboratory access/equipment. The clinic should be located away from antenatal clinics or wards.
- Provision of information – there should be adequate time for explanation and written information should be provided also
- Appropriate evaluation – investigations should be tailored to the woman's personal history with adequate explanation of their significance and expected timelines
- Care tailored to the psychological needs of couples - careful listening, sensitive terminology and consideration of the woman/couples' experience and feelings
- Treatment plan – this should be explained to the couple, especially in instances where all investigations are normal and treatments are not necessary (29).

Management of subsequent pregnancy following RM

Both the RCOG and ESHRE have integrated the findings of Musters et al. into their recommendations for the management of care in a subsequent pregnancy (438). Specifically in a subsequent pregnancy women/couples appreciate:

- A plan with one doctor who shows understanding, takes them seriously, has knowledge of their obstetric history, listens to them, gives information about recurrent miscarriage, shows empathy, informs on progress and enquires about emotional needs
- An ultrasound examination during symptoms, directly after a positive pregnancy test and every 2 weeks
- If a miscarriage occurred, most women would prefer to talk to a medical or psychological professional afterwards
- The majority of women expressed a low preference for admission to a hospital ward at the same gestational age as previous miscarriages and a low preference for bereavement therapy (32,438).

1.7.2 Structure of Recurrent Miscarriage care in the ROI

Structure of maternity care

Every woman who is pregnant and ordinarily resident in Ireland is entitled to maternity care under the Maternity and Infant Scheme (439). Care is provided in 19 maternity units. These units include four larger units (>6,000 births per annum), three in Dublin and one in Cork, six medium (2001-6000 births per annum) and nine small (<2000 births per annum) (440). Four units are stand-alone, i.e., not co-located with a general hospital, three of which are located in Dublin and one in Limerick (440). The medium and small units, also referred to as "peripheral units", can transfer women with a high-risk pregnancy or critically ill women to the larger units for neonatal or obstetric care.

All 19 maternity units are in public ownership with no remaining private maternity hospitals and only a small number of planned home deliveries (441). The hospital maternity services are funded by a hybrid of government funding through the Health Services Executive and through private health insurance (441). All hospitals provide public and private maternity care, with the three Dublin hospitals also offering semi-private care (441). Almost always, women choosing private or semi-private care have private health insurance which covers all their hospital costs and part of their medical fees (441). All women are entitled to free public care which is funded by the government based on an annual service level agreement whereby outpatient and inpatient services before and after delivery are provided without charge for the woman and her baby (441). However, this structure of care may change with the introduction of Sláintecare, which is the current government's plan to establish a universal, single-tier health service where patients are treated solely on the basis of health need, and in essence, remove private care from public hospitals (442).

Structure of miscarriage and early pregnancy care

A number of significant events occurred in Ireland after 2010 which prompted change within the maternity services regarding early pregnancy and miscarriage care. Firstly, several misdiagnoses of first-trimester miscarriage came to light which prompted a HSE review (443). The *National Miscarriage Misdiagnosis Review* made a number of recommendations regarding early pregnancy care, including the need for specialist early

pregnancy care units and supports for women experiencing miscarriage (443). Specifically, the report outlined that:

- All units that provide emergency gynaecological care should have a dedicated early pregnancy assessment unit with adequate staffing, equipment and facilities
- Staff should receive training in basic counselling skills, support techniques
- If a woman has experienced early pregnancy loss, the news should be broken to her sensitively, in an environment that provides privacy and with time for questions to be answered fully (443).

While this report resulted in the publication of two national guidelines, "Ultrasound Diagnosis of Early Pregnancy Miscarriage" and "Management of Early Pregnancy Miscarriage," no guidance on RM was issued (444).

Clinical guidance for RM care in Ireland

Up to 2010, in the absence of local guidelines, obstetrics and gynaecology care in Ireland was influenced by RCOG guidance. Subsequently, the issuance of Irish National Guidelines was commenced by the Royal College of Physicians in Ireland in an endeavour towards independent guidance. However, no national guideline on RM was published at this time and Irish clinicians predominantly used the RCOG 2011 guideline (21,34). This is significant as UK guidance distinguished between recurrent first-trimester miscarriage and second trimester miscarriage, directing investigations for a single pregnancy loss after 13 weeks (21). This differed from the European and American guidelines at the time which considered first and second trimester miscarriages together under RPL (24,31) and only after three and then later two losses (18,23). This longstanding variance in definitions between UK, Europe and American guidance has permeated research studies and RM cohorts outside of the UK and Ireland are often mixed with second-trimester loss cohorts, which can be problematic in determining associations or treatment effects. It has been positive however in directing investigation and treatment for women experiencing a second-trimester pregnancy loss.

National Standards for Bereavement Care

Following on from the changes in miscarriage and early pregnancy care outlined in Section 1.7.2.2, a review of 28 perinatal deaths (445) prompted further complaints by bereaved

parents and a further HSE review (446). The National Maternity Strategy 2016-2026 and the National Standards for Safer Better Maternity Services were developed as a consequence (447,448) and the recommendations from these reports prompted the development and publication of the National Standards for Bereavement Care Following Pregnancy Loss and Perinatal Death (449). The purpose of the Standards is to enhance bereavement care services for parents who experience a pregnancy loss or perinatal death. These Standards cover all types of pregnancy loss that women and parents may experience, from early pregnancy loss to perinatal death, including the end of a pregnancy as well as situations where there is a diagnosis of fetal anomaly that will be life-limiting or may be fatal(449). With regards to RM, the standards clearly state that:

"All Maternity Units should streamline their provision of, or referral to, a dedicated recurrent pregnancy loss clinic for women who have experienced recurrent pregnancy loss. This clinic team should include a consultant obstetrician and specialist nurse(s)/ midwife(ves) in bereavement and loss"(449).

Data collection in miscarriage and RM

It is recognised that data collection regarding the number and type of miscarriage is difficult, regardless of geographical location (450,451). As well as the variation in international definitions as discussed previously, early pregnancy losses can be difficult to capture, given that a significant proportion of them occur outside of hospital (452). Moreover, there can be variation in what is included in miscarriage data (i.e., biochemical versus clinically recognised miscarriage, inclusion of second-trimester miscarriages), with training required for all staff involved in data recording regarding the types of miscarriage and terminology used (such as "threatened miscarriage"), all of which can lead to errors in data collection (451). One study demonstrated significant variability when comparing definitions of type of miscarriage (i.e., missed miscarriage, incomplete, and complete) between electronic, paper and admission data sources (451). Therefore, it may affect reliability and accuracy of these data in epidemiological studies.

Currently in the ROI, there is no national miscarriage register, with miscarriage data limited to that collected routinely as part of hospital admissions or individual early pregnancy unit data (451,452). Some hospitals also have an electronic health record which can enable easier recording and searches (452). The Scandinavian countries have

well-established healthcare registers which have provided data for some of the largest population-based studies on miscarriage (53,58,450,453), but such a register would require significant resources to implement and upkeep. The Lancet Series recommended that "miscarriage data are gathered and reported to facilitate comparison of miscarriage rates among countries, to accelerate research, and to improve patient care and policy development"(1). Subsequently the Scottish Government has committed to improving data collection on miscarriage (454). While there have been attempts made to collect miscarriage data in the UK via general practice records (454), there are no definite plans regarding collecting data on miscarriages before 12 weeks at present due to the difficulty in data verification and accuracy (455). However, both Scotland and England have introduced a voluntary memorial book or certificate as an alternative to a national register and a means to acknowledge pregnancy loss for women and their families (454,455), alongside concerted efforts to record all losses after 12 weeks (455). Thus, data collection and registration of pregnancy loss are additional contemporary issues in miscarriage care that need to be addressed in the ROI.

Current structure of RM care in the ROI and future directions

A recent service evaluation identified that just 9/19 units in the ROI had a dedicated RM clinic (34). A 2021 audit of the implementation of bereavement standards also identified that four units remain without a pregnancy loss clinical lead and two bereavement midwife vacancies remained at that time (456). In the absence of qualified staff with the required skillset and dedicated clinics, it remains the case that, in some maternity units, women have no access to specialised RM care. A national RM care experience survey also highlighted the impact of these specific care deficits. Almost half of women, 44%, described their care received while experiencing RM as poor, with 51% describing an overly long wait for investigations and just half (52%) receiving a treatment plan for future pregnancy (457). These findings were echoed in the recent *"Health Information Quality Authority (HIQA) National Maternity Bereavement Experience Survey"*; while 74% received good care, women and their partners expressed a need for follow-up and information after pregnancy loss (458). Subsequently the *"HSE Response to the Findings of the National Maternity Bereavement Experience Survey 2022"* was published which identified the need for RM clinics to be established in some units and pledged to work alongside the National Women and Infants Health Programme (NWIHP) to develop

resources for information provision, including implementing a National Clinical Practice Guideline on RM (459).

Internationally, miscarriage and RM care have received traction with the publication of the Lancet Series on Miscarriage and RM (1,14,460,461), which as well as calling for action, provided a suggested template for RM care. Nonetheless, neither miscarriage nor RM featured in the Irish Government's Women's Health Action Plan for 2022-2023 (462), in contrast to the Scottish Government's commitment to establish a dignified and compassionate miscarriage service by the end of 2023 (463). Therefore, apart from exploring workplace leave, it is not clear what the current Government in the ROI intends to provide for women and their families experiencing RM and other types of pregnancy loss or how the required care and resources will be provided.

1.7.3 Structure of fertility care in the ROI

Legislation and policy regulating fertility care

Ireland is an outlier in Europe for a lack of legislation regarding ART and associated practices. While any clinics which undertake the donation, procurement, testing, processing, preservation, storage and distribution of human tissue such as oocytes, sperm and embryos must be registered and monitored by the Health Products Regulatory Authority (HPRA) under Statutory Instrument No. 158 of 2006 (Quality and Safety of Human Tissues and Cells) Regulations (464), there is no other fertility care register or mandatory outcomes reporting or auditing (43). In the absence of Irish legislation, Irish fertility clinics have optionally abided by regulations and clinical guidelines published by institutions such as the Irish Medical Council, the HFEA, RCOG and ESHRE (43). For example, in the Code of Practice of the HFEA, it is laid out in detail how licensed fertility practices should operate under the legislation in the United Kingdom, the Human Fertility and Embryology Act (465). It outlines the regulatory principles that licensed centres must demonstrate adherence to when operating under the Act and includes topics such as staffing, documentation and record keeping, informed consent for all procedures, the management of gametes and embryos and their donation, PGT-A, premises, facilities, equipment and materials (465).

In response to this need for legislation and to facilitate public ART in the ROI, the Assisted Human Reproduction Bill was drafted and brought to the Houses of the Oireachtas in

2022. This Bill aimed to regulate the provision of ART in Ireland, including setting up an Assisted Human Reproduction Regulatory Authority to standardise all of the potential treatments and procedures, storage and handling of gametes and embryos, as well as overseeing licensing for those undertaking such procedures (466). This Bill will also mandate the collection and publication of success rates between service providers. Additionally, the Bill addresses issues such as surrogacy and the rights of persons born as a result of ART (466). Legislation regarding donor gametes had been previously covered in the Children and Family Relationships Act 2015, which defined parentage in these circumstances and revoked donor anonymity (467). The Assisted Human Reproduction Bill is currently being processed by the Houses of the Oireachtas and should be enacted into legislation this year. This is an important step towards regulation of fertility services and increased transparency.

Fertility data collection

Data on medically assisted reproduction from European countries are collected by the European IVF monitoring Consortium for ESHRE annually, but while the last report recognised nine fertility clinics in Ireland, just two were included for analysis (42). The Merrion Fertility Clinic is the sole not-for-profit clinic in the ROI and is unique in publishing an annual report of treatment outcomes (43). Thus, the numbers of women undergoing assessment for infertility and/or having fertility treatment in the ROI are not known. Additionally, details of service provision, care pathways, treatments undertaken and treatment outcomes from all fertility centres are not publicly available.

Organisation of fertility care

Current structure of care

Public fertility care in Ireland is currently very limited. These limitations apply to capacity and geographical location, as well as to the fertility treatments available. Presently, there are specialist public fertility clinics in just five maternity hospitals: Galway and the four larger maternity hospitals in Dublin and Cork. These clinics are in a position to offer basic fertility investigations, including semen analysis, and treatments such as ovulation induction or intra-uterine insemination (up to three cycles). As a consequence of this limited public fertility service provision, most ART in the ROI is provided by private or not-for-profit healthcare operatives (43). As mentioned in 1.5.3.2, fertility services in the

private and not-for-profit sector currently encompass nine main providers, some with multiple clinics nationwide (464).

Funding of fertility care

At present there is no public funding for ART, with tax-relief on medical expenses and reimbursement on medications through the Drugs Payment Scheme the only financial assistance available (43). Ireland is an outlier in Europe in this regard, being the sole European country to not provide state-funded ART or reimbursement (41). The costs involved in ART are not insignificant. Research by the Health Research Board (2017) noted the following prices for fertility treatments: "The cost of a single in vitro fertilisation cycle in a private Irish fertility clinic ranges from €4,100 to €5,900, whereas ICSI costs between €5,200 and €6,400" (43). This poses a significant financial burden to Irish women and men seeking fertility treatment.

To address this issue, the Minister for Health announced in September 2022, that public IVF would be made available in September 2023 (468). In order to achieve this, six fertility hubs were to be established, adding a Limerick hub in addition to further development of the pre-existing public fertility clinics (468). However, in order for ART to be performed in these clinics, issues such as specialist staffing for services such as andrology and embryology will need to be overcome, a point emphasised in the new National Clinical Practice Guideline on Fertility (469).This new National Clinical Practice Guideline on Fertility – Investigation and Management in Secondary Care does not cover best practice in ART techniques generally or for RM (469). The Guideline has also not laid out how miscarriage management and bereavement care for those experiencing pregnancy loss while undergoing fertility treatment is to be integrated into these new services, a particular concern given the geographical distribution of the new hubs (469). At present, while these services are being established, ART will be provided by private facilities and funded by the HSE; albeit with several restrictions, including that women must be aged under 40, with a BMI of <30 and must have no living children and no prior IVF treatment (470). The ART offered is also limited to the current three cycles of IUI in addition to one round of IVF (470). Thus, while these measures are welcome, they will not eradicate the financial liability for many women and couples with infertility.

1.7.4 The intersection of miscarriage and fertility services in the ROI

The exact structure of services involved in care provision for women and couples experiencing RM and infertility is not clear and appears to be highly variable. However, some recent work has provided insights into RM care provision in the ROI and some indications of the dual experience. The "REcurrent miscarriage: evaluating CURRENT services" or RE:CURRENT study was a Health Research Board funded project which sought to inform efforts to standardise and improve the quality of these services (471). In order to do so the following studies were undertaken:

- A systematic review of clinical practice guidelines for recurrent miscarriage in high-income countries (472)
- A qualitative study on stakeholder views on recurrent miscarriage services (408,473,474)
- Development of key performance indicators for RM care using international clinical practice guidelines (475)
- A national service evaluation of RM care (34)
- RM care experience survey (457)
- Health economic analysis (476).

Without a national miscarriage or pregnancy database, or a requirement for fertility clinics to publish outcomes data, it is unknown how many women and couples in Ireland experience RM and infertility, or even miscarriage within fertility services. Within the RE:CURRENT study, it was evident that women were also seeking RM care within private fertility services, even in the absence of a defined fertility issue (473). It was also evident that due to issues around the definition of RM, women were sometimes encouraged by staff within the public health system to seek investigations within private fertility clinics (408). Separately, a review of websites providing RM information found smaller clinics or individual fertility specialists provide a variety of RM investigations and some treatments, in a more limited capacity (477). From the RE:CURRENT study's systematic review of clinical guidelines on RM, it is known that women and couples experiencing RM and infertility are not considered within the international clinical guidance and thus it is unclear how this dual diagnosis is being managed currently within services in the absence of national guidance and standards (472). The clinical pathways within private services or

between public and private sectors for the management of RM and infertility are also uncertain. Fertility services therefore potentially provide a separate care stream for those with RM with and without infertility, of which little is known.

Women and men in the ROI face very specific obstacles as previously described, such as disparities in the public and private care and the discreteness of miscarriage and fertility care. Wider societal issues such as the ongoing housing and cost of living crises may also be influential in determining whether couples can afford IVF or which provider they choose to access for either RM or infertility care. Another important contextual issue is the recent introduction of legal termination of pregnancy in Ireland, a complicated reproductive health issue which had mirroring themes of stigmatisation and isolation (478). The referendum followed 35 years of legal cases, human rights advocacy, feminist activism and governmental and parliamentary processes and represented the significant changes within Irish society since the Constitution was developed (479). This legation has continued to struggle with implementation. As mentioned, other women's health legislation such as the Assisted Human Reproduction and Reproductive Health Related Leave Bills have yet to be approved by government. Thus, the experience of RM and infertility in the ROI has distinct influences and impacts, which merits exploration in order to enhance service provision and improve care.

1.8 Gaps in Literature

Considering the above topics and literature related to RM and infertility, a number of research gaps are evident.

There are many conditions with which RM and infertility are separately and jointly associated, however it is less clear which merit investigation and treatment for women/couples with a dual experience in the absence of a National Clinical Practice Guideline for either RM or infertility. Best practice in this regard must be identified.

It is also unclear how care is being provided to women/couples with RM and infertility in Ireland, in terms of care pathways, providers and clinical management. It is unknown how these practices, locally and nationally, compare to international best practice.

While cohort studies have examined subsequent pregnancy outcomes of women with RM, there is a need for larger studies and better scrutiny of the impact of maternal history, identified causes of RM and prescribed treatments on outcomes. Additionally, there are no well-defined cohorts of women with RM and infertility within the literature.

There are very few qualitative studies examining RM and infertility care in the literature, and none involving male partners or healthcare providers working in this area. Moreover, the lived experience of RM and infertility in the ROI may encompass unique obstacles and burdens due to the public/private divide within the healthcare system that are important to identify as they should influence future development of services. The lived experience may also reveal positive supports or alternate care pathways that should be retained as women's healthcare undergoes many changes, including the suggested changes to miscarriage care from the RE:CURRENT Study, the provision of public infertility services and the National Clinical Guideline Programme, as well as the wider changes to public and private services invoked by Sláintecare.

1.9 Overall aim and research questions

This thesis will seek to set out the relevant literature regarding RM and infertility, to identify the current issues and differences in experiences, and to evaluate the evidence that should be taken into account when caring for Irish women and couples with RM and infertility, as well as in the development of new services.

In order to do so, the following questions will be posed and addressed through research:

- What do we know about concomitant RM and infertility from the wider literature?
- What are the standards of care for women with RM and infertility – internationally and nationally?
- How are women with RM and infertility currently being treated nationally compared to international guidelines?
- How are women in one tertiary maternity hospital with RM being treated and what are their pregnancy outcomes?
- How does management for women in a tertiary maternity hospital with RM and infertility compare to international guidance?

- What are the views and experiences of people with lived experience of RM and infertility of current services and supports?
- What are the views and experiences of healthcare professionals of the current services and supports available for women/couples with RM and infertility?

1.10 Thesis outline

As demonstrated in Figure 1.1 overleaf, this thesis will seek to answer the above questions within the following chapters.

The introduction (Chapter 1) and literature review (Chapter 2) will lay out the background and rationale for the subsequent study questions and projects.

Chapter 3 will include a brief overview of my work within the RE:CURRENT study and a summary of the National Clinical Practice Guideline for RM. International guidelines were reviewed and used to develop key performance indicators (KPIs) for RM care within RE:CURRENT (485,487). These KPIs were the foundations of the National Clinical Practice Guideline.

Chapters 4, 5 and 6 will look at "Reproductive Outcomes and Service Provision". Chapter 4 is a retrospective cohort study of women with experience of RM. Additionally, the KPIs from chapter 3 were adapted for use in a National Service Evaluation (chapter 5) and a clinical audit of RM and infertility (chapter 6) to compare current services to international best practice, which are both be included here.

Chapter 7 will examine the experience of RM and infertility in the ROI. This study encompasses a qualitative exploration of women and relevant stakeholders' experiences of RM and infertility care and the supports and services available.

This work is summarised and future directions for research in this area outlined within the discussion, which forms chapter 8.

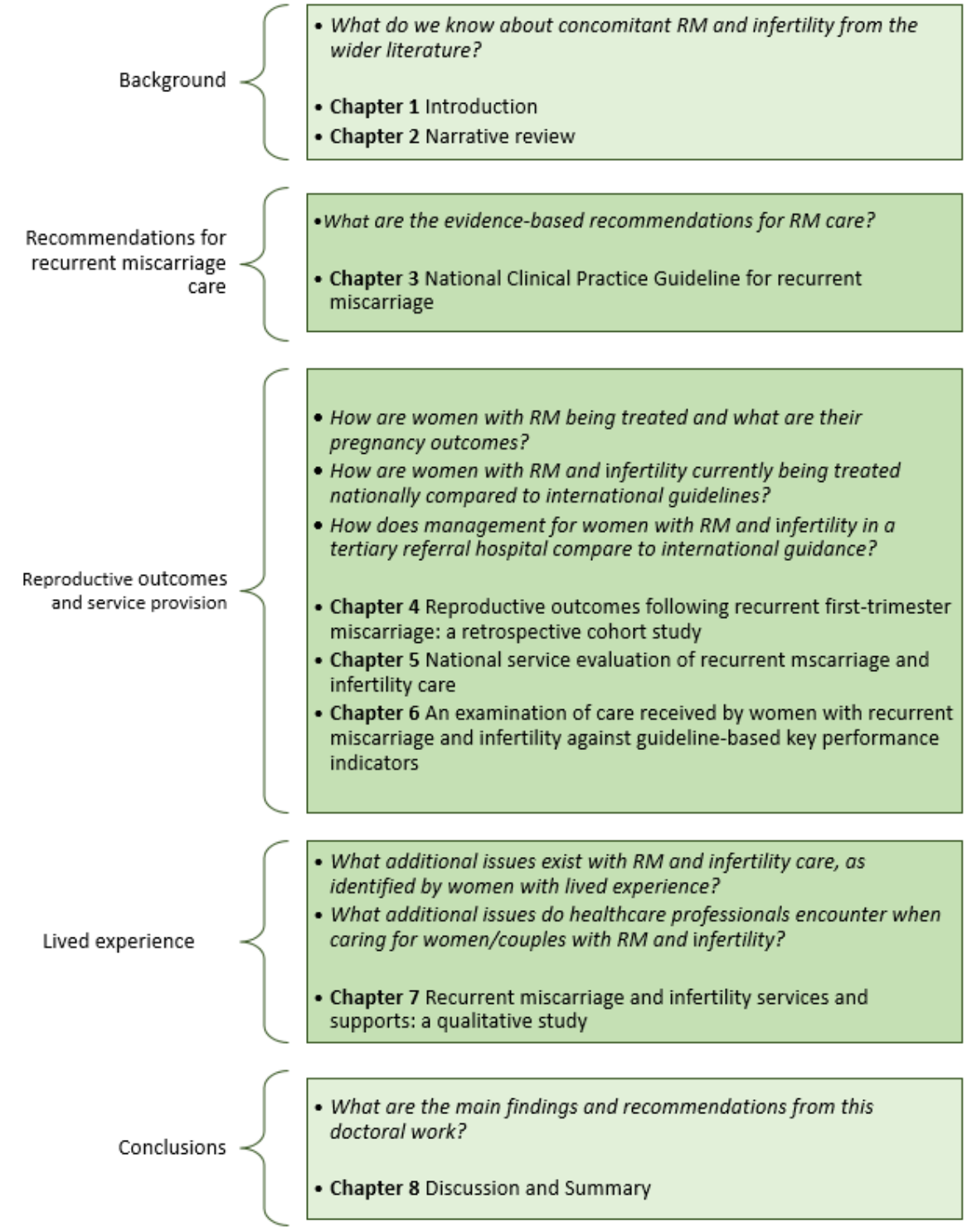


Figure 1. 1: Thesis overview.

Chapter 2 – Infertility and subsequent recurrent miscarriage: Current state of the literature and future considerations for practice and research.

Linehan L, Hennessy M and O'Donoghue K. Infertility and subsequent recurrent miscarriage: Current state of the literature and future considerations for practice and research [version 1; peer review: 1 approved with reservations]. HRB Open Res 2021, 4:100 (https://doi.org/10.12688/hrbopenres.13397.1)

Chapter 2 – Infertility and subsequent recurrent miscarriage: Current state of the literature and future considerations for practice and research.

2.1 Abstract

Background

Recurrent miscarriage (RM) and infertility are independently associated with adverse pregnancy outcomes, in addition to psychological sequelae. Experiencing pregnancy loss alongside infertility is particularly difficult. International guidance regarding RM is conflicting, and applicability to women with infertility is undetermined. The aim of this study was to: (i) establish if women/couples with a history of infertility are recognised in the literature on the investigation and management of RM, and (ii) determine if the specific needs of women/couples experiencing RM and infertility are ascertained and incorporated into clinical management strategies.

Methods

We examined the wide-ranging literature to ascertain what gaps existed. Studies were retrieved through searches of PubMed and Google Scholar up to 21 January 2021 using appropriate controlled vocabulary and combinations of key words. No language or study design restrictions were applied.

Results

While women/couples experiencing RM after infertility appear in studies evaluating investigations and proposed treatments, high-quality studies are lacking. Furthermore, they are largely excluded from international clinical guidance and qualitative research.

Conclusions

The experiences of women/couples with RM and infertility and their specific care needs within maternity and fertility services are underexplored. It is unclear from current RM guidelines how best to manage and support this complex cohort. Women/couples with

infertility and RM are underserved in the literature and in clinical guidance. Further robust studies are warranted to examine pregnancy outcomes, investigations and treatments currently used. Qualitative research is also required to identify their medical and psychological needs to better support this vulnerable group.

Keywords

Infertility, recurrent miscarriage, pregnancy loss, artificial reproductive technology.

2.2 Introduction

2.2.1 Infertility

Infertility is defined by the World Health Organisation as, “a disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular protected intercourse”(40). Infertility is a significant global health issue. However, variances in infertility definitions internationally make calculations of prevalence difficult (481).Using consistent definitions of primary infertility (inability to have any live birth) and secondary infertility (inability to have an additional live birth), 48 million women world-wide were calculated to be sub-fertile in a 2010 global study across 190 countries (3). In Europe, the European Society of Human Reproduction and Embryology (ESHRE) approximate that 25 million or one in six couples, are affected (41). Consequently, the number of pregnancies conceived by Artificial Reproductive Technology (ART) is increasing. In 2015, 849,811 cycles of ART took place in Europe.(482) The reasons for increasing infertility are complex, with Western diet, obesity and environmental toxins attributed to falling sperm counts and reduced ovulation (483,484). While male factors exclusively account for 20-30% of infertility cases, they are contributory in up to 50% (484). Maternal age remains the single most important determinant of fertility (56,485). The current average age of first-time mothers in Europe is 29.5 years, and the number of primigravid women aged 40 and over is increasing (41). In addition, older mothers are more likely to have complications of pregnancy and to experience pregnancy loss (53,56).

2.2.2 Miscarriage and recurrent miscarriage

A pregnancy loss (miscarriage) is defined as the spontaneous demise of a pregnancy before the fetus reaches viability (18) . The term therefore includes all pregnancy losses from the time of conception until 24 weeks of gestation (18). There is increasing recognition that although miscarriage is common, occurring in 15% of pregnancies, it is also associated with subsequent adverse pregnancy outcomes (1). Recurrent miscarriage (RM) is a more debated definition. Stirrat defined recurrent pregnancy loss (RPL) as the loss of three consecutive pregnancies before viability (20), and this remains the position of the Royal College of Obstetrics and Gynaecology and the American Society of Reproductive Medicine (ASRM) today (21,23). ESHRE however defines RPL as the loss of any two pregnancies before viability (18). RM is also stipulated to describe cases where

all pregnancy losses have been confirmed as intra-uterine miscarriages (18). However, these terms are interchangeable within the literature. These broad definitions span a wide range in gestational age and do not confer significance to a second-trimester miscarriage, which has a different aetiology to very early pregnancy loss and where the pathology may be more aligned to that of stillbirth (33). Additionally, the gestation at which a first-trimester miscarriage occurs matters in relation to pathology and outcomes of subsequent pregnancies (486). Furthermore, this umbrella term of RPL implies a shared mechanism of loss, which may not be the case - even in the same woman. Recommendations regarding investigation and treatment cannot be wholly applicable to such a varied cohort and without clear categorisation, discerning any effects of clinical management can be challenging. In this review, RM refers to at least two consecutive first-trimester miscarriages (<12 weeks' gestation), inclusive of biochemical pregnancy, with any variances as per publication specified.

RM is calculated to affect 1-2% of the fertile population, but it is difficult to determine the exact prevalence (15). RM is recognised as a prognostic indicator for subsequent pregnancies and adverse pregnancy outcomes including antepartum haemorrhage, diabetes, preterm birth, small for gestational age and perinatal death (15). It is recognised that even when adjusted for the effects of ART, infertility is also an independent risk factor for adverse pregnancy outcomes, including preeclampsia, placental abruption, and placenta previa in spontaneous singleton pregnancies in women with a history of infertility compared with women in the general population (5). It is not unreasonable to conclude that a cohort of women experiencing infertility with subsequent RM would be at greater risk of pregnancy complications. Similarly, there are established psychological sequelae following adverse pregnancy outcomes and infertility (6,7). There is evidence that enhanced support in subsequent pregnancies following RM is an effective intervention and is welcomed by women, as is counselling of those experiencing infertility (410,420,487).

2.2.3 Recurrent implantation failure

Parallel to those experiencing RM after infertility are women who experience recurrent implantation failure (RIF), with shared experiences of infertility services and the disappointment of unsuccessful treatments. RIF is the absence of implantation after

repeated embryo transfers (52). There is no agreed international definition of RIF and a recent Canadian guideline counted 13 variations on the definition (52). These reflect inconsistencies in the number of failed embryo transfers, the number, stage and quality of embryo(s) transferred, as well as the definition of implantation (52). The ESHRE Preimplantation Genetic Diagnosis Consortium in RIF defined RIF as "three embryo transfers with high quality embryos or the transfer of ≥10 embryos in multiple transfers" with exact numbers to be determined by each centre (488). Implantation failure itself was defined as "the absence of a gestational sac on ultrasound at ≥5 weeks post-embryo transfer" (488). Women who experience infertility and subsequent pregnancy loss, such as RM or RIF after in vitro fertilisation (IVF) or other ART, are a cohort bearing a combination of complex losses and accordingly, would have similar needs for additional support in trying to conceive or in pregnancy.

Given the concerns raised about the guidance for RM (323,472), we hypothesised that current clinical guidelines would not incorporate women experiencing infertility and RM, and that a review of the guidelines and literature was merited. We anticipated that overlaps would exist in the care pathways of those experiencing RIF or RM after infertility, and thus the review was extended to include studies of the investigation and management of RIF.

2.3 Methods

The objective was to examine the literature regarding RM in women with infertility. Within this, the aim was to establish if women with a history of infertility were recognised in the literature pertaining to the investigation and management of RM. We sought to identify any common aetiology or risk factors for RM and infertility and current research interests. A further purpose was to determine if the specific needs of women (and their partners) experiencing RM and infertility were identified and subsequently incorporated into management or care strategies. These broad aims and the breadth of topics which needed to be explored precluded a systematic review.

Studies examining RM after primary or secondary infertility were included. Studies including RIF were also examined as it is often discussed alongside RM after ART. Published literature was retrieved through searches of PubMed and Google Scholar up to 21 January 2021 using appropriate controlled vocabulary and combinations of key words

(recurrent miscarriage, recurrent pregnancy loss, recurrent implantation failure, habitual abortion, infertility, assisted reproduction, assisted reproductive technology, and in vitro fertilization). The search was conducted without a timing restriction, but with prioritization of publications since 2010 to align with current guidelines and the latest research developments. Studies of all designs published in English were reviewed, and additional publications were identified from the bibliographies of these articles.

2.4 Results

The management of women or couples presenting with either infertility or RM is well described within international guidelines and the pursuit of new treatments is ongoing. In this overview, the common links between RM and infertility will be discussed, including age, aneuploidy, pre-implantation genetic testing (PGT), diminished ovarian reserve, male factors, implantation, as well as the current international guidance and the psychological impacts of these conditions.

2.4.1 Recurrent miscarriage and infertility

Although they are largely treated as separate entities, RM and infertility share many common risk factors. In an overview of these reproductive issues, Agenor and Bhattacharya identified maternal age, obesity, smoking, alcohol, medical conditions (specifically diabetes, polycystic ovarian syndrome, endometriosis, thyroid disorders, and cancer treatments such as radiotherapy and chemotherapy) and uterine defects such as polyps, fibroids and septae as being common to both groups (2). However, after assessment for anatomical defects, endocrine abnormalities, autoimmune disease, thrombophilia (RM cohort), infection (infertility cohort) and contributory male factors, up to 50% of those with RM and 30% of those with infertility will be left without explanation as to why they cannot achieve or maintain pregnancy (2). This implies that much has yet to be discovered in this area and reflects the complex process of conception.

2.4.2 The relationship between miscarriage and infertility

The literature demonstrates that infertility and miscarriage are likely to co-exist. As far back as the 1950s, an American prospective cohort study demonstrated that women who required at least six months to conceive were more likely to miscarry, with this effect augmented by a history of prior miscarriage and maternal age greater than 35 years (20). In structured interviews examining obstetric history for miscarriage risk factors in a

stratified random sample of Danish women in 1986, delayed time to conception (>1 year) was associated with a higher rate of miscarriage (489). Many European and American studies examined this link in the 1990s. Two large cohort studies of over 5000 women demonstrated times to conception for first pregnancies which ended in miscarriage were 1.68 and 1.23 times longer respectively, than the time to conception of live births (489,490). A smaller cohort study found that women diagnosed as having unexplained secondary infertility (n=43) had a three-fold risk of miscarriage and half the expected number of live births compared with the general population (491). A prospective observational study of 124 women found an increased rate of pregnancy loss in women with infertility compared to controls (70% vs 21%, relative risk (RR) 2.6) (492). In their retrospective cohort study of 3053 women, Whitley *et al.* found that women with primary or secondary infertility had an approximately fourfold increase in risk of fetal death (stillbirth or miscarriage) compared with women who reported no fertility issues [odds ratio (OR): 3.92; 95% confidence interval (CI): (3.02, 5.07)](493). Gray and Wu determined that miscarriage rates were higher in pregnancies preceded by infertility in a cohort of 1572 women (23% vs 14%, aOR = 1.71, 95% CI = 1.26-2.94)(9). A case-control study from 2007 showed that women who took over 12 months to conceive were twice as likely to miscarry (aOR 2.01, CI 1.42-2.84) (147). Women with a known fertility issue were also at greater risk of miscarriage, with those experiencing tubal causes having the highest odds, even after adjustment for fertility treatment (aOR 2.28, CI 1.24-4.20) (147).

The relationship between RM and infertility Is illustrated less frequently in the literature. In 1991, Cauchi *et al*. in a small (n=165) double-blinded randomized control trial of white cell immunization in women with RM, identified that higher order miscarriage (> 5), longer miscarriage history, increased intervals between conceptions and delayed or assisted conception, were associated with further subsequent miscarriage (494). Likewise, in 1994 Clifford *et al*. in a cohort of 500 with RM, 32% reported delayed time to conception (>12 months) and 23% received fertility treatment (495). More recently in 2016, Kling *et al.* endorsed this link between RM and infertility, demonstrating in an observational study (n=228) that couples with RM aged 35-39, who have had subfertility for over 3 years, with more than 3 miscarriages are less likely to conceive and have a live birth, with 17.9% (n=10) of those ages 35-39 developing secondary infertility (496).

This trend towards secondary infertility following miscarriage is demonstrated in other studies. The self-reported questionnaire data of 2983 women trying to conceive demonstrated a prolonged time to pregnancy following a miscarriage (OR=2.1, (1.4-3.0) p<0.001) (497). A prospective study of 70 women also demonstrated an increased time to conceive after miscarriage and decreased fecundity (OR 0.42, 95% CI 0.28-0.65)(498). A separate prospective cohort also showed a 35% decreased fecundity in women after two miscarriages, however numbers were small (n=23) and the decrease appeared to improve over 12 months (499).

These studies suggest that women with RM who have preceding infertility or delayed conception have lower live birth rates and are at a greater risk of further miscarriage and secondary infertility. These studies are not homogenous, with varying sample sizes and populations, as well as definitions for RM and infertility, and so are not directly comparable. Several studies are over 25 years old. Furthermore, some are retrospective and self-reported, increasing the risk of recall bias (500–503). Nonetheless, a definite trend is seen; RM following infertility is poor prognostic indicator for future live birth. Overlapping factors such as maternal age, aneuploidy, diminished ovarian reserve (DOR), male factors and implantation may offer insights and are reviewed below.

2.4.3 Other associations between RM and infertility

Maternal age

The dominant common link to both RM and infertility is maternal age. It is well established that there is a gradual decline in female fertility, with the effects most pronounced after the age of 35.(504) This is due to a combination of a reduction in the number of oocytes and a deterioration in oocyte quality. Studies using population registers of pregnant women in Denmark and Norway have demonstrated in very large cohorts that advanced maternal age is strongly associated with lower birth rates, maternal and fetal morbidity as well as miscarriage.(505–507) Age alone has an independent negative effect on fecundity. It is also evident that age is a greater predictor of pregnancy success than other markers of fertility such as follicle-stimulating hormone (FSH).(508) The risk of miscarriage in women aged 45 years and older is approximately 65%.(509) A consistent higher miscarriage rate and lower pregnancy and live birth rate is seen in older women, even in cases with IVF and oocyte donation.(510,511) This trend is commonly observed across all

European countries, despite advancements in IVF techniques.(482) Although age is an important prognostic indicator for future pregnancy, there are significant associations for younger women with RM and infertility which will be outlined below.

Aneuploidy

Aneuploidy is a definitive cause of pregnancy loss that is strongly associated with age.(512) Aneuploidy is any chromosomal condition that arises from having an additional (trisomy) or missing chromosome (monosomy). Aneuploidy is associated with pregnancy loss in RM and women with infertility. In RM, cytogenetic analysis of pregnancy tissue demonstrated aneuploidy and a cause for miscarriage in 80% of cases in women over 35.(513) Similarly, in an IVF population who had a sporadic miscarriage and subsequent cytogenetic testing, the rate of aneuploidy was 63% in those under 38 years and 80% in those older.(514) In other examinations of pregnancy tissue in RM cohorts however, the rate of aneuploidy in subsequent miscarriages appeared to be lower in women with more than two miscarriages than in those women experiencing sporadic miscarriage, and appeared to decrease further with successive miscarriages.(515–517) This trend was more evident in women under 35 with RM; older women regardless of RM history in these cohorts still demonstrated higher rates of aneuploidy.(514,515,517)

Cytogenetic testing only partially reveals the potential role of aneuploidy in miscarriage as many pregnancy losses are sub-clinical or occur at the implantation stage.(518) PGT has also demonstrated an increase in aneuploidy with maternal age, even in those embryos that appeared developmentally and morphologically appropriate.(519) Pre-implantation and sub-clinical pregnancy losses were suggested as explanations for unexplained infertility, that is, women were experiencing very early pregnancy losses, rather than failing to conceive.(520) This was refuted in a study of urinary hCG levels in 120 women prior to menstruation, which detected just one implantation in the infertile group against 30 in the control group.(521)

Aneuploidy can therefore explain a significant proportion of miscarriage in those over 35. More studies are required in younger women with RM and infertility to better understand the role of aneuploidy in their pregnancy losses. PGT offers an insight into the early embryo and a possible route to pregnancy for those with a history of aneuploid pregnancy.

2.4.4 Pre-implantation genetic testing

PGT is the process of screening cells from embryos for genetic diseases or chromosomal disorders prior to transfer during IVF. A recent review of the evolution of PGT over the last two decades discussed the change in genetic analysis and embryonic biopsy and applicability to couples with RM (522). Using earlier PGT, Rubio *et al*. demonstrated the percentage of abnormal embryos was significantly increased in women with RM compared with controls (70.7 vs. 45.1%, $p < 0.0001$), and that aneuploidy was significantly increased in younger women with RM ($P < 0.0001$) than in women ≥ 37 years ($P = 0.046$) (523). A review of studies using early PGT techniques demonstrates miscarriage rates were lower after PGT than natural conception (9% vs 28%) (524). A recent study compared the aneuploidy rate in women with idiopathic RM (≥2 miscarriages) undergoing PGT for aneuploidy (PGT-A) to a control group without a history of RM undergoing PGT for monogenic defects (PGT-M) (74). A higher rate of aneuploidy was observed in the RM group compared to the control group (57.4% vs 42% $p<0.001$), with a significant difference (48.9% vs 36.9%, $P<0.001$) observed in those under 35 years (74). A higher rate of miscarriage in the younger RM group despite euploid transfer was also seen (26% vs 3% $p=0.03$) (74). Shahine and colleagues noted women with RM with diminished ovarian reserve had a higher percentage of aneuploid blastocysts (57% vs 48%, $p=0.03$) and a higher incidence of no euploid embryos to transfer (25% vs 13%, $p=0.02$), with a significantly higher rate of aneuploidy in those <38 years (67% vs 53%, $p=0.04$) (84). A large study of 3,378 IVF cycles demonstrated an increased rate of aneuploidy among patients with RPL (not defined) (OR 1.330, $p < 0.001$), prior aneuploid pregnancy (OR 1.439, $p < 0.001$), or previous failed IVF cycles (OR 1.356, $p = 0.0012$) compared to fertile controls, even when adjusted for age (525). In an examination of PGT-A outcomes in women with RIF, RPL (stratified into late and early miscarriage) and other adverse pregnancy outcomes, women with higher order RIF (≥5) had increased aneuploidy compared to controls (48.8% vs 33%, $p = 0.02$), as did those with ≥4 early miscarriages (41% vs 33%, $p = 0.03$)(392). Compared to controls, the miscarriage rate in the RM cohort was higher (6.58% vs. 31.11%, $p < 0.001$, OR = 6.49) and the live birth rate was lower even after euploid transfer (53.49% vs. 34.18%, $p = 0.007$, OR = 0.56)(392).

These studies suggest that PGT-A detects significant levels of aneuploidy in RM and RIF cohorts and the transfer of euploid embryos does not diminish the risk of implantation

failure or miscarriage. This is in keeping with the chromosomal analysis of pregnancy tissue in RM cohorts; younger women with RM are more likely to miscarry euploid embryos (73,178,526). Recent guidelines and reviews on the topic still do not recommend the use of PGT-A in RM cohorts. A recent review of PGT-A, which was not focused on RM cohorts, highlights that the reduction in miscarriage rates is offset against the loss of potentially viable embryos due to false positives (527). Kirshenbaum and Orvieto echoed these concerns and called into focus the high false positive and false negative rates of the technique and questioned the methodology and interpretation of recent RCTs, and indeed the dissonance between the technique and the biology of the pre-implanted human embryo (205,528). The most recently published guideline on PGT-A reviewed just two studies focused on RM cohorts, (Murugappan *et al.* and Shahine *et al.*), and had no clear guidance for PGT-A in RM (529). Murugappan *et al.* in particular highlight the cost, with a 91% live-birth rate required for PGT-A to become cost effective for couples experiencing RM compared to expectant management (391). Greco *et al*. conclude that IVF/PGT-A is a very expensive way to reduce miscarriage, without increasing the chance of achieving a live birth, and indeed, "given the uncertainty about self-correction, false positive PGT-A results, and/or accuracy of a mosaic diagnosis, there is concern that one may be discarding embryos that may have resulted in healthy babies" (522). Further high-quality studies are necessary prior to recommending IVF or PGT in RM cohorts, particularly in younger women. Those with infertility requiring ART and subsequently experiencing RM also need greater analysis to determine the role of aneuploidy and any possible role for PGT.

2.4.5 Tests of ovarian reserve

Given the associations with age and aneuploidy, it is reasonable to consider egg quality and ovarian reserve as contributory factors in RM and infertility. Diminished ovarian reserve (DOR) refers to a reduced ovarian follicle count that is measured by FSH level, Anti-Mullerian Hormone (AMH) level or by ultrasound of the antral follicle count (530). It is hypothesized that women with low ovarian follicle counts also have reduced oocyte quality. These oocytes are at greater risk of abnormal development, including meiotic non-disjunction and subsequent aneuploidy, resulting in failed implantation or miscarriage (531). Women who have had an aneuploid pregnancy have so far not been

proven to have statistically significant DOR or earlier menopause, that is aneuploidy is not predictive of premature ovarian failure (81–83).

As mentioned above, Shahine *et al.* noted in a RM cohort (n=102) that aneuploidy rates were highest in women with DOR defined by AMH level <1ng/ml or FSH >10IU/ml on day three(84). Women with spontaneous conceptions with severe DOR (n=26, AMH <0.4ng/ml) were found to miscarry at twice the rate as those with AMH ≥1ng/ml (hazard ratio, 2.3; 95% CI, 1.3, 4.3), even with adjustment for age, race, history of RM and obesity (87). RM was associated with a low AMH (p=0.04), but just six women had RM (87). A systematic review included 15 studies (n=3,082 women) and showed that women with RPL (included losses <20 weeks) were more likely to have DOR, defined by low AMH levels, compared with women who did not have RPL, ([OR] 2.77; 95% confidence interval [CI], 1.41–5.46) and low antral follicle count (OR 2.45; 95% CI, 1.16–5.19) (88). Women with unexplained RPL also seemed to have a higher association with DOR compared with women whose RPL had a known aetiology, as measured by low AMH levels (OR 3.23; 95% CI, 1.81–5.76) (88). Wald *et al*. also noted DOR rates were higher in the unexplained RPL (two losses <20 weeks) cohort (n=177), compared to patients with an identified cause for RPL (n=87) (48% vs 29%, p =.005), and the DOR rate was increased in those under 38 years old with RPL (22% vs. 12%, p =.04)(89). Notably, these studies did not include chromosomal analysis of pregnancy tissue in investigations for RM and thus DOR and previous aneuploidy could not be correlated.

Abnormal AMH results can also signpost to other disorders associated with RM and infertility. Low AMH levels are also associated with endometriosis, a disorder of ectopic endometrial tissue (532). Infertility affects 11.6% of women with diagnosed endometriosis (533). Endometriosis is also implicated in RM and RIF (47,276). AMH is not however a definitive diagnostic test for endometriosis. Conversely, higher levels of AMH (>10ng/ml), are associated with polycystic ovarian syndrome (PCOS) (534). Diagnostic hallmarks of PCOS include oligo or anovulation, hyperandrogenism, and antral follicular excess on ultrasound (535). It is thus associated with anovulatory infertility and RM. Higher AMH levels in women with PCOS appear to be associated with poorer ART outcomes (536). However, PCOS can be diagnosed by clinical history and ultrasound, and

thus the role of AMH in women with PCOS in addition to RM and infertility has yet to be determined.

Overall, ovarian reserve testing in women with RM and infertility does not appear to generate a clear management strategy. The conclusion of the above studies is that a low AMH result would facilitate counselling regarding the prospects of spontaneous conception (88,537,538), and may direct care towards PGT or oocyte donation (88). Ovarian reserve testing merits RCTs in more defined cohorts of women with infertility and RM if it is to have such a pivotal role in ART counselling (87,88).

2.4.6 Male fertility

Male factors are an important yet often overlooked link between RM, infertility and aneuploidy. After three miscarriages, most guidelines recommend parental karyotyping (23,539). While balanced translocations are found more frequently in RM populations, they are still uncommon overall, and a small proportion are attributable to the male partner (362). Globally, male fertility rates are in significant decline (540). Further, advanced paternal age (APA) (<40 years) appears to be a more common and significant risk factor for infertility and RM than previously thought (1,541). APA is a suggested contributor to sperm DNA fragmentation and aneuploidy (541). Sperm DNA fragmentation is the "separation or breakage of DNA strands into pieces" (362). Several case-control studies have now associated sperm aneuploidy with RPL (354,356,358), and that aneuploidy was higher in those men with a RM history, even with a normal sperm count and morphology (354). Conversely, Coughlan *et al*. found variances in sperm DNA fragmentation testing parameters and no clear evidence of an association with RM or RIF (50). The clinical significance of sperm aneuploidy, and subsequent management, is uncertain (542). Advanced sperm selection techniques are often paired with intra-cytoplasmic sperm injection to ensure structurally intact and mature sperm with high DNA integrity are chosen for fertilisation (365). A Cochrane review found that there was insufficient high-quality evidence for sperm selection techniques in RM cohorts to improve live birth rates or reduce miscarriage rates, as did other reviews (365,528,542,543). The Society for Translational Medicine clinical practice guidelines suggest sperm DNA fragmentation testing should be done for cases of unexplained fertility, failed IUI and in RM (544). After initially advising that testing for spermploidy or

DNA fragmentation should not be done in RPL (23), the ASRM conceded that sperm aneuploidy testing may be of some benefit in RM or recurrent IVF failure, but needed further study (545). In cases of RM and infertility, the male contribution merits greater consideration, as unlike the oocyte, factors affecting sperm quality such as alcohol, smoking and presence of a varicocele are modifiable (362). The role of sperm studies beyond semen analysis in RM and infertility and their clinical application remains unknown.

2.4.7 Implantation Processes

Cytogenetics and PGT have demonstrated that women with infertility may still experience RM even in the absence of aneuploidy. The processes of fertilization and implantation are complex, and a number of reviews have attempted to shed light on the multiple systems which work collectively for successful implantation to occur (546–548).The endometrium has an active role in receptivity, signalling and cell recruitment (549–552). This is influenced by the health or genetic make-up of the embryo, which signals to the endometrial decidual cells, permitting or rejecting implantation (552). A current theory is that disruption of these signalling processes allows aneuploid embryos to implant in a "highly receptive" decidualised endometrium, resulting in "superfertility" and consequently, RM (551,553). However, this process appears to be associated with short times to conception (<3 months) and is thus less likely in infertile cohorts, but superfertility rates of 32% have been found in the RM population (554,555). Conversely, a "highly selective" endometrium results in delayed conception or recurrent implantation failure (551).

The identification of the cellular and molecular mechanisms involved in endometrial receptivity and decidualization is ongoing in a search for clinically applicable therapies. Natural killer (NK) cells have been of particular interest, and while they play a role in pregnancy maintenance, their relationship with cell receptors, cytokines and hormones, and their role in infertility and RM remains unclear (289,551,556). Endometrial biopsy or "scratch" prior to implantation of an embryo has been purported to increase implantation rates, particularly in the RIF cohort (557). The biopsy allows for examination to diagnose chronic endometritis and quantification of uterine natural killer cells, but the resulting

endometrial injury is also proposed to increase growth factor and cytokines which improve endometrial receptivity (557). In a recent review, Günther *et al.* point to two large reviews in RIF populations, one meta-analysis (n=2062) (558) and a Cochrane review (n=1063 (intervention), n=1065 (controls)) (559), which showed an increase in pregnancy rates following endometrial "scratch" (560). However, a recent robust RCT with 1063 patients in each arm, demonstrated no difference in birth rates (adjusted OR, 1.00; 95% confidence interval, 0.78 to 1.27) and sub-group analysis showed no benefit to women with RIF (estimated interaction OR, 0.63; 95% CI, 0.35 to 1.15; P = 0.14) (561). Considering the evidence quality of the preceding reviews, Günther *et al.* concluded that endometrial "scratch" should no longer be offered (560). There are no published results of RCTs in RM cohorts, and the results of the Scratch in Miscarriage trial are awaited (562).

Endometrial biopsy in women with endometriosis has produced some potential insights into RM and infertility. Endometriosis is known to cause structural and functional abnormalities to the hypothalamic-pituitary-ovarian-endometrial axis and thus affects conception, endometrial receptivity and may contribute to embryonal loss.(563,564) Additionally, endometriosis can take four to 11 years to diagnose.(565) Freitag *et al.* demonstrated that women with RIF and endometriosis (n=67) were 1.3 times more likely to have chronic endometritis compared to controls without endometriosis, as demonstrated by raised plasma cell counts on endometrial biopsy.(566) This is potentially amenable to doxycycline therapy and merits further study to determine the impact on pregnancy rates and outcomes. Fox *et al.* (2019) performed endometrial biopsies in women with RM (n=29) or unexplained infertility (n=53) and examined the levels of a postulated marker for endometriosis, nuclear protein B-Cell CLL/lymphoma 6 (BCL6), in endometrial samples. A subset of cases with abnormal BCL6 went to laparoscopy, and endometriosis was found in 9 out of 11 cases of RM and in 20 out of 21 cases of unexplained infertility.(567) While endometrial biopsy may direct further research in the context of endometriosis, these small studies are insufficient to support routine use in women with RM and infertility.

Immunotherapy has also been a focus of research in these cohorts. Recent systematic reviews have sought to establish if any immunotherapies have made a significant impact

on live birth rates, pregnancy rates or miscarriage rates in RM cohorts(568–571) and RIF cohorts,(572,573) as have a number of literature reviews.(574–578) While Achilli *et al*. looked at women undergoing IVF with and without RM, no specific work has been done in infertility cohorts experiencing RM. A review of five studies demonstrated intravenous immunoglobulin (IVIG) increased live birth rates and pregnancy rates in RIF populations, but did not find a significant difference in miscarriage rates.(572) Christiansen *et al*. performed sub-analyses on 13 RCTS in which meta-analyses had shown no benefit to IVIG in RM populations and found some increase in live birth rates in RM populations who received IVIG (RR 1.17, 95% CI 0.95-1.44, p=0.14).(571) A more focused review of women with RM and abnormal NK cell activity/levels found potential benefit in offering immunotherapy to such women but this covered just seven studies and one RCT (intravenous immunoglobulin (IVIG) (four studies), prednisolone, etanercept and intralipid (one study each)).(573) These reviews concluded that there is a paucity of well-designed and adequately powered RCTs in this area and that significant further research is required in order to make clear recommendations. Furthermore, there is no consensus on the function of NK cells (peripheral or uterine), how best to measure cell levels or activity, what immunotherapy is most appropriate, and if these therapies are safe to use in a pregnant population.(573) These costly investigations and therapies merit rigorous examination in RCTs prior to recommendation.(573) Genes have been identified related to implantation and immune pathways in RPL and fertility cohorts which may better direct biomolecular research and identify future genetic or immune therapies.(579–582)

2.4.8 International Guidelines Related to Recurrent Miscarriage

Current guidelines in RM and related conditions such as thrombophilia and thyroid disease do not provide substantial guidance with regards to investigation or treatment of women with infertility and RM. In their 2017 guideline, ESHRE mention that a history of infertility should have a bearing on investigations, and reference the works of Cauchi *et al*. in acknowledging that delayed time to conception in RM can affect pregnancy prognosis; however, they do not make any specific recommendations for care of this cohort (18). Four RM guidelines make reference to IVF treatment but in the context of PGT-A or sperm DNA fragmentation studies, which the guidelines do not currently recommend (18,544,583,584). American Thyroid Association guidelines on thyroid disease recommend that thyroid stimulating hormone is measured in women with

infertility or RM, and that thyroid peroxidase antibodies should be measured in women with RM and/or infertility (233,585). Wall *et al*. provide guidance on imaging in this cohort (586). The remainder of guidelines on RPL do not discuss infertility in this cohort (30,539,587–589). A recent publication highlighted how national clinical guidance was inconsistently applied by clinicians in RPL clinics during investigation and treatment of women with RM, but did not discuss the management of women with infertility and RM (323). A recent Lancet Series on miscarriage found that despite ample clinical guidance, "clinical practice is inconsistent and poorly organised" (14). A graded care plan for women with sporadic and recurrent miscarriage was suggested, focused on evidence-based investigations and treatments, with additional supportive care (14). While this Series brings much-needed attention to early pregnancy care and the needs of those experiencing miscarriage, RM after infertility was not addressed. Thus, in the absence of high-quality evidence and robust clinical guidance, the management of this cohort requires greater scrutiny and directed research efforts.

2.4.9 Psychological Impact of Recurrent Miscarriage and Infertility

The majority of guidelines acknowledge the psychological needs of the RM population (18,23,30,584,588,589). However, there is no mention of the additional psychological needs of those with infertility or who are undergoing ART. The wider literature, while it addresses the psychological impacts of infertility (7,590) and RM (6,399) treats them as discrete entities. Women with RM are at increased risk of high stress and moderate to severe depression (591). Research also demonstrates that they would like increased support, as well as awareness of the psychological impact of their experiences (406,592),and the recognition from medical staff of an individual life event (593). Infertility is also associated with depression and anxiety, with stresses exacerbated by financial concerns (425). It would follow that women experiencing infertility and subsequent RM would be at high risk of psychological morbidity (590). The sole qualitative study of women experiencing miscarriage after infertility identified that they feel "profoundly alone and grieve intensely" (437).Additionally, these women feel responsible for the loss, face significant financial burdens and find it difficult to hope that they will ever become pregnant again (437). RM and infertility also impact on male partners, however current care models can place men in secondary roles with limited opportunities to articulate their loss and grief (413,594). The specific needs of those men and women in

their fertility and antenatal care are largely unidentified and likely unmet by current clinical guidance.

2.5 Discussion

We sought to examine the literature regarding RM in women and couples with infertility, and to identify gaps which could be addressed in future research. It is evident that this cohort are not recognized in the literature and international clinical guidance. We found that women with infertility feature within RM cohorts but are not highlighted as a distinct group. The literature suggests that women experiencing RM with a history of infertility would be at increased risk of further miscarriage and secondary infertility, in addition to lower live birth rates, but more studies are needed to examine pregnancy outcomes in detail. Aneuploidy plays a significant role in RM in women over 35. However, declining aneuploidy rates in successive miscarriages in younger women with RM and infertility deserves greater scrutiny. Further, persistent higher aneuploidy rates compared to controls, but lower successful euploid transfer, indicates more high-quality studies are required to determine any role for PGT or DOR testing in those under 35. In addition, the mechanisms behind successful implantation are not fully understood and larger high-quality RCTs are required to determine the benefits of investigations and immunotherapies. The male contribution to RM and infertility is likely underestimated and potentially improved by lifestyle modification; thus meriting greater consideration and investigation. Furthermore, the lived experiences of women and their partners following RM and infertility and their subsequent needs are sparsely documented and are deserving of attention. The international guidelines on RM reflect the lack of high-quality studies and qualitative research and thus fail to consider women and couples with concomitant infertility in recommendations for investigation, treatment and supports in future pregnancy.

Our study has several strengths. This examination of the literature has not been previously conducted to date. It identifies important gaps in the care of women with RM and infertility and their under-representation as a distinct cohort in research. Limitations must also be noted. While all English language study types were included, we did not formally assess the quality of studies. Further, we aimed to identify the over-lapping issues

between RM and infertility, not the particular conditions, investigations or managements linked to each individual topic. The broad definition of RPL prevents proper stratification and comparison of different types of pregnancy loss, which could advance knowledge in this area. This study has nonetheless (attempted to) established the current state of knowledge and future research areas.

This research identifies a distinct gap in the literature. Women with infertility and subsequent RM are not adequately considered. This may be due to several potential reasons, including a lack of identification of women experiencing RM in infertility cohorts, or a focus on spontaneous conceptions within RM cohorts. These cohorts are also compromised by women without fertility problems undergoing IVF as a treatment for RM (528), a decision which in itself merits further exploration as to whether this is driven by clinicians or women seeking these services.

2.6 Conclusions

In conclusion, this examination of the literature shows that women and men experiencing infertility and RM are not well represented. Although there is significant overlap between infertility and miscarriage, including but not exclusive to; advanced maternal age, aneuploidy, DOR, PCOS, endometriosis, there is no clear unifying aetiology. Rather, this is a complex cohort of women where – in addition to co-morbidities and parallel pathologies – they are grieving the loss of wanted pregnancies and, with trepidation, are contemplating future pregnancy and associated medical treatments. It is unclear from current RM guidelines how best to manage this cohort. The focus of research appears to be on costly investigations, ART and immunotherapy, which are not based on strong evidence. There is limited research on pregnancy outcomes, with a concentration on rates of implantation and live births. Further studies are warranted in women and men with infertility and RM to examine pregnancy outcomes, to review investigations and treatments currently used, and qualitative research is required to identify their medical and psychological needs. Such findings can initiate better supports for this vulnerable group which are currently underserved by the published literature and in clinical guidance.

Chapter 3 – Evidence-based care in Recurrent Miscarriage

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Chapter 3 – Evidence-based care in RM

3.1 Chapter overview

This chapter will set out the role I undertook in leading the development and writing of the first National Clinical Practice Guideline (CPG) on behalf of the National Women and Infants Health Programme (NWIHP) and the Institute of Obstetricians and Gynaecologists (IOG) of the Royal College of Physicians in Ireland. This chapter will also outline my roles within the Recurrent Miscarriage: Evaluating Current Services, RE:CURRENT Study, (discussed in Section 1.6.4) and how the studies conducted within this project and this thesis contributed to the development of the recommendations for RM care.

3.2 Development of the RM Guideline

3.2.1 Guideline development process

The Guideline Development Group comprised of Marita Hennessy, PhD (Postdoctoral Researcher), Dr Azy Khalid (Consultant Obstetrician and Gynaecologist), Ms Jill Whelan (Clinical Midwife Specialist in Bereavement & Loss), Professor Keelin O'Donoghue (Consultant Obstetrician and Gynaecologist) and I. The objective of the guideline was to provide a comprehensive, evidence-based guidance for the management of RM within the Republic of Ireland (ROI). This guidance was to encompass the structure of care, supportive care, investigation and treatment of RM, as well as care in a subsequent pregnancy. The primary target users of the guideline were primary, secondary and tertiary health and social care professionals who are involved in the care of women/couples with recurrent miscarriage. I wrote the Guideline with the support of the Guideline Development Group, under the direction of the Guideline Programme Team (Prof Keelin O'Donoghue and Ms. Nicolai Murphy). Stakeholders with lived or professional experience of RM were also involved in the development of the Guideline, as well as the review of the final document (595). The Expert Advisory Group for the National Maternity and Gynaecology Clinical Guideline Programme reviewed the Guideline prior to submission for final approval by the National Women and Infants Health Programme and Royal College of Physicians of Ireland. Details on the members of this group and the formal

Guideline development process and governance is in Appendices 4 and 8 of the Guideline (595).

3.2.2 Guideline content

The Guideline was informed by the recommendations for clinical care identified through the RE:CURRENT Study, in addition to the findings of the literature review conducted for this thesis (Chapter 2). I performed further reviews of the literature for individual topics to ensure that the Guideline contained the most up to date evidence at the time of publication.

Identification of the recommendations for clinical care

The RE:CURRENT Study evaluated recurrent miscarriage (RM) services in Ireland to inform efforts to standardise and improve the quality of these services (471). It was funded by the Health Research Board (HRB) Ireland (ILP- HSR-2019-011) (471) . One of the initial goals of this project was to identify what the current recommendations for RM care were within the international literature, namely within CPGs for RM or associated conditions. These recommendations were then used to develop Key Performance Indicators (KPIs) for RM care. KPIs are specific and measurable elements of health and social care, based on standards determined through evidence-based academic literature and/or through the consensus of experts, which can be used to assess care quality (596). These KPIs were employed for a national service evaluation of RM care (34), and adapted for use within the service evaluation of RM and infertility care (chapter 5) and the audit of RM and infertility care (chapter 6) within this thesis. The identified recommendations for clinical care subsequently formed the scaffold for the development of the National Clinical Practice Guideline in RM.

Overview of the development of KPIs

The development of the KPIs involved six stages which will be discussed briefly in this section under two headings:

1. Development of a list of recommendations and outcomes from which KPIs could be generated [stages 1-3]
2. Generating, refining and agreeing a suite of KPIs [Stages 4-6] (475).

These processes were carried out using a protocol developed according to the Guidelines International Network Performance Measures Working Group reporting standards for guideline-based performance measure development and re-evaluation (597). They are described in detail in the accompanying research papers provided in Supplementary files 1 and 2. An overview is presented in fig 3.1.

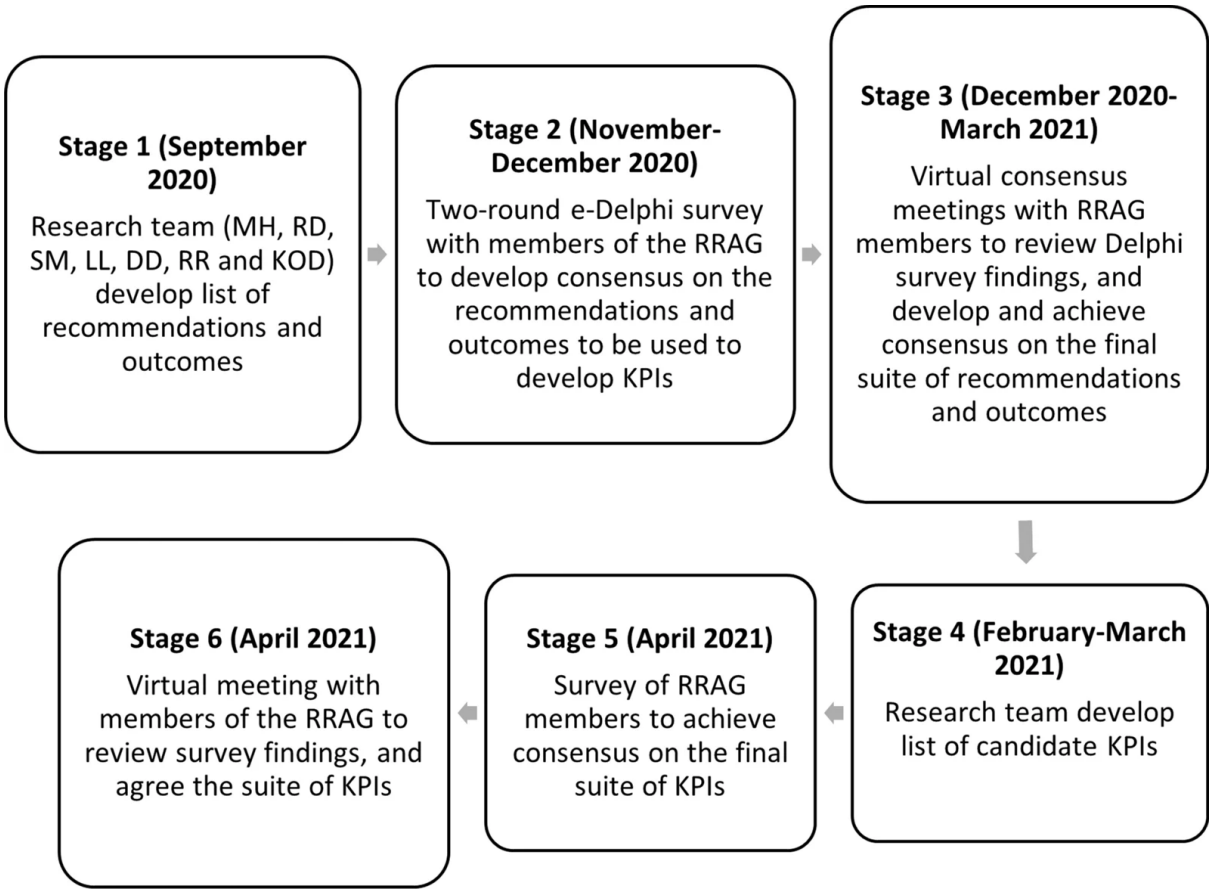


Fig 3.1 The KPI Development Process (475)

1. Development of a list of recommendations and outcomes from which KPIs could be generated (stages 1 to 3)

Clinical practice guidelines (N=32) for the investigation, management, and/or follow-up of recurrent miscarriage within high-income countries, published between January 2000 and March 2020 were identified through a systematic review of major databases, guideline repositories, and the websites of professional organisations (472,598). The quality of each clinical practice guideline was assessed using the Appraisal of Guidelines for Research and Evaluation (AGREE II) Tool, a validated tool (599), independently by three

authors (MH, SM and LL). The review and synthesis of guideline recommendations was published in a peer-reviewed journal (see full paper in Supplementary File 1) (472).

All recommendations relevant to the investigation, management and follow-up of recurrent miscarriage from the included CPGs were then extracted without restriction (n=373), alongside the strength of evidence and grade of recommendation where available. Members of the research team (KOD, SM, MH, RD and LL) reviewed and synthesised recommendations from the clinical practice guidelines identified in the systematic review, together with findings from qualitative interviews with service providers and women and men with experience of recurrent miscarriage regarding their views and experiences of current services (408,475). We also identified outcome metrics through the extant literature and topic/clinical expertise within the research team (475). The resulting 373 recommendations and 14 outcomes then went forward to the next stages of the KPI development process.

The subsequent five stages were undertaken with the support of the RE:CURRENT Research Advisory Group (RRAG) which comprised 22 individuals with clinical, methodological and lived experience: healthcare and allied health professionals, representatives from advocacy and support organisations, those involved in the administration, governance and management of maternity services, academics, and women and men who have experienced recurrent miscarriage. Due to the COVID-19 restrictions in place at the time (end 2020 to mid-2021), Stages 2 and 3 were conducted remotely, as described briefly here.

- *Stage 2: Development of consensus on the recommendations and outcomes to be included in the development of a final suite of KPIs for recurrent miscarriage care—e-Delphi surveys.*

  Duplicate recommendations were removed by the study team (KOD, SM, MH, RD and LL) to simplify the processes; 201 recommendation/outcomes were brought forward to the online Delphi surveys for rating and review by the RRAG.

- *Stage 3: Development of consensus on the recommendations/outcomes to be included in the development of a final suite of KPIs for recurrent miscarriage care—consensus meetings*

  Four online consensus meetings were held with the RRAG to discuss and vote on which recommendations should be brought forward, which reduced the number of recommendations/outcome measures from 201 to 113.

2. Generating, refining and agreeing a suite of KPIs

The recommendations and outcomes generated then underwent the remaining three stages of the KPI development process as shown in Figure 3.1, which will be very briefly described here.

- *Stage 4: Translation of recommendations into candidate KPIs*

  The research team (KOD, SM, MH, RD and LL) generated 117 KPIs from the 113 recommendations and outcomes agreed during Stage 3 and four additional outcomes/KPIs suggested.
- *Stage 5: Achieving consensus on the final suite of KPIs— survey*

  The RRAG then voted online on which KPIs should be retained and provided feedback on their wording or clinical applicability, resulting in a final suite of 110 KPIs.
- *Stage 6: Virtual meeting to review the survey findings and agree the final suite of KPIs*

  There was a final meeting to confirm the suite of KPIs in the context of the above vote and to provide feedback on the process.

This extensive process is detailed in the published peer-reviewed article (475) provided in supplementary file 2. The adaption of the KPIs for the inclusion within the service evaluation of infertility and RM services (Chapter 5) and the audit of RM and infertility care (Chapter 6) is detailed within each chapter of this thesis.

3.3 Development of the CPG

In order to fully utilise the work undertaken in identification and assessment of the recommendations for RM care, namely the systematic review and the consensus process, the ADAPTE process for guideline adaptation was undertaken to develop a guideline for

RM. The ADAPTE process takes into consideration that guideline development utilises significant resources and facilitates standardised guideline adaptation that "takes advantage of existing guidelines in order to enhance the efficient production and use of high-quality guidelines" (600). Moreover, it allows for recommendations to address specific health questions in the context of particular health settings as well as considering relevant needs, priorities, legislation, policies and resources (472).

The ADAPTE process has 22 steps, divided into three main phases:

1. Set-up phase (steps 1-6)

   The set-up phase is primarily the assembly of the team to be involved and planning for the resources and skills required. This process over-lapped significantly with the initiation of the RE:CURRENT Study and establishment of the RRAG.

2. Adaption phase (steps 7-18)

   The adaption phase is the longest part of the ADAPTE process. It involves a systematic review of guidelines, screening the selected guidelines using the AGREE II tool, narrowing down guidelines based on quality, currency, content, consistency and considering the acceptability and applicability of recommendations. The systematic review of guidelines on RM and the assessment with the AGREE II tool aligns with the 'Search and Screen and Assess Guidelines' aspects of the ADPATE process (steps 8 to 15). The extraction of recommendations and discussion and achievement of consensus on the KPIs also aligned strongly with the Decision and Selection Modules of the ADAPTE process (steps 16 and 17).

3. Finalisation phase (19-22)

   This phase involves seeking external review of the guideline and acknowledgement of the contributing guidelines, which are covered within the NWIHP guideline development processes and set out in the final guideline (595).

While the RRAG was not assembled for the purposes of guideline development and does not fully equate to a guideline development group, the overlap of the KPI development

process and the ADAPTE process was evident. To essentially replicate this lengthy and complex process with a similar group of stakeholders to produce similar results and recommendations would not have been justified in terms of time and resources. Thus, the decision was made to proceed to guideline development with adoption or adaption (following an updated review of the literature, where necessary) of the recommendations identified and agreed by the RRAG.

A new guideline development group was established (LL, MH, JW, AK and KOD) to write the guideline on behalf of the NWIHP and the IOG. The group used the recommendations, quality assessments and underpinning evidence gathered from the guidelines as well as at consensus meetings to generate up-to-date recommendations. This involved meetings for discussions about which recommendations from existing guidelines to adopt and/or adapt. The AGREE II scores from the systematic review had some bearings on which guidelines to include, but ultimately the currency and standing of the updated RCOG and ESHRE guidelines meant they were the best candidates for adaptation (32,35). Select recommendations on niche topics were retained from other guidelines also. Overall, the 113 recommendations and outcome measures were adapted to become 58 key recommendations within the guideline. This condensation was to merge similar recommendations or encompass key points and to aid functionality of the guideline.

Due to the number of international guidelines used in this guideline and the variation in how the evidence and strength of recommendations were graded, it was decided by the Guideline Development Group to retain the grading as per guidelines of origin. Thus, evidence strengths from international guidelines were retained and a modified version of GRADE recommendations was used (601). The Guideline Development Group accepted that this translation may not be wholly accurate. Good Practice Points were developed by the group to provide guidance on important aspects of RM management that had little existing evidence base but were agreed by consensus, from either the Guideline Development Group or previously from the RRAG. These were highlighted within the Guideline.

3.4 Publication of the RM Guideline

The first draft of the guideline was compiled in June 2022. It was reviewed by the Guideline Programme Team and recommendations for change were made regarding

layout and content. A further draft version was sent to the Oversight Group for the National Standards for Bereavement Care Following Pregnancy Loss and Perinatal Death in August 2022, as well as to stakeholders with relevant professional expertise, for review with incorporation of comments and appraisals. The Guideline was then reviewed by the Expert Advisory Group in September 2022. An updated version of the Guideline incorporating their recommendations was then sent to the Clinical Advisory Group for NWIHP in October 2022. The final version of the Guideline was approved in December 2022.

The finalised National Clinical Practice Guideline for RM was published in January 2023 and is available for review at https://www.rcpi.ie/Faculties-Institutes/Institute-of-Obstetricians-and-Gynaecologists/National-Clinical-Guidelines-in-Obstetrics-and-Gynaecology. The summary of recommendations is presented here to provide an overview of the guidance for the management of RM.

3.5 Quick summary document: recurrent miscarriage

This Quick Summary Document (QSD) is a resource for all clinicians working in healthcare in Ireland who are involved in the care of women/couples with Recurrent Miscarriage.

Following a comprehensive literature review a number of evidence-based recommendations for management of Recurrent Miscarriage were agreed upon.

Key Recommendations

3.5.1 Structure of care

1. Investigation/evaluation of women/couples with RM can proceed after two consecutive pregnancy losses.
2. Couples should be referred to a RM clinic; this should have the appropriate staffing and clinical expertise, be appropriately located, with access to the required equipment and facilities.
3. Written information should be given in advance of appointments in the RM clinic, and further written information should accompany explanation of investigative findings, treatments and future pregnancy plans.

3.5.2 Counselling and supportive care

4. Psychological counselling and support should be offered to couples with RM and be tailored to their needs.

3.5.3 Investigations

5. Medical, obstetric (for women) and family history should be used to tailor diagnostic investigations for women and men experiencing RM.
6. Maternal age and previous pregnancy history offer the best available prognostic information.
7. Advise women/couples regarding changes to potentially modifiable risk factors as relevant, including smoking cessation, maintaining a BMI between 19-25, healthy eating and physical activity (normal exercise pattern; not excessive), abstaining from alcohol and drug consumption (including caffeine, which should be reduced to <200mg/day).
8. Routine antenatal advice regarding folic acid and vitamin D supplementation should also be given.

9. Information and explanation about RM should be provided, in particular; the challenge in identifying a cause, the lack of evidence-based treatments and that there is an excellent prognosis for future pregnancy outcome without pharmacological intervention if offered supportive care alone in the setting of a dedicated early pregnancy assessment unit.

Anatomical investigations

10. As part of standard investigations for RM, women should have a pelvic ultrasound performed by an experienced ultrasonographer, with 3D ultrasound available if required to diagnose uterine anomalies.
11. Magnetic resonance imaging (MRI) is not recommended as first line option for the assessment of uterine malformations in women with RM but can be used where 3D ultrasound is not available and/or to examine complex malformations in greater detail.
12. It is recommended that imaging or imaging with hysteroscopy should be used to diagnose uterine septa rather than laparoscopy with hysteroscopy because this approach is less invasive.
13. If a Müllerian uterine malformation is diagnosed, further investigation (including investigation of the kidneys and urinary tract) should be considered.
14. At a minimum, all women should have a 2D transvaginal ultrasound to exclude any contributory gynaecological pathology.

Immunological screening

15. Women with recurrent miscarriage should not be offered routine immunological screening (such as HLA, cytokine and NK cell tests) outside of the research context.

Haematology

16. For women with RM, screening for hereditary thrombophilia should not be undertaken, unless:
    - in the context of research.
    - in women with additional risk factors and after consultation with local haematology services.

17. For women with RM, we recommend testing for antiphospholipid antibodies after two miscarriages.
18. The recommended antibodies for testing are lupus anticoagulant, anticardiolipin antibodies (IgG and IgM), and β2 glycoprotein I antibodies (IgG and IgM).

Metabolic and endocrinologic factors

19. Thyroid stimulating hormone (TSH), thyroid peroxidase antibody (TPOab) levels and free thyroxine (FT4) levels should be tested routinely in women with RM.
20. There is insufficient evidence to support testing prolactin levels, luteal phase insufficiency, androgens, PCOS or vitamin D.
21. In select cases with a relevant menstrual or fertility history, testing 'day 2-5' hormone profile, LH, FSH, oestradiol and/or testing for ovarian reserve may be appropriate.

Infectious screening

22. Infectious screening in asymptomatic women using vaginal swab specimens is not recommended.

Screening for genetic factors

23. Cytogenetic analysis should be performed on pregnancy tissue of the third and subsequent miscarriage(s) or on the second and subsequent miscarriage if aged <35 years and no prior livebirth.
24. For genetic analysis of the pregnancy tissue, standard procedures for testing should have due regard for maternal cell contamination and risk of test failure, as well as the ability to detect chromosomal anomalies especially relevant to recurrent first-trimester miscarriage.
25. Parents should not undergo routine peripheral karyotyping. Karyotyping may be performed however after individual assessment of risk or if there is no pregnancy tissue available for testing after the third miscarriage or second miscarriage if aged <35 and no prior livebirth.
26. All individuals and couples with an atypical parental karyotype result, and a proportion of those with an atypical fetal karyotype, should be offered genetic counselling.

Histopathological Investigations

27. Any available histopathological results from previous miscarriages should be reviewed to ensure that placental pathologies with a recurrence risk, such as chronic histiocytic intervillositis or massive perivillous fibrinoid deposition, are not missed.

Investigations for male factors

28. In couples with RM, it is recommended to assess factors in the male partner that may contribute to sperm health (paternal age, smoking, alcohol consumption, medications, exercise pattern and body weight).
29. Couples with RM should not be offered routine sperm DNA fragmentation screening outside of the research context.

3.5.4 Treatment

Anatomical factors

30. There is low-quality evidence in favour of hysteroscopic uterine septum resection that suggests a reduction in miscarriage rates, but no improvement in live birth rates.
31. Metroplasty in women with bicorporeal uterus and double cervix (former American Fertility Society (AFS) didelphic uterus) and RM is not recommended due to insufficient evidence that it reduces miscarriage or improves livebirth rates.
32. Uterine reconstruction is not recommended for hemi-uterus (former American Fertility Society (AFS) unicornuate uterus) and RM due to insufficient evidence that it reduces miscarriage or improves livebirth rates.
33. Selection and treatment of women for hysteroscopic metroplasty of a uterine septum should be done by a multidisciplinary team including specialists in reproductive medicine, uterine imaging and hysteroscopic surgery.
34. Surgical management of acquired uterine anomalies are not recommended due to insufficient evidence at present, but it may be considered for select cases.

Immunological treatments

35. Immunotherapies (such as corticosteroids, intralipid, lymphocyte immunity factor, granulocyte colony- stimulating factor, tumour-necrosis factor -α blockers) are not recommended to women with unexplained RM due to insufficient evidence.
36. Paternal cell immunisation, third-party donor leucocytes, trophoblast membranes and intravenous immunoglobulin in women with previous unexplained RM are not recommended as they do not improve the live birth rate.

Treatment for thrombophilia

37. For women with hereditary thrombophilia and a history of RM, antithrombotic prophylaxis should not be used unless in the context of research, or if indicated for VTE prevention.
38. For antiphospholipid syndrome – if laboratory and clinical criteria are fulfilled, referral to local haematology service should be considered and potential for treatment with low dose aspirin (75mg) and prophylactic LMWH in next pregnancy discussed.
39. For APLS, treatment with low dose (75mg) aspirin should commence before conception and prophylactic LMWH must be initiated as soon as the pregnancy test is positive.

Treatment of endocrine factors

40. Overt hypothyroidism arising before conception or during early gestation should be treated with levothyroxine in women with RM.
41. There is low-quality evidence that levothyroxine (LT4) treatment of women with mild-moderate sub-clinical hypothyroidism (TSH levels: 4.0-10mIU/l) is associated with improved pregnancy and livebirth rates; there is insufficient evidence of benefit in women with upper normal TSH concentrations (2.5-4.0mIU/l). Treatment of women with upper normal TSH levels may reduce the risk of miscarriage, but the potential benefit of treatment should be balanced against the risks.
42. There is insufficient evidence to support treatment with levothyroxine in euthyroid women with thyroid antibodies and RM outside a clinical trial.

43. 400mcg vaginal progesterone twice daily may improve livebirth rate in women with one or more miscarriages and vaginal bleeding in a subsequent pregnancy.
44. Bromocriptine treatment can be considered in women with RM and hyperprolactinemia to increase live birth rate.
45. There is insufficient evidence for HCG supplementation or metformin in the treatment of RM.

Infectious factors

46. Given the lack of prospective studies linking any infectious agent to RM, any use of antibiotics is not supported by the evidence and therefore should not be recommended.
47. There is no evidence to recommend endometrial scratching or biopsy in women with unexplained RM.

Genetic factors

48. Options for couples with chromosomal rearrangements include attempting a further natural conception, preimplantation genetic testing for structural rearrangements (PGT-SR) or gamete donation.
49. There are currently insufficient data to support the routine use of pre-implantation genetic testing for couples with unexplained recurrent miscarriage.

Male factors

50. There is no evidence to recommend treatments for male factors.

Unexplained RM and empiric treatments

51. In women with three or more consecutive miscarriages immediately preceding their current pregnancy, empiric vaginal progestogen administration of 400mg twice daily may be of some potential benefit.
52. LMWH and corticosteroids are not recommended for unexplained RM.
53. Women with RM are at increased risk of placental dysfunction and for this purpose low-dose aspirin (75mg) is recommended in a future pregnancy, with consideration of prophylactic dose LMWH based on individual risk factors and history.

54. While low dose folic acid (0.4 mg/day) is routinely started preconceptionally to prevent neural tube defects, it has not been shown to prevent pregnancy loss in women with unexplained RM.
55. Women with risk factors for folic acid deficiency, such as obesity, epilepsy or diabetes mellitus, should be considered for high dose (5mg) folic acid supplementation; in an Irish context, it should be considered for women with RM.

3.5.5 Future pregnancy planning

56. As part of their visit to a RM clinic, women/couples should receive written information regarding the results of investigations, treatment plans, contact numbers for available supports, (including the early pregnancy assessment unit and emergency room), in addition to necessary prescriptions and a personalised plan should a further pregnancy loss occur.
57. Provisions should be made for women to receive appropriate supportive care in terms of communication with healthcare professionals, ultrasound examinations and access to services in case of subsequent miscarriage(s).
58. At a minimum, women with an ongoing pregnancy should be booked into a consultant-led clinic for obstetric care, ideally a “high-risk” or perinatal medicine clinic whereby screening for conditions associated with RM may take place, e.g., pre-term birth, growth restriction and stillbirth.

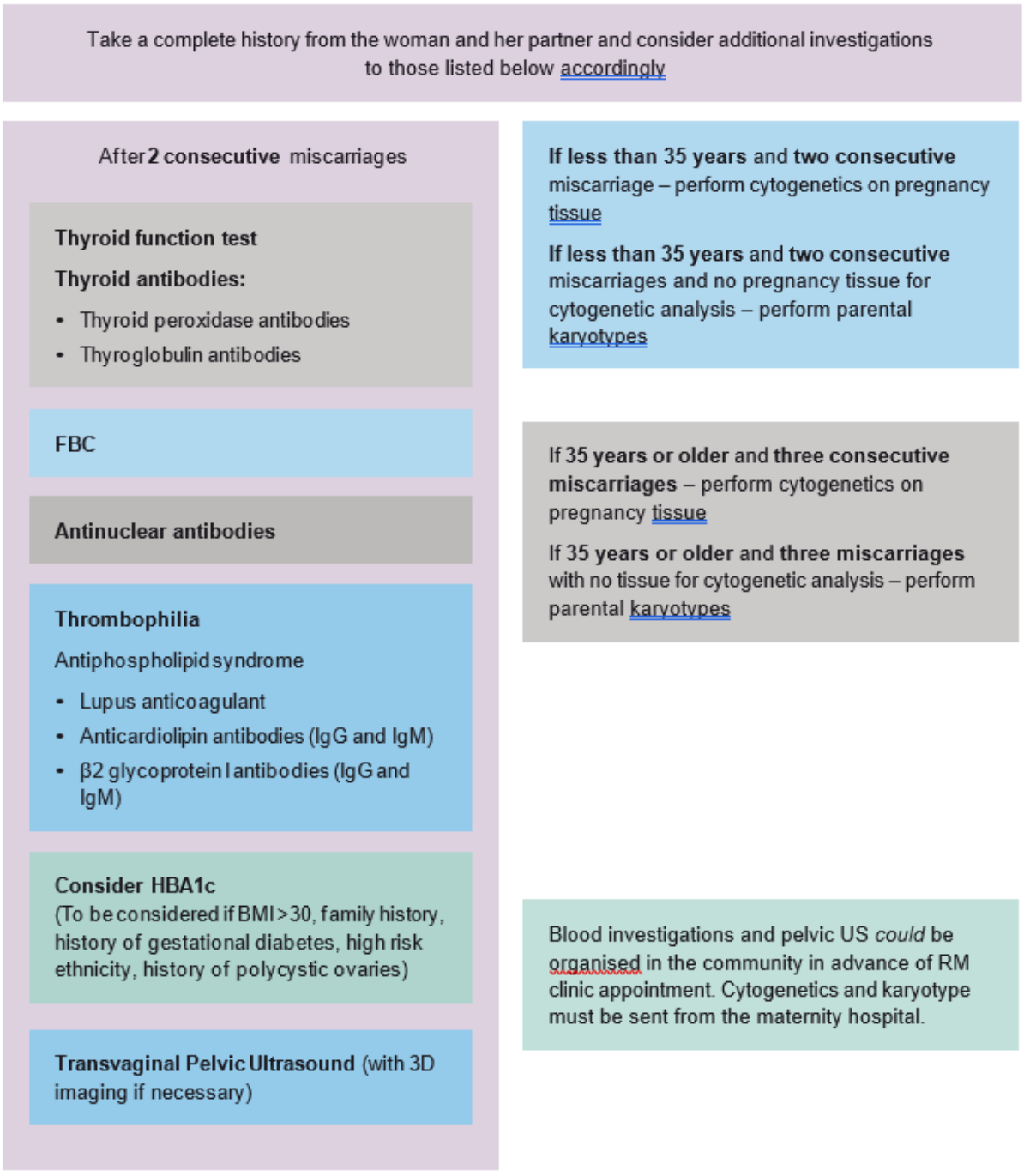


Figure 3. 1: Algorithm for investigations Recurrent Miscarriage

Test	Department	Bottle **
Thyroid function test	Biochemistry	Red
Thyroid antibodies: • Thyroid peroxidase antibodies • Thyroglobulin antibodies	Biochemistry	Red
FBC	Haematology	Purple
Antinuclear antibodies	Immunology	Red
Thrombophilia Antiphospholipid syndrome • Lupus anticoagulant • Anticardiolipin antibodies (IgG and IgM) • β2 glycoprotein I antibodies (IgG and IgM	Haematology	Red/Purple
HBA1c **(To be considered if BMI >30, family history, history of gestational diabetes, high risk ethnicity, history of polycystic ovaries)**	Haematology	Purple

** may vary in each maternity unit according to phlebotomy/laboratory products used, verify with local laboratory prior to taking bloods

Figure 3. 2: Blood tests to investigate recurrent miscarriage.

3.5.6 Auditable standards

Audit using the key recommendations as indicators should be undertaken to identify where improvements are required and to enable changes as necessary, and to provide evidence of quality improvement initiatives.

Auditable standards for this Guideline include:

1. Percentage of women/couples receiving the recommended investigations (100%)
2. Percentage of women with pregnancy outcome recorded (100%) – to include numbers who:
    - Achieve a new pregnancy
    - Achieve a new pregnancy without any form of artificial reproductive

technology (ART) OR with all forms of ART

- Go on to experience: a first trimester miscarriage/a second trimester miscarriage/fetal growth restriction/ placental abruption/pre-eclampsia/baby born at ≥37 weeks' gestation/stillbirth/neonatal death (defined as: death of a live born baby occurring within 28 completed days of birth)
- Achieve a new pregnancy within six months of their last miscarriage/≥6 months and <12 months of their last miscarriage.

3. Numbers of parents with an abnormal karyotype referred for genetic counselling annually/waiting times/ number who conceive without receiving counselling

3.5.7 Recommended reading

1. HSE Nomenclature for Clinical Audit – https://www.hse.ie/eng/about/who/nqpsd/ncca/nomenclature-a- glossary-of-terms-for-clinical-audit.pdf
2. HSE National Framework for developing Policies, Procedures, Protocols and Guidelines at https://www.hse.ie/eng/about/who/qid/nationalframeworkdevelopingpolicies/
3. Quenby S, Gallos ID, Dhillon-Smith RK, Podesek M, Stephenson MD, Fisher J, et al. Miscarriage matters: the epidemiological, physical, psychological, and economic costs of early pregnancy loss. Lancet. 2021 May 1;397(10285):1658-67. https://pubmed.ncbi.nlm.nih.gov/33915094/
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5. ESHRE Early Pregnancy Guideline Development Group E. Guideline Recurrent Pregnancy Loss Update 2022. 2022. https://www.eshre.eu/Guidelines-and-Legal/Guidelines/Recurrent-pregnancy-loss

6. Coomarasamy A, Dhillon-Smith RK, Papadopoulou A, Al-Memar M, Brewin J, Abrahams VM, et al. Recurrent miscarriage: evidence to accelerate action. Lancet. 2021 May 1;397(10285):1675-82. https://pubmed.ncbi. nlm.nih.gov/33915096/
7. RE:CURRENTStudy Website https://www.ucc.ie/en/obsgyn/plrg/plrgresearchactivity/therecurrentstudy/
8. www.pregnancyandinfantloss.ie

Authors

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https://www.hse.ie/eng/about/who/acute-hospitals-division/woman-infants/clinical-guidelines/

https://www.rcpi.ie/faculties/obstetricians-and-gynaecologists/national-clinical-guidelines-in-obstetrics- and-gynaecology/

Chapter 4 – Reproductive Outcomes Following Recurrent First Trimester Miscarriage: A Retrospective Cohort Study

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Chapter 4 – Reproductive Outcomes Following Recurrent First Trimester Miscarriage: A Retrospective Cohort Study

4.1 Abstract

Study question: What are the subsequent reproductive outcomes (livebirths, miscarriages or other adverse pregnancy outcomes or no further pregnancy) of women with recurrent miscarriage (RM) attending a dedicated clinic?

Summary answer: Of women with RM, 77% had a subsequent pregnancy, and among these pregnancies, the livebirth rate was 63%.

What is known already: RM affects approximately 1-3% of women of reproductive age. RM has known associations with advanced maternal age, obesity, diabetes, inherited thrombophilias, thyroid dysfunction, endometriosis and parental balanced translocations. However, approximately 50% of women or couples will be left without an explanation for their pregnancy loss, even after completing investigations. RM is also associated with secondary infertility and adverse pregnancy outcomes including preterm birth and perinatal death.

Study design, size, duration: We undertook a retrospective cohort study to identify subsequent pregnancy outcomes in women with RM, defined as three consecutive first-trimester miscarriages. Women attending the RM clinic at a tertiary university hospital in the Republic of Ireland over 12 years (2008 – 2020) with a confirmed diagnosis of primary or secondary first-trimester RM were eligible for inclusion. In total, 923 charts were identified for review against the eligibility criteria.

Participants/materials, setting, methods: Women with non-consecutive first trimester miscarriages or ectopic pregnancy were excluded. Epidemiological and clinical information regarding medical history, investigation and management was gathered from paper and electronic medical records. Data were analysed using SPSS (Version 27). Associations between maternal characteristics and outcomes were explored using χ^2 test, with significance set at $p<0.05$. Multinomial regression analysis was performed using a stepwise approach.

Main results and role of chance: There were 748 women included; 332 (44%) had primary RM and 416 (56%) had secondary RM. The median age was 36 years (range 19-47). Fetal aneuploidy was the most common investigative finding (15%; n=111/748); 60% had unexplained RM. In addition to supportive care, most women were prescribed aspirin (96%) and folic acid (75%). Of the 748 women, 573 had a subsequent pregnancy (77%) and 359 (48% of all women; 63% of pregnancies) had a livebirth, while 208 had a further pregnancy loss (28% of all women; 36% of pregnancies) and six were still pregnant at the end of the study. Women aged 35-39 were more likely to have a livebirth than no further pregnancy (RRR 2.29 (95% CI: 1.51, 5.30)). Women aged 30-34 were more likely to have a livebirth (RRR 3.74 (95% CI: 1.80, 7.79)) or a miscarriage (RRR 2.32 (95% CI: 1.07, 4.96)) than no further pregnancy. Smokers were less likely to have a livebirth (RRR 0.37 (95% CI: 0.20, 0.69)) or a miscarriage (RRR 0.45 (95% CI: 0.22, 0.90)) than no further pregnancy. Couples with an abnormal parental karyotype were less likely to have a miscarriage than another pregnancy (RRR 0.09 (95% CI 0.01,0.79)). Including successive pregnancies conceived over the study period, the overall livebirth rate was 63% (n= 466/742), but this was reduced to 44% in women aged ≥40 years and 54% in women with infertility.

Limitations, reasons for caution: This work covers 13 years, however, those included in the later years have a shorter follow-up time. Although electronic health records have improved data availability, data collection in this cohort remains hampered by the absence of a formal booking visit for women presenting with miscarriage and a national miscarriage database or register.

Wider implications of the findings: Our findings are largely reassuring as most women with RM and hoping to conceive achieved a livebirth. In addition to older age, smoking and parental balanced translocations were associated with a reduced likelihood of further pregnancy. No investigation or treatment was associated with pregnancy outcome, reiterating the importance of the supportive aspects of care for women and their partners after RM and counselling regarding individual risk factors. This contributes to the limited international data on the investigative findings and treatment of women with RM. The high rate of prescribed medications merits greater scrutiny, in conjunction with other pregnancy outcomes, and reiterates the need for a national guideline on RM.

Study funding/competing interest(s): LL is a PhD scholar funded through the Pregnancy Loss Research Group, Department of Obstetrics and Gynaecology, University College Cork.

MH and CF are Postdoctoral Researchers on a project funded by the Health Research Board Ireland [ILP-HSR-2019-011] and led by KOD, titled: "Study of the impact of dedicated recurrent miscarriage clinics in the Republic of Ireland". The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. The authors have no conflicts of interests to declare.

Key Words: recurrent miscarriage, miscarriage, pregnancy, infertility, aneuploidy, counselling

4.2 Introduction

A miscarriage is defined as the spontaneous demise of a pregnancy before the fetus reaches viability (24 weeks gestation in the UK and Ireland) (21). Miscarriage is the most common pregnancy complication, with the most recent data estimating 23 million miscarriages worldwide per year (1).

Recurrent pregnancy loss (RPL) must be distinguished from RM; RPL is defined as any two non-consecutive losses before viability (18,23) whereas RM has been defined as three consecutive first-trimester miscarriages (18,21,30). The population prevalence is approximately 1.9% for women with two miscarriages and 0.7% for three or more (1) . Risk factors for RM include maternal age (>35 years), paternal age, maternal body mass index (BMI), number of previous miscarriages, smoking, Black ethnicity, alcohol and stress, of which the strongest association is with maternal age (1). RM is associated with subsequent adverse pregnancy outcomes, including antepartum haemorrhage, gestational diabetes, preterm birth, small for gestational age and perinatal death (15). The risk of preterm birth, in particular, rises with each successive miscarriage (1). Moreover, RM is associated with significant psychological distress extending to post-traumatic stress disorders, anxiety, depression and suicidality (400). Therefore, supportive care and reassurance scans are of significant psychological benefit to couples with RM (410).

International guidelines recommend that for women with RM, a detailed medical history should direct investigations and treatments (18,21). Associated medical conditions include antiphospholipid syndrome (APLS), inherited thrombophilias, thyroid disease, uterine anomalies and parental chromosomal rearrangement, and are the focus of investigations alongside fetal chromosomal analysis for explanatory purposes (14). After investigations, approximately 38-60% of women will have unexplained RM (254,384,495,602). There is no high-quality evidence for any treatments in miscarriage prevention; however, there is some evidence for the use of progesterone in women with a previous miscarriage with bleeding in a subsequent pregnancy, thyroxine in sub-clinical hypothyroidism and low molecular weight heparin (LMWH) and aspirin in women with APLS (14). It is recommended that women are counselled about investigative findings and treatments in a specialised RM clinic setting, where additional supportive management can also be instigated (18,21).

Inconsistent recommendations and definitions have resulted in a variance in when and how women with RM are investigated and treated (323). A UK survey on the care of women with RM demonstrated that just a third of respondents had attended a dedicated RM clinic and that investigation and treatment deviated significantly from RCOG guidelines, often at the women's request (323). A Lancet Series on Miscarriage also noted the significant economic burden and psychological impact of RM on women and couples (1). Their suggested graded approach advocates for earlier access to psychological supports, reassurance scans and preliminary investigations (14). This is reflected in drafts of updated guidelines on RM which suggest investigation after two non-consecutive miscarriages (603,604).

In the Republic of Ireland, 19 maternity units provide obstetric care to women and their families. The structure of RM care in these individual units and the specifics of care offered, is not clear. Nationally, there is no data collection pertaining to miscarriage or RM; thus, incident rates are unknown, as are the maternal characteristics and subsequent pregnancy outcomes, which is a sizeable gap in the literature. An Irish cohort study demonstrated that women with RM were more likely to have a BMI ≥30, to have had assisted conception or a previous perinatal death and were more likely to have a further preterm birth or perinatal death, compared to women with no RM history (388). While this contributes to the limited international data on pregnancy outcomes following RM, it

is unclear what percentage of these women attended a RM clinic and what investigations, treatments or supports were provided (388).

The pregnancy loss service in Cork University Maternity Hospital (CUMH) was established in 2008 to provide specialised medical care and support to bereaved women and their families (which has always included women with primary RM or secondary RM, i.e., RM after a previous viable birth), who are seen within a specialised RM clinic. This study aimed to address the following research question: what were the subsequent reproductive outcomes for women who attended this RM clinic with three or more consecutive first-trimester miscarriages? More specifically, what were the different maternal characteristics, investigations, and treatments associated with a livebirth, a further pregnancy loss or no further pregnancy after RM, and what was the overall livebirth rate in the cohort during the study period?

4.3 Materials and Methods

4.3.1 Study design

A retrospective cohort study was conducted to examine subsequent reproductive outcomes for women with three or more consecutive first-trimester miscarriages. This study is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement (605).

Women with a confirmed history of primary or secondary first-trimester RM attending the RM clinic at CUMH from 1st Jan 2008 to 31st Dec 2020 were included. The cohort was followed until 28th February 2022 to identify any subsequent pregnancies. This study was conducted at CUMH, a large tertiary university hospital in the Republic of Ireland with approximately 8,000 births per year. The RM clinic is a consultant-led clinic, with ongoing supportive care provided by Clinical Midwife Specialists (CMS) in Bereavement and Loss. Approximately 70 women/couples a year are seen in the clinic to discuss results of RM investigations and potential treatments. All women who attended the RM clinic met with a CMS at their appointment and had supportive follow-up as required. Additionally, women were facilitated with an early ultrasound scan in a subsequent pregnancy and recommended to attend the consultant-led perinatal medicine antenatal clinic.

4.3.2 Ethical approval

Ethical approval for this study was obtained from the Clinical Research Ethics Committee of the Cork Teaching hospitals (ECM 6 (m) 06/12/16 and ECM 3 (z) 10/01/2017).

4.3.3 Study population

Women were identified from the clinical database of the RM clinic and inpatient registers. Paper and electronic charts, clinic letters, radiology records, electronic hospital laboratory systems and the Patient Information Management System (PIMS) were reviewed to confirm inclusion eligibility and gather information on primary and secondary outcome measures Women who had non-consecutive first-trimester miscarriages or whose three consecutive losses included an ectopic pregnancy, second-trimester miscarriage (defined as a pregnancy loss at 13 to 23+6 weeks gestation), stillbirth (defined as loss after 24 weeks gestation or of a fetus weighing ≥500g) or termination of pregnancy were excluded as per international definitions of RM (18,21). All women with secondary RM were confirmed as having had at least three consecutive miscarriages, but fourth and subsequent miscarriages were not necessarily consecutive. Women who were previously seen for preliminary investigations after two miscarriages and who returned for additional investigations and treatment after a third consecutive miscarriage were included. A minority of women who attended a different consultant within the hospital group for RM care were included if clinical correspondence outlining their history, investigations and treatment was available and if these were in keeping with the RM clinic protocols. Women who attended the RM Clinic for investigations and treatment but later received antenatal care or gave birth in another unit were excluded.

4.3.4 Outcome measure

The primary outcome measure was the reproductive outcome for women following at least three consecutive miscarriages, either a livebirth, a further pregnancy loss (which included first or second-trimester miscarriage, stillbirth, ectopic pregnancy or termination of pregnancy) or no subsequent pregnancy. If women who had experienced a further pregnancy loss in their first pregnancy after RM had any additional successful pregnancy in the study period, this was also recorded to determine the overall livebirth rate.

4.3.5 Covariates

Sample characteristics

Maternal characteristics included age (≤29, 30-34 years, 35-39 years, ≥40 years), primary RM versus secondary RM, smoking (current, non-smokers, previous smokers, unknown smoking status) and BMI (<25, ≥25, not documented). If data on medical history, gynaecological conditions, gynaecological procedures, fertility history, assisted reproductive therapy history and male partner history were available, this was recorded and coded as binary data (present/absent). Maternal age was recorded as age at attendance at RM clinic, as were other characteristics, if available.

Investigations and treatments

Routine investigations within the RM clinic and typically recommended pharmacological treatments with the standard dosages are presented in Table 4.1. The types of investigations were recorded, along with the results (normal versus abnormal). For treatment, dosing and timings varied for some patients (approximately 3%) (e.g., 150mg aspirin, aspirin from 6 weeks gestation only, progesterone 400mcg twice daily or therapeutic doses of LMWH). Therefore, this analysis was restricted to whether an individual drug was prescribed, and not its specific dosage or timing.

Table 4. 1: Data collected for investigations & treatments

Investigations	Notes
Thrombophilia Screen	Factor V Leiden (FVL) screen Anti-Cardiolipin Antibodies (ACLA) Lupus Anti-coagulant, Protein S Protein C Anti-Thrombin III
Prothrombin gene	Previously part of thrombophilia screen but due to a change in laboratory policy during the study period was only performed when a FVL screen was positive
Autoantibody Screen	Anti-nuclear antibodies (ANA), Extractable nuclear antigen, Anti-neutrophil cytoplasmic antibody, Rheumatoid factor others, as clinically indicated
Thyroid function tests	Thyroid stimulating hormone (raised if <2.5mIU/L) Thyroid antibodies (present/absent)
HbA1c	≥39mmol/mol
Pelvic US	Positive ultrasound findings were included as a positive investigative finding unless there was adequate clinical information to regard the finding as insignificant, e.g. ovarian cysts <5cm.
Fetal karyotyping	Fetal karyotyping was performed if pregnancy tissue was available at the time of a third or subsequent miscarriage
Parental karyotyping	Performed on both partners together if possible
Treatments	
Folic acid	5mg
Aspirin	75mg
Progesterone	400mcg vaginally OD

Low Molecular Weight Heparin	prophylactic dose OD subcutaneously (typically 4500iu tinzaparin)
Prednisolone	20mg twice daily
Metformin	500mg twice daily
Hydroxychloroquine	200mg OD

In keeping with clinical practice and international guidelines, we focused on Factor V Leiden (FVL) Prothrombin (PT) gene, Lupus anticoagulant and anti-cardiolipin antibodies (ACLA) in the thrombophilia screen (14) and the remaining thrombophilias were grouped as one covariate "other thrombophilia". Diagnosis of antiphospholipid was made in women with abnormal antiphospholipid antibodies (lupus anticoagulant, anti-cardiolipin antibodies and anti-B2 glycoprotein-I antibodies) associated with a history of adverse pregnancy outcome and vascular thrombosis. The diagnosis was confirmed by two positive tests three months apart as per international guidelines (587).
A finding of autoantibodies alone or a weak lupus anticoagulant were grouped as "tests of uncertain significance" when considering abnormal investigations.

4.3.6 Data Collection

Data from 2008 to 2016 were collected by four clinical staff and managed by a researcher (ICSL). This data was then verified and merged with the 2017-2020 data, which the primary author collected. Data collected from clinical notes or correspondence were confirmed by checking laboratory and radiology systems and inpatient records. Data were stored securely as per hospital and university data protection guidelines.

Collected data was entered into a Microsoft Excel file. The data were cleaned, and relevant variables were entered into SPSS, version 27, for analysis. Associations between participant characteristics and subsequent reproductive outcomes were explored using $\chi 2$ test for categorical variables with significance defined as $p<0.05$. Similar analysis was undertaken to investigate associations between participant characteristics and subsequent pregnancy outcomes, i.e., livebirth or a further pregnancy loss.

Multinomial logistic regression was conducted using a stepwise approach. Model 1 included maternal characteristics and model 2 added the RM investigations. Only

variables that were statistically significant in the unadjusted regression model were included. Estimated coefficients are reported as relative risk ratios (RRRs) with 95% CI using women who had no subsequent pregnancy as the reference category. This is because the exponentiated coefficient in multinomial logistic regression is the ratio of two relative risks (RR) and should not be interpreted as an odds ratio (OR).

4.4 Results

A review of the RM clinic database and inpatient registers between 2008 and 2020 identified 923 charts for analysis; of these, 748 women with RM were eligible for inclusion in the study. Exclusions are presented in Figure 4.1. The median follow-up time was 7 years 1 month (range 1 year 2 months -14 years).

4.4.1 Maternal characteristics

The median age in this cohort was 36 years (range 19-47, standard deviation 5.06). Most women experienced a secondary RM (55.6%, n=416), were non-smokers (80.4%, n=403 of 501) and had no documented medical history (73.5%, n=535 of 728) (see Table 4.2). Further, 81% of women had no documented history of infertility (n=606).

Previous delivery information was available for 201 women with secondary RM (48%; 201/416); 142 (71%) had a prior vaginal birth, with the remainder having at least one caesarean section (n=59, 29%). Of 265 women with four or more miscarriages, 76% had at least one previous livebirth (n=202/265). Of the 42 women with six or more miscarriages, 26% of women had no previous livebirth (11/42).

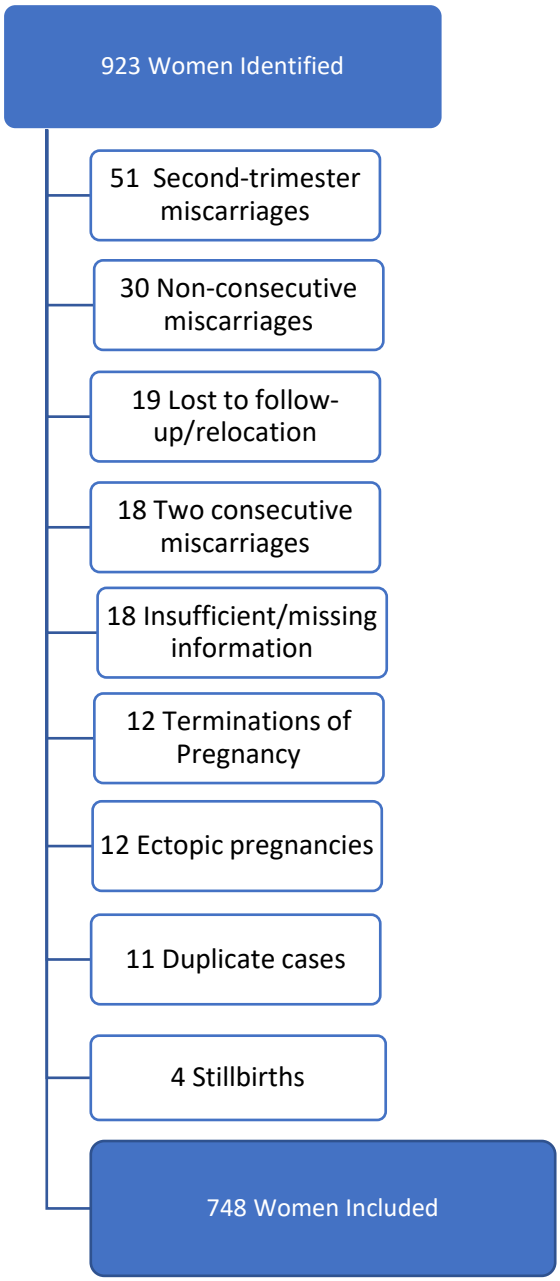


Figure 4. 1: Recurrent Miscarriage Cohort – Reasons for Exclusion

Table 4. 2: Maternal characteristics at the time of RM Clinic attendance

Demographics (n=748)	N	Frequency	Percentage %
Age *<29*	748	89	11.9
30-34		182	24.3
35-39		283	37.8
>40		194	25.9
Recurrent miscarriage	748		
Primary		332	44.4
Secondary		416	55.6
Previous Adverse Pregnancy Outcomes	748		
Stillbirth		3	0.4
Preterm Birth		18	2.4
Previous Livebirths	748		
0		333*	44.5
1		264	35.2
2		110	14.7
3		29	3.9
4+		12	1.6
No of miscarriages	748		
3		483	64.6
4		166	22.2
5		57	7.6
6		25	3.3
7		11	1.5
8		1	0.1
9		2	0.3
10		2	0.3
12		1	0.1
Smoking status	501		
Current smoker		85	11.4
Non-smokers		403	54.5
Previous smoker		13	1.7
Body Mass Index	287		
<25		218	29.0
>25		61	8.2
>40		8	1.0
Documented medical history	728		
No medical history		535	74.0
Medical history		193	25.8
Recorded Medical Conditions	748		
Hypothyroidism		48	6.4

Autoimmune disorder		24	3.2
Mental Health Disorder		22	2.9
Documented gynaecological history	728		
Gynaecological history		50	6.7
No gynaecological history		678	90.6
Gynaecological conditions	39		
PCOS		18	2.4
Endometriosis		12	1.6
Fibroids		9	1.2
Documented gynae surgical procedure(s)	727		
Gynaecological procedure(s)		142	19.0
No gynaecological procedure(s)		585	78.2
Gynaecological procedures	108		
Caesarean section		43	5.7
Surgical Management of Miscarriage		34	5.2
Large Loop Excision of Transitional Zone		16	2.1
Diagnostic Laparoscopy +/- Dye		15	2
Documented Fertility History	748		
Fertility history		142	19.0
No fertility history		606	81.0
Fertility Type	142		
RM as Primary Reason for Investigations		46	32.4
Unexplained Primary Infertility		19	13.4
Prolonged time to conception		15	10.6
Prior IVF (reason undocumented)		15	10.6
Anatomical cause		10	7.0
Male factor		8	5.6
Unexplained Secondary Infertility		7	4.9
PCOS		7	4.9
Endometriosis		6	4.2
Advanced Maternal Age		5	3.5
Balanced Translocation		3	2.1
Premature Ovarian Failure		1	0.7
ART type	66		
IVF		25	37.9
Ovulation Induction		12	18.2
Intra-uterine Insemination		11	16.7
Egg Donation		9	13.6
ICSI		3	4.5
PGT		2	3.0
IVF – reasons undocumented		4	6.0

*Recorded as having had no previous live birth (stillbirth in first pregnancy (n=1))

4.4.2 Investigations performed

Almost all women had the RM clinic standard investigations performed, (727/748; 97%). An overview of these investigations and prescribed treatments is provided in Table III.

Overall, 297 women had at least one investigative finding (297/748; 39.7%); 53 women had two or more positive results and six women had three. The most common positive finding was an abnormal fetal karyotype (n=111), followed by a positive ANA result (n=89), abnormal thyroid function tests (n=59), a finding of FVL (n=35) or a balanced translocation in either parent (n=28). Eight women had a sole positive finding of a test of uncertain significance.

4.4.3 Treatments

Prescribed medical therapies are also outlined in Table 4.3. In addition to supportive care and medications, cervical surveillance was recommended in a subsequent pregnancy for seven women and three women with a history of preterm birth were advised to have a cervical cerclage.

Table 4. 3: Details of standard investigations results and prescribed treatments

Investigation	N=748 (%)	Frequency	Percent
Prothrombin Gene	344(46)		
Mutation present		7	2.0
Mutation absent		337	98
Factor V Leiden	737 (98.5)		
Mutation Present		35	4.7
Mutation Absent		702	95
Anti-Cardiolipin Antibodies	740 (99)		
Present		10	1.4
Absent		730	98.6
Re-test positive and APLS diagnosed		4	5.4
Other Thrombophilia	740 (99)		
Weakly+ Lupus anticoagulant		5	0.7
Protein S deficiency		1	0.1
All autoantibodies	743 (99)		
One or more present		94	12.7
No antibodies		655	87.3
ANA present		89	12.0
HbA1c	742 (99)		
Elevated		7	1
Not elevated		735	99
Thyroid function tests	742 (99)		
Normal		683	92.0
Abnormal		59	8.0
Previous Fetal karyotype	141 (19)		
Euploid		30	21.3
Aneuploid		111	78.7
Most common aneuploidies	111 (15)		
Trisomy 16 (T16)		17	15.3
T21		14	12.6

T22		14	12.6
T15		10	9.0
Triploidy		10	9.0
T13		8	7.2
45XO		6	5.4
Parental Karyotype	697 (93)		
Balanced translocation present*		28	4.0
Normal karyotype		669	96.0
Pelvic US	748 (100)		
Finding on US		46	6.1
No finding		702	93.9
Most common US findings	46 (6)		
Polycystic ovaries		13	28.3
Uterine fibroids		11	23.9
Bicornuate Uterus		10	21.7
Medical Therapies Initiated			
Aspirin	728 (97)	696	96
Folic Acid 5mg	728 (97)	548	75
Progesterone	728 (97)	389	52
Low Molecular Weight Heparin	727(97)	175	24
Prednisolone	727(97)	28	4
Metformin	727(97)	12	2
Hydroxychloroquine	727(97)	7	1

*19 Maternal balanced translocations and 9 paternal

4.4.4 Outcomes

There were 573 women (77%) who had a subsequent pregnancy following at least three consecutive miscarriages; the majority of whom conceived within one year of attending the RM clinic (441/573; 77%). Of the 573 women, 93% (531) had at least one early pregnancy ultrasound scan before their routine booking ultrasound at 12 weeks. The livebirth rate overall was 48% (359/748) and 63% among the women who became

pregnant (359/573) while there were six additional pregnancies still ongoing at the end of the follow-up period; other pregnancy outcomes are shown in Figure 4.2.

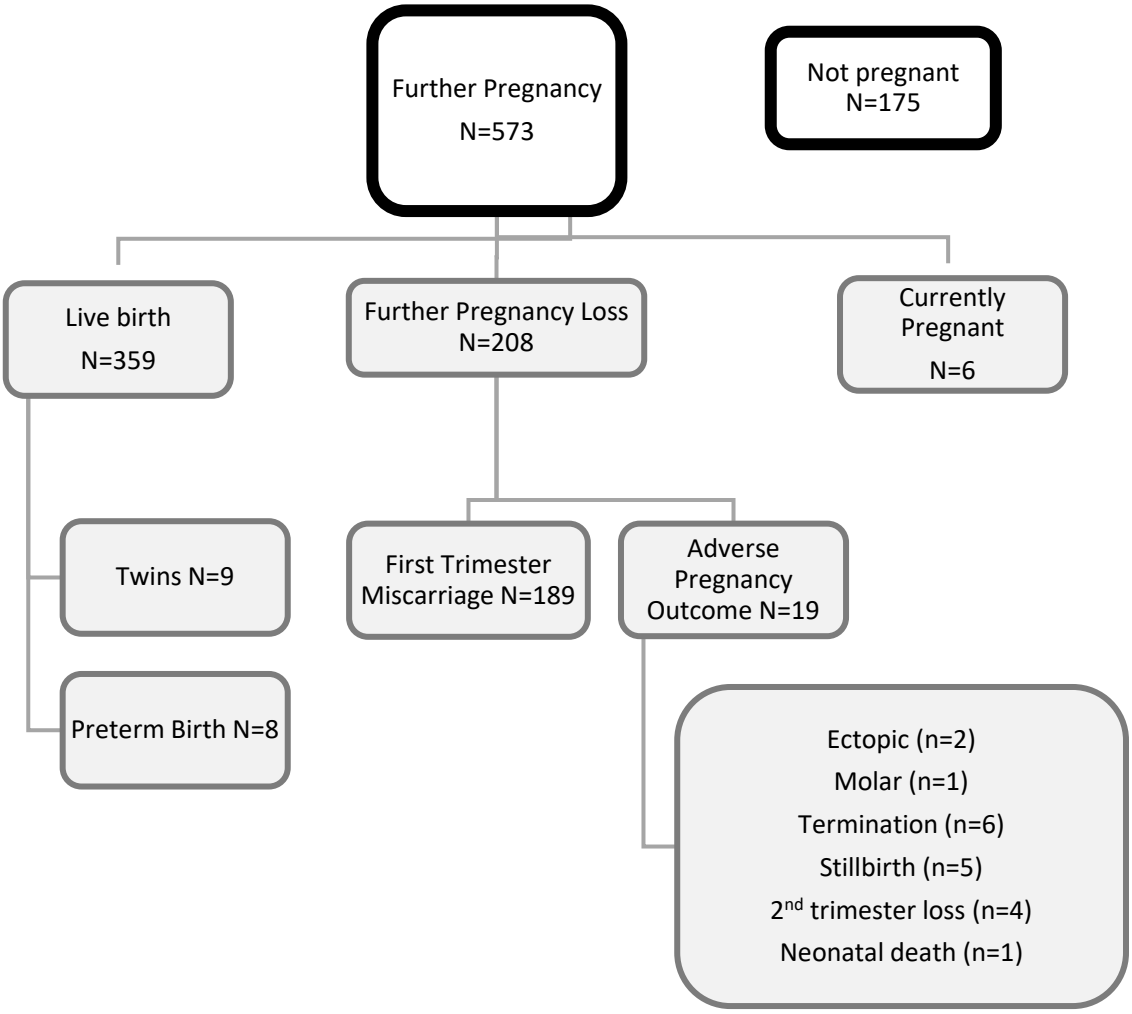


Figure 4. 2: Pregnancy Outcomes Following RM

Including successive pregnancies over the study period, the cumulative livebirth rate among those who had one or more subsequent pregnancies was 81% (466/573) and 63% (466/742) among all of the women with RM (after excluding the six women with ongoing pregnancies). When examined according to age, the cumulative livebirth rate for the 742 women with RM was 67% in women aged under 30 (n=59/88), 73% in women aged 30-34 (n=131/180), 68% in those aged 35-39 years (n=191/281) and 44% in women aged over age 40 (n=85/193) ($p<0.001$). The cumulative livebirth rate for women with any history of infertility was 54% (n=75/140), compared to 65% for those with no infertility history (n=391/602) (p=0.019).

4.4.5 Maternal characteristics versus reproductive outcome

Maternal characteristics were examined compared to reproductive outcomes (livebirth, pregnancy loss or no further pregnancy), and are shown in Table 4.4. Based on chi-square test, age was associated with reproductive outcome ($p<0.01$), as was current smoking (p=0.011), a history of an abnormal karyotype in either partner (p=0.014) and treatment with progesterone (p=0.007). Specifically, women ≥40 had a lower livebirth rate (32%), higher miscarriage rate (34%) and higher rate of no further pregnancy (34%) compared to younger women in the cohort. Smokers and couples with balanced translocations had higher rates of no further pregnancy and women prescribed progesterone had a higher rate of pregnancy loss.

To determine any differences between women who had a livebirth and those who had a further loss, chi-square test was performed on maternal characteristics that were associated with reproductive outcomes as per Table 4.4 (see Supplementary File 4.1). Only age ≥40 was shown to be associated with having a further pregnancy loss. A previous livebirth was not associated with achieving a further pregnancy or a livebirth (Table 4.4 and See Supplementary File 4.1). Binary regression analysis was not performed to compare maternal characteristics and pregnancy outcome as the data were too small in some covariate groups to be conclusive.

Table 4. 4: Maternal Characteristics versus Reproductive Outcome

Maternal Characteristic (n, %)	Livebirth (n=359)	Pregnancy Loss (n=208)	No further pregnancy (n=175)	p-value
Maternal age				
≤29	45 (51.1)	21 (23.9)	22 (25)	
30-34	102 (56.7)	54 (30)	24 (13.3)	
35-39	151 (53.7)	67 (23.8)	63 (22.4)	
≥40	61 (31.6)	66 (34.2)	66 (34.2)	<0.001
Previous Livebirth				
Yes	202 (49.0)	111 (26.9)	99 (24.0)	
No	157 (47.6)	97 (29.4)	76 (23.0)	0.759
Medical history[a]				
Yes	95 (44.2)	60 (27.9)	60 (27.9)	
No	259 (50.8)	144 (28.2)	107 (21.0)	0.105
Gynaecological condition[b]				
Yes	18 (37.5)	14 (29.2)	16 (33.3)	
No	333 (49.4)	188 (27.9)	153 (22.7)	0.174
Gynaecological Procedure[c]				
Yes	64 (45.7)	36 (25.7)	40 (28.6)	
No	287 (49.4)	166 (28.6)	128 (22.0)	0.257
BMI				
Not documented	222 (48.3)	128 (27.8)	110 (23.9)	
<25	103 (48.1)	61 (28.5)	50 (23.4)	
>25	34 (50.0)	19 (27.9)	15 (22.1)	0.997
Smoker[d]				
Yes	35 (41.8)	20 (23.5)	29 (34.5)	
No	212 (51.5)	119 (28.9)	81 (19.7)	0.011
Fertility History				
Yes	58 (41.4)	40 (28.6)	42 (30.0)	
No	301 (50.0)	168 (27.9)	133 (22.1)	0.093
ART History				
Yes	31 (47.0)	22 (33.3)	13 (19.7)	
No	328 (48.5)	186 (27.5)	162 (24.0)	0.543
Prothrombin Gene				
Not performed	189 (47.5)	109 (27.4)	100 (25.1)	
Mutation present	3 (42.9)	4 (57.1)	0 (0.0)	
Mutation absent	167 (49.6)	95 (28.2)	75 (22.3)	0.321
Factor V Leiden[e]				
Mutation Present	20 (57.1)	6 (17.1)	9 (25.7)	
Mutation Absent	335 (48.1)	199 (28.6)	163 (23.4)	0.334
Anti-Cardiolipin Antibodies[f]				
Present	6 (54.5)	4 (36.4)	1 (9.1)	
Absent	351 (48.5)	200 (27.7)	172 (23.8)	0.504
All autoantibodies[g]				

1 or more present	48 (51.1)	24 (25.5)	22 (23.4)	
No antibodies	309 (48.0)	183 (28.5)	151 (23.5)	0.817
HbA1c[g]				
Elevated	2 (28.6)	2(28.6)	3 (42.9)	
Not elevated	355 (48.6)	205 (28.1)	170 (23.3)	0.426
Thyroid function tests[h]				
Normal	329 (48.5)	196 (28.9)	153 (22.6)	
Abnormal	28 (48.3)	11 (19)	19 (32.8)	0.119
Previous Fetal karyotype				
(n=129)	54 (49.1)	28 (25.5)	28 (25.5)	
Aneuploid	8 (27.6)	10 (34.5)	11 (37.9)	0.114
Euploid				
Parental Karyotype[i]				
Balanced translocation	13 (46.4)	3 (10.7)	12 (42.9)	
present	326 (49.2)	193 (29.1)	144 (21.7)	0.014
Normal karyotype				
Pelvic US				
Finding on US	21 (46.7)	15 (33.3)	9 (20.0)	
No finding	338 (48.5)	193 (27.7)	166 (23.8)	0.68
Any positive investigation				
finding	155 (48.7)	85 (26.7)	78 (24.5)	
Yes	204 (48.1)	123 (29.0)	97 (22.9)	0.755
No				
Prescribed Aspirin*				
Yes	336 (48.7)	196 (28.4)	18 (22.9)	
No	14 (46.7)	9 (30)	7 (23.3)	0.974
Prescribed Folic Acid 5mg*				
Yes	257 (47.3)	161 (29.7)	125 (23.0)	
No	95 (53.1)	44 (24.6)	40 (22.3)	0.340
Prescribed Progesterone*				
Yes	175 (45.5)	129 (33.5)	81 (21.0)	
No	177 (52.5)	77 (22.8)	83 (24.6)	0.007
Prescribed LMWH[§]				
Yes	76 (44.4)	52 (30.4)	43 (25.1)	
No	276 (50.2)	153 (27.8)	121 (22)	0.416
Prescribed Prednisolone[§]				
Yes	12 (44.4)	11 (40.7)	4 (14.8)	
No	339 (48.9)	194 (28.0)	160 (23.1)	0.306
Prescribed Metformin[§]				
Yes	5 (41.7)	3 (25.0)	4 (33.3)	
No	347 (48.9)	202 (28.5)	160 (22.6)	0.677
Prescribed				
Hydroxychloroquine[§]	3 (50.0)	3 (50.0)	0 (0.0)	
Yes	349 (48.8)	202 (28.3)	164 (22.9)	0.306
No				

a-missing data (n=17), b- missing data (n=20), c- missing data (n=21), d- missing data (n=244), e- missing data (n=10), f – missing data (n=8), g- missing data (n=5), h -missing data (n=6), i - missing data (n=41)
*n=728
§n=727

4.4.6 Multinomial logistic regression analysis

In the unadjusted multinomial logistic regression, maternal age, any medical history, current smoking, any infertility history, abnormal thyroid function tests, parental balanced translocations and prescribed progesterone were linked to either livebirth or a further pregnancy loss (see Supplementary File 4.2).

In the fully adjusted model, age, smoking status and the presence of a parental balanced translocation remained associated with pregnancy outcome (Table 4.5). With respect to women aged over 40, women aged 35-39 were 2.3 times more likely to have a livebirth than no further pregnancy (RRR 2.29 (95% CI 1.51-5.30)), and women aged 30-34 were more likely to have a livebirth (RRR 3.74 (95% CI 1.80-7.79)) or a miscarriage (RRR 2.31 (95% CI 1.07-4.96)) than no further pregnancy. With respect to non-smokers, smokers were less likely to have a livebirth (RRR 0.37 (95% CI 0.20-0.69)) or a miscarriage (RRR 0.45 (95% CI 0.22-0.90)) than no further pregnancy. With respect to couples with normal parental karyotypes, couples with an abnormal parental karyotype were less likely to have a miscarriage than no further pregnancy (RRR 0.09 (95% CI 0.01-0.79)).

Additional analyses were performed to examine whether women who smoked or who had an abnormal karyotype had other characteristics which could account for differences in reproductive outcomes (see Supplementary File 4.3). Smokers were younger (41.7% of those ≤30 smoked compared to 12.6-15.9% of women in the other age categories, $p<0.001$), with a BMI ≤25 ($p=0.043$) and 50%of smokers had no previous livebirths compared to 40% of non-smokers (50.6% vs 40.6%, $p=0.09$). No other characteristics were associated with karyotype.

Table 4. 5: Adjusted Multinomial Regression Analysis of Maternal Characteristics vs Reproductive Outcome.

Variable		Model 1*			Model 2*		
	Live birth[a] RRR (95% CI)	p-value	Further pregnancy loss[a] RRR (95% CI)	p-value	Live birth[a] RRR (95% CI)	p-value	Further pregnancy loss[a] RRR (95% CI)	p-value
Maternal characteristics								
Age category <29 years	1.95 (0.89-4.28)	0.096	0.61 (0.24-1.54)	0.294	2.03 (0.90-4.61)	0.089	0.73 (0.277-1.91)	0.517
30-34 years	3.99 (1.94-8.22)	<0.01	2.33 (1.11-4.91)	0.026	3.74 (1.80-7.79)	<0.01	2.31 (1.07-4.96)	0.033
35-39 years	2.54 (1.40-4.61)	0.010	1.15 (0.61-2.15)	0.669	2.29 (1.51-5.30)	0.001	1.33 (0.68-2.61)	0.402
≥ 40 years [b]	1		1		1		1	
Medical history Yes	0.675 (0.41-1.12)	0.127	0.86 (0.50-1.48)	0.581	0.71 (0.42-1.21)	0.210	0.98 (0.55-1.75)	0.946
No [b]	1		1		1		1	
Fertility history Yes	0.79 (0.45-1.40)	0.422	0.82 (0.44-1.52)	0.523	0.74 (0.41-1.34)	0.320	0.70 (0.370-1.34)	0.284
No [b]	1		1		1		1	
Smoking No [b]	1		1		1		1	
Yes (Current smokers)	0.43 (0.24-0.79)	0.006	0.52 (0.26-1.01)	0.053	0.37 (0.20-0.69)	0.020	0.45 (0.22-0.90)	0.024
Investigations								
Thyroid function tests Yes					0.95 (0.37-2.47)	0.920	0.40 (0.11-1.42)	0.155
No [b]					1		1	
Parental karyotype Yes					0.51 (0.17-1.51)	0.224	0.09 (0.01-0.79)	0.029
No [b]					1		1	

[a]Reference category: no pregnancy; [b]1 denotes reference category.

4.5 Discussion

4.5.1 Principal findings

This retrospective cohort study aimed to examine the subsequent pregnancy outcomes in women with at least three consecutive miscarriages, and to determine whether any maternal characteristics, investigations or recommended treatments were associated with subsequent pregnancy outcomes.

Women attending the RM clinic were older (64% >35 years) and slightly more likely to experience secondary RM than primary RM. Of the attending women, 74% of women had no medical history; however, notable proportions had a previous gynaecological procedure (19%) or a history of infertility (19%). While maternal age, smoking status and parental karyotype were all associated with pregnancy outcomes, no investigations or treatments were associated with any outcomes.

4.5.2 Strengths and limitations

This was a large retrospective cohort study of 748 women with consecutive RM. Women included in this study had at least three confirmed consecutive miscarriages; in contrast, previous large register-based studies have not been able to confirm that the secondary RMs were consecutive, or they were restricted to solely examining outcomes after primary RM (334,388,606–608). Moreover, this study provides information on investigations and treatments, which is also omitted in larger published cohorts. Few women were lost to follow-up (n=19, Figure 1). As women attended a single hospital in their subsequent pregnancy, they were treated consistently and given similar support in follow-up, including bereavement midwife support, early ultrasounds, antenatal care and miscarriage management.

Nonetheless, this work covers a 13-year period, and while the RM clinic staffing and care structures are mainly unchanged, certain aspects of supportive care for RM patients has adapted to reflect up-to-date evidence and greater public awareness and expectations (393,593). While women from early years in the study had a long follow-up period, this is much shorter for women attending the clinic in later years, potentially underestimating their eventual livebirth rate. Initial data collection was completed by a team of health care professionals with clinical experience in RM. While a data collection protocol was followed, it does not rule out potential discrepancies in data collection. Every effort was

made to locate missing data and data were re-checked for accuracy by the primary author. Nonetheless, women may not always present to hospital with a miscarriage, particularly in very early pregnancy, thus the subsequent miscarriage rate is potentially underestimated. As the sole tertiary referral hospital in the region however, our rate of return is high and, anecdotally, we find women do report early miscarriages to our CMS in Bereavement and Loss and thus the potential omissions should be minimal. Similarly with livebirths, as the largest maternity hospital in the region, transfer of care is uncommon and is usually documented in the chart, with the decision to transfer care often relayed to the Bereavement CMS or evident in the electronic health record. For those women who did not conceive, it was not possible to determine definitively their reproductive intentions, i.e., whether they attempted to conceive again or sought private fertility treatments. Therefore, "no further pregnancy" cannot be assumed to be infertility following RM and should be interpreted with caution. Whether or not women attempted conception, it is important to include women with no further pregnancy in the analysis, to identify factors that may be associated with not conceiving and provides relevant clinical information with which to counsel women. The decision to not pursue further pregnancy after RM is also an important issue that requires greater exploration in qualitative studies.

The introduction of the electronic health record in 2017 significantly improved the availability of some data compared to paper charts. However, data collection in this cohort remains problematic. Women experiencing miscarriage were not formally booked into an antenatal clinic, thus some information was obtained solely from clinical correspondence. BMI was only recorded as "normal" or "raised" in some clinical correspondence, determining how this was reported. Additionally, relevant negative findings such as non-smoking status, BMI <25, no significant medical, surgical or partner histories or investigative findings (particularly pelvic ultrasound) may not have been explicitly stated in clinic letters accounting for levels of missing data for some variables. We are limited to reporting those medications prescribed in the clinic, rather than adherence to prescribed medications. However, electronic antenatal records were checked for the years 2017-2020, which suggested compliance of 90% where information was available (n=179/198). Similarly, attendance at a consultant-led perinatal medicine clinic was suggested for all women and examination of the electronic records from 2017-

2020 showed 55% (n=94/169) attended a perinatal medicine clinic, 26% chose private care (43/169), and 19% received routine antenatal care (32/169).

4.5.3 Interpretation of results in context of available literature

Our findings confirm that advanced maternal age, smoking, and having a medical or infertility history in addition to experiencing RM is associated with subsequent infertility (1,388). The majority of women had unexplained RM (60%), consistent with previous studies (254,495,602). Only 19% of women had chromosomal analysis performed on products of conception, but fetal aneuploidy was the most common investigative finding. The low rate of chromosomal analysis performed for women attending the clinic may be due to miscarriages at early gestations, complete miscarriage, loss of pregnancy tissue prior to analysis, culture failure or lack of awareness regarding the need for testing upon a third miscarriage, and therefore this merits further scrutiny through clinical audit. The chromosomal analysis demonstrated fetal aneuploidy in 79% of samples, which mirrors the rate of 80% identified in other studies (71). This finding reiterates the relationship between aneuploidy and miscarriage and the significance of chromosomal analysis of products of conception as an explanatory investigation (609).

Anti-nuclear antibodies (ANA) were another frequent positive investigative finding, however, their association with RM is not fully understood to be wholly attributable to recurrent losses (306). Overall, 12% of women had a finding of ANA, which is slightly lower than quoted rates in women with RM in a recent systematic review (13.2-50%) (306), and the rate found in our cohort of women with two consecutive miscarriages (15%), and more in keeping with rates seen in women without RM (0.9-16%)(306,386). This suggests a weaker association between ANA and RM in our cohort but this is limited by sample size, so it is difficult to draw conclusions. Of the women in our cohort, 8% had abnormal thyroid function tests, which is close to the 7.2% rates previously quoted in RM cohorts (254). Thrombophilia screening in our cohort found a 5% rate of FVL which was lower than rates in similar cohorts (7.2-17%), and other thrombophilias such as Prothrombin gene mutation (2.0%) and APLS (1.4%) were comparatively much lower in our cohort compared to other RM cohorts in a systematic review (182), but were in keeping with a more recent cohort study which demonstrated rates of 2.9% and 0.5% for prothrombin gene mutations and APLS respectively (215). Larger cohort studies are required to determine the clinical value of thrombophilia testing in women with RM.

Parental karyotyping demonstrated balanced translocations in 4% of parents, which is comparable to the wider literature (182). Parental karyotype was the only investigation shown to be significantly associated with pregnancy outcome; these parents were more likely not to conceive than have a miscarriage or a livebirth. We suggest that this likely represents the additional considerations for these parents to embark on a subsequent pregnancy, such as the potential for deferral in conception to consult a clinical geneticist or consideration of ART to facilitate pre-implantation genetic testing, although conception rates and livebirths in parents with balanced translocations are not significantly reduced among those who choose to conceive naturally over ART (183,610). Furthermore, these couples were equally likely to be nulliparous and were not significantly older than those with a normal karyotype.

Most women received high dose folic acid and low-dose aspirin with supportive care for a future pregnancy. Folic acid is prescribed to reduce the risks of neural tube defects, particularly in women with obesity, epilepsy or diabetes, particularly in the Irish population as there is no fortification of food (611,612). However, folic acid has not been shown to reduce the risk of miscarriage in women with RM (35). Aspirin was prescribed to almost all women attending the RM clinic. Rather than reducing subsequent miscarriage risk, aspirin was given to reduce placental dysfunction in a subsequent pregnancy, to reduce the risk of preeclampsia and intra-uterine growth restriction, particularly for women aged >35, smokers, women with hypertension or women undergoing ART (334–336). The rate of LMWH and aspirin prescription is much higher than the rate of thrombophilia within the cohort, which is in keeping with the findings of Manning et al (323). This combination has not been shown to be of benefit to women with RM without APLS (14). At a local level, these prescribing practices merit greater scrutiny, but should be examined alongside other relevant pregnancy outcomes such as pre-eclampsia or fetal growth restriction to assess any attributable benefits and in distinct cohorts. For example, women attending with two miscarriages and prescribed any medication were more likely to have a livebirth than those given no medication (386).

Progesterone was prescribed to 56% of women with RM. An updated meta-analysis suggests progesterone may reduce miscarriage in RM, particularly in first-trimester bleeding or with higher-order miscarriage and should be considered (14). Our unadjusted regression model suggested that women prescribed progesterone were more likely to

have a miscarriage than no further pregnancy. Our interpretation is that this represents how this group are more likely to attempt conception following attendance at the RM clinic than not, which is mirrored in the high rate of conception in the first 12 months after attending the RM clinic (77%), as seen previously (613). In the adjusted model, however, this association was not significant. Prednisolone, hydroxychloroquine and metformin were prescribed infrequently, in keeping with international guidance (18). No other prescribed treatments had a significant association with outcome in our cohort, echoing findings in the international literature (14).

The livebirth rates of 48% overall and 63% in women with subsequent pregnancies is lower than rates reported in the literature of 74-86% (381–384). It is also lower than the livebirth rate of 73% reported in women attending our RM clinic with two miscarriages (386). Almost a quarter of women had no further pregnancies; this may be due to the shorter follow-up period for a minority (52/742 (7%) were followed for <24 months). When including successive pregnancies, the overall livebirth rate climbed from 48 to 63%, but remained lower for women with infertility issues (54%) and those over 40 (44%). Notably, over a quarter of our cohort was aged over 40 years and 67% in this age group had a living child. These factors, which may influence whether couples pursue a further pregnancy or not, merit further exploration. The psychological impact of RM itself may also influence this decision (614). Qualitative studies are required to better understand patient experiences, particularly those of women/couples with infertility (436). Women aged 30-34 and 35-39 were more likely to have a livebirth than no further pregnancy, and women aged 30-34 were also more likely to have a miscarriage than no further pregnancy. This reflects greater fecundity in this age group and desire to conceive, as mentioned previously. Smoking is well recognised as a risk factor for infertility and miscarriage (1) and smokers in our cohort were significantly less likely to have a subsequent pregnancy despite being younger and having no prior livebirths.

It is notable that there was little information available on male partner history and so this data was excluded from the analysis. This is reflective of long-standing bias within research on the developmental origins of health and disease that maternal pregnancy effects are of greater influence than paternal contributions (615,616). The role of male health, in particular sperm quality, in RM is increasingly recognised (545). The psychological impact of RM on male partners is well established, but may not be

acknowledged in the hospital setting, leaving male partners feeling unsupported and unimportant (412,413). Healthcare professionals must take a holistic and couple-focused approach to RM, to better meet their psychological needs (406).

4.5.4 Clinical implications

These findings provide useful information with which to counsel women or couples with RM. The findings are largely reassuring with the majority of women conceiving over time. For those women who smoke, have a balanced translocation, are older or have a concurrent fertility issue, our findings can alert the women and their clinicians to their potential reduced likelihood of conception and livebirth and thus allow for greater counselling regarding individual risk factors as well as facilitating additional supports.

4.5.5 Research Implications

This research demonstrates important information on the reproductive outcomes following RM. There is a need for larger similar studies with greater details on pregnancy outcomes. While antenatal and delivery complications were beyond the scope of this current paper, it is recognised that preeclampsia, gestational diabetes, preterm birth, placental abruption and stillbirth are associations with RM (334,382,388–390). Induction of labour and Caesarean section rates in subsequent pregnancies have also been reported as increased among women with RM (388). The lack of a national register on miscarriage remains a significant limitation in obtaining accurate data on miscarriage and subsequent pregnancy outcomes. Alternatively, consideration should be given to a local prospective database, such as recently employed by “Tommy’s Net” to better capture this data (614). Qualitative work is also needed to explore couples’ experiences of trying to conceive after pregnancy loss, including cessation of trying, and to identify the supports and needs of these couples.

4.6 Conclusion

Following RM, 77% of women had a subsequent pregnancy, of whom 63% of women had a livebirth. Younger women were more likely to conceive than to have no further pregnancy. Women over 40 or with infertility, were also less likely to have a livebirth over time. In addition to older age, smoking and parental balanced translocations were associated with a reduced likelihood of further pregnancy. No investigation or treatment

was associated with pregnancy outcome, reiterating the importance of the supportive aspects of care for women and their partners after RM, as well as counselling regarding individual risk factors. There is a need for greater information on pregnancy outcomes in women with RM, and to facilitate this, consideration should be given to prospective RM databases and a national register.

Chapter 5 – Recurrent Miscarriage and Infertility: A National Service Evaluation

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Chapter 5 – Recurrent Miscarriage and Infertility: A National Service Evaluation

5.1 Abstract

The appropriate clinical care of women/couples with infertility experiencing recurrent miscarriage (RM) is overlooked in international guidelines. We sought to evaluate care provision for women/couples with RM and infertility across public (19 clinics providing RM care, five fertility clinics) and private sectors (nine fertility clinics) using adapted guideline-based key performance indicators (KPIs) for RM.

An online survey comprised of multiple-choice/open questions was administered via Qualtrics from Nov 2021-Feb 2022, encompassing: (i) structure of care, (ii) investigations, (iii) treatments, (iv)counselling/supportive care, and (v) outcomes. Clinical leads for pregnancy loss and fertility and Clinical Nurse/Midwife Specialists within each unit/clinic were invited to participate.

The response rate 73% (24/33), varied by provider: Public RM care (18/19;95%), 2/5 Public fertility (40%); Private fertility (3/9; 33%). Access to fertility expertise was limited in public RM clinics (39%). While investigations and treatments provided mostly adhered to guidelines, there was uncertainty regarding immunotherapies. Educational needs identified included fertility counselling, informative and supportive care resources. Clinical outcomes were seldom audited (2/22; 9%). Greater engagement with the private sector is required to unify care across sectors and to ensure standardised evidence-based care. Audit and outcomes reporting should be mandated. Lived experience of current care structures should inform service improvements.

Keywords: Miscarriage, infertility, audit, recurrent miscarriage, pregnancy outcomes, ART

Impact statement

What is already known on this subject?

There is a paucity of research into the appropriate clinical care of women/couples with infertility experiencing recurrent miscarriage, with a resulting deficit within international RM guidelines. It is known that RM care is variable and often not in line with guidance.

What do the results of this study add?

This study demonstrates that while care is largely in line with clinical practice guidelines, there was variation in counselling, imaging and surgical treatments offered. Areas for education identified included fertility counselling and resources for information provision and supportive care. Clinical outcomes were seldom audited.

What are the implications of these findings for clinical practice and/or further research?

Fertility care must expand to ensure access for women with RM and infertility. Further research exploring barriers and facilitators to the delivery of evidence-based care for women/couples with infertility and RM is required. The lived experiences of service users must inform service improvements.

5.2 Introduction

The traditional definition and care model for recurrent miscarriage (RM) whereby three consecutive miscarriages are the threshold for investigation, treatment, or supportive care has been challenged recently (14,182,607). This move to implement care after any two pregnancy losses before viability (29,617) has been driven, in part, by women's experiences (408,618) and identification of a need for greater support after miscarriage (410,419,438). Increasingly, miscarriage is recognised as a risk factor for both future pregnancy outcomes and maternal cardiovascular disease (1).

The need of women/couples to understand why a miscarriage has occurred has been linked to subsequent psychological wellbeing (618). It is unsurprising that in an examination of clinical practice in the UK, a proportion of investigations and treatments for RM outside of Royal College of Obstetricians and Gynaecologists (RCOG) guidance were requested by women (323). Other factors attributed to deviation from clinical practice guidelines (CPGs) included the acceptability of guidelines and the low-quality evidence underpinning them (323). Reduced compliance to CPGs has previously been demonstrated internationally (619,620). Advanced maternal age and higher order miscarriage were also highlighted as driving factors for performing investigation and treatment outside of CPG recommendations (620).

These studies did not consider the fertility history of the couple in applying CPGs, although gamete donation was considered by over a third of Dutch gynaecologists as a treatment for RM(619). Updated draft clinical guidance has not considered couples who experience RM and concurrent infertility (26,29), reflecting their exclusion from studies in the wider literature (621). An international evaluation of RM CPGs showed that recommendations for the management of RM, including supportive care, do not incorporate the fertility history of women/couples experiencing RM (472). This oversight is not insignificant; RM and infertility share risk factors such as maternal age, have a reciprocal association and are independent risk factors for adverse pregnancy outcomes (621). Moreover, the psychological impact of the dual experience results in differing supportive care needs (437).

In the Republic of Ireland (ROI), several factors complicate the care of women with RM and infertility. Primarily, to date there has been no national RM guideline, rather the

RCOG guideline was adopted by most Obstetricians and Gynaecologists (34). Public fertility care is limited in capacity and geographical location, therefore most fertility care is provided by private or not-for-profit healthcare operatives (43). Fertility services in the private and not-for-profit sector currently encompass nine main providers, some with multiple clinics nationwide (464). While clinics which handle human tissue are registered and monitored (464), there is no other fertility care register or mandatory outcomes reporting (43). A review of websites providing RM information found smaller clinics or individual fertility specialists provide a variety of investigations and some treatments, including artificial reproductive technologies (ART), in a more limited capacity (477). Without a national miscarriage or pregnancy database, or a requirement for fertility clinics to publish outcomes data, it is unknown how many women and couples in Ireland experience RM and infertility. The clinical pathways within private services or between public and private are also unclear. Furthermore, how care is delivered to women and couples with RM and infertility within the ROI or how this care varies nationally is unknown.

This study sought to evaluate care provision for women/couples with RM and infertility within the current framework across public and private sectors, using adapted guideline-based key performance indicators for RM.

5.3 Materials and Methods

The Clinical Research Ethics Committee of the Cork Teaching Hospitals granted ethical approval for this study (ref ECM 4 (i) 13/4/2021 & ECM 3 (aaa) 19/10/2021).

This online survey on RM and Infertility was administered via Qualtrics and modelled on guideline-based KPIs for RM care developed within the RE:CURRENT Project through a six-phase consensus study (475). The survey comprised 41 questions, mainly multiple choice, across five sections pertaining to the care of women/couples with RM and infertility: (i) structure of care, (ii) counselling/supportive care, (iii) investigations, (iv) treatments and (v) outcomes (Supplementary File 5.1).

The survey was distributed alongside a national service evaluation on RM care. Respondents to the RM service evaluation in each of the 19 maternity hospitals/units in Ireland (named lead clinician, and/or clinical midwife/nurse specialist (CMS) in

bereavement and loss, or Director of Midwifery), were asked to complete the survey (34). Additionally, the named lead clinician for fertility in maternity units which had a public fertility service were approached (n=5). The survey was also distributed to the clinical lead or specialist with an interest in RM each private fertility clinic (n=9). The survey algorithm was constructed such that questions were tailored towards those working in the public RM service, public fertility, or private fertility sectors accordingly. Only one response per service was required.

Participants were invited to complete an online survey between 15 November 2021 and 18 March 2022. To facilitate recruitment, individual invites were emailed to potential participants, and clinic managers, where applicable. Participants provided informed consent prior to survey commencement. They were advised that the survey would take about 45-60 minutes to complete and reassured that reported findings would not identify individual participants, clinics, or hospitals. Alternative modes of completion included telephone, or in-person, completion with a research team member. Regular (n=3) email reminders were used to maximise the response rate. Data was analysed in Microsoft Excel using descriptive statistics.

5.4 Results

5.4.1 Demographics

The response rate was 73%, with 24 of 33 individuals completing the survey for their clinic/service. This included 18 healthcare professionals (HCPs) in public maternity services (18/19; 95%), two consultants in public/not-for-profit fertility services (2/5; 40%); three HCPs from private fertility clinics (3/9; 33%). Nine stated that they were clinical lead for a RM clinic (9/24; 38%). Greater details on respondents are presented in Table 5.1.

Table 5. 1: Respondent demographics and counselling/supportive care

Respondent Demographics	N = 24	Frequency	Percentage
Health professional role			
Consultant obstetricians/gynaecologists		16	75
Fertility Specialists		1	4
Clinical Midwife Specialists		5	21
Fertility Nurse/Midwife Specialist		2	8
Length of experience in RM or Fertility Services			
< 1 year		2	8
1-5 Years		7	29
6-10 Years		6	25
11-20		6	25
>20 years		3	13
Sector			
Public		8	33
Private		3	13
Public and private		13	54
Counselling Resources	N = 24	Frequency	Percentage
International Guidance used*			
RCOG		22	92
European Society of Human Reproduction and Embryology (ESHRE)		14	58
American Society of Reproductive Medicine (ASRM)			
British Fertility Society (BFS)		4	17
Society of Obstetrics and Gynaecology Canada		2	8

National Institute for Health and Care Excellence (NICE)		1 1		4 4
Additional educational supports*				
National Guideline (unspecified)		12		50
Local guideline/protocol		9		38
Online resources		15		63
Onsite training/CPD		8		33
External training/CPD		13		54
Other		2		8
Counselling and Supportive Care	N = 24	Yes	No	Unsure
Age-related Miscarriage Risk		20 (83%)	1 (4%)	3 (13%)
Age-related Aneuploidy Risk		18 (75%)	3 (13%)	3 (13%)
Tests of Ovarian Reserve		19 (79%)	3 (13%)	3 (13%)
PGT-A		12 (50%)	8 (33%)	4 (17%)
Intra-Cytoplasmic Sperm Injection		8 (33%)	12 (50%)	4 (17%)
Egg Donation		15 (63%)	6 (25%)	3 (13%)
Semen Analysis		14 (58%)	7 (29%)	3 (13%)
Sperm DNA Fragmentation		4 (17%)	16 (67%)	4 (17%)
Sperm Donation		11 (46%)	9 (38%)	4 (17%)
Surrogacy		8 (33%)	12 (50%)	4 (17%)
Adoption		8 (33%)	12 (50%)	4 (17%)

*More than one response possible

5.4.2 Structure of Care

Responses to questions for structure of care in both public and private sectors are laid out in Table 5.2.

In half of cases, the consultant with training in RM management was the respondent. Reasons for referral from private clinics to public or private RM clinics included to obtain investigations not available within a particular clinic, to avoid costs of investigations for women/couples, or for expertise in the interpretation of results or further management. Regarding referral for surgical treatments, 11/19 (58%) respondents referred within or to public and private services, 7 referred within or to public services only (7/19; 37%), with one stating no referral pathway existed (1/19; 5%).

5.4.3 Counselling and Supportive Care

Respondents were asked what topics they regularly discussed with women with RM and infertility; these results, in addition to the guidance employed, are presented in Table 5.1.

Additional sources of education and guidance cited included the Human Fertility and Embryology Authority (HFEA) (n=1) and colleagues working in other jurisdictions (n=1). Written information on RM and infertility or related topics was provided by four providers (4/24; 17%); one respondent cited a local leaflet, the remainder directed women to the websites of international bodies such as ESHRE, RCOG, NICE, ASRM or BFS.

Eleven respondents (11/20; 55%) provide information to women/couples about reputable sources of support for infertility and RM, both within the hospital and externally, while nine answered no (9/20; 45%). Sources of support included national support groups for miscarriage or pregnancy loss (n=5), local leaflet (n=4), bereavement midwife contact details (n=3) national websites (n=2) and international bodies (n=2).

Table 5. 2: Structure of care

Structure of care (N=24)	n	Frequency	Percentage
No. of women/couples with RM and infertility seen annually	24		
0-10		6	25
10-30		6	25
40-65		4	17
100-150		2	2
Not stated/unsure		5	21
Time allocated for consultations	23		
15-20 mins		3	13
20-30		4	17
30-45		9	39
Up to 60		3	13
Unsure/Not stated		5	22
Public RM clinic only (N=18)			
Fertility specialist available to consult where women have experienced RM after infertility?	18		
Yes		7	39
No		11	61
If external referral, where are referrals made?	13		
Public fertility clinic		7	54
Private fertility		3	23
Patient choice		1	8
No pathway		1	8
Unsure		1	8
Counsellor specialising in infertility?	18		
Yes		5	28
No		11	61
Not answered		2	11
Fertility sector only (N=4)			
Obstetrician with training in management of RM available?	4		
Yes		3	75
No		1	25
External referrals	4		
Public RM clinics		3	75
Private consultant/clinic		1	25
Referral criteria	4		
2 consecutive miscarriages		1	25
2 non-consecutive miscarriages		1	25
3 consecutive miscarriages		4	100
3 non-consecutive miscarriages		4	100
Age dependent (>35years)		1	25
Artificial Reproductive Technology dependent		0	0
Bereavement counsellor experienced in pregnancy loss available?	4		
Yes		4	100
No		0	0

5.4.4 Investigations

Respondents were asked if they performed additional investigations outside of routine fertility testing (e.g., full blood count, liver, renal and thyroid function tests, prolactin, diabetic screen, day 2 FSH/LH, day 21 progesterone, pelvic US, ovarian reserve testing, male partner semen analysis and hysterosalpingogram (HSG)) which feature in the KPIs; results are presented in Table 5.3.

Six respondents would routinely perform imaging in addition to a pelvic ultrasound (6/20; 30%), 13 would do so in certain clinical circumstances (13/20; 65%), and one would never do so (1/20; 5%). Named additional imaging obtained included CT (n=5), MRI (n=13), HSG (n=13) and hysterosalpingo-contrast sonography (HyCoSy) (n=2).

Ten respondents said they would treat chronic endometritis if found (10/22; 45%), six said they would not treat (6/22; 28%) and six were unsure (28%). The purpose of a HVS would be to test for chlamydia (n=7), gonorrhoea (n=3), other unnamed sexually transmitted infection (n=3), bacterial vaginosis (n=5) or candida (n=1.) Fourteen respondents said they would subsequently treat with antibiotics (14/20; 70%).

5.4.5 Treatments

Respondents were asked which treatments within the KPIs that they would provide to women with RM and infertility, which are shown in Table 5.3. Hysteroscopy and laparoscopy are included as treatments as they require placement on a surgical operating list, in addition to the potential to "see and treat". Embryoscope was mentioned by one provider as a potential add-on treatment for this cohort. Progesterone therapy was also examined, with notable variety in the duration of prescriptions (N=14): up to end of 12th week (n=6), up to eight weeks (n=2), up to the 10th week (n=1), up to 16 weeks (n=2), and variably according to history (n=1). Reasons cited for varying progesterone regimes included use of donor oocytes, frozen cycles or a preterm birth history.

Eight respondents (8/20; 40%) provided written information to women/couples on medication commencement/cessation, while 12 did not (60%). Two respondents (2/22; 9%) indicated that audit of subsequent pregnancy outcomes is performed in their unit (no audit; 20/22 (90%); no response, n=2). Both providers recorded livebirth rates, while just one examined the subsequent pregnancy rate and first or second-trimester miscarriage rate.

Table 5. 3: Investigations and Treatments

Investigations	N	Yes	No, never	If clinically indicated	Don't Know
Anti-phospholipid antibodies (APLA)	24	18 (75%)	0	3 (13%)	3 (13%)
Thrombophilia Screen		10 (42%)	4 (17%)	7 (29%)	3 (13%)
Thyroid Peroxidase Antibodies		11 (46%)	2 (8%)	7 (29%)	4 (17%)
Androgen Testing[a]		7 (29%)	3 (13%)	10 (42%)	4 (17%)
Autoimmune Screen*		8 (33%)	4 (17%)	9 (38%)	3 (13%)
Anti-Nuclear Antibodies		9 (38%)	7 (29%)	5 (21%)	3 (13%)
HLA Antibodies[a]		0	16 (67%)	2 (8%)	6 (25%)
Cytokines[a]		0	16 (67%)	1 (4%)	6 (25%)
Anti-HY Antibodies[a]		0	15 (63%)	3 (13%)	6 (25%)
Natural Killer Cells[a]		0	16 (67%)	2 (8%)	6 (25%)
Additional Investigations					
Endometrial Scratch[a]	22	4 (18%)	15 (68%)	0	3 (14%)
If yes: 1. Uterine Natural Killer Cells[a] 2. Chronic endometritis[a]	4	 0 3 (75%)	 3 (75%) 0	 1 (25%) 1 (25%)	 0 0
Endometrial Biopsy[a]	24	5 (21%)	12 (50%)	0	5 (21%)
If yes: 1. Uterine Natural Killer cells[a] 2. Chronic endometritis[a]	5	 1 (20%) 2 (40%)	 2 (40%) 0	 1 (20%) 3 (60%)	 1 (20%) 0
High vaginal swab[a]	20	4 (20%)	4 (20%)	12 (60%)	0
Spermploidy[a]	22	2 (9%)	18 (82%)	0	2 (9%)

Sperm DNA fragmentation[a]	22	1 (5%)	19 (86%)	0	2 (9%)
Would you routinely recommend any of the following treatments for women with RM and infertility?	N	Yes	No, never	Only in Certain Circumstances	Don't Know
Aspirin	24	13 (54%)	0	7 (29%)	4 (17%)
LMWH		3 (13%)	1 (4%)	15 (63%)	5 (21%)
Prednisolone		0	6 (25%)	13 (54%)	5 (21%)
Hydroxychloroquine		0	13 (54%)	6 (25%)	5 (21%)
Progesterone[b]		17 (71%)	0	3 (13%)	4 (17%)
Metformin		1 (4%)	0	19 (79%)	4 (17%)
ICSI		0	7 (29%)	11 (46%)	6 (25%)
PGT-A		2 (8%)	6 (25%)	8 (33%)	8 (33%)
IVIG		0	12 (50%)	3 (13%)	9 (38%)
Intralipid therapy		0	13 (54%)	2 (8%)	9 (38%)
Immune therapy (other)**		0	11 (46%)	3 (13%)	9 (38%)
Hysteroscopy		5 (21%)	1 (4%)	15 (63%)	3 (13%)
Laparoscopy and dye		5 (21%)	1 (4%)	15 (63%)	3 (13%)
Myomectomy for fibroids		2 (8%)	1 (4%)	17 (71%)	4 (17%)
Metroplasty		2 (8%)	8 (33%)	8 (33%)	6 (25%)
Hysteroscopic Adhesiolysis		6 (25%)	2 (8%)	10 (42%)	2 (8%)

[a] represents investigations not recommended within CPGs

[b] sole recommended treatment within KPIs

* Extractable nuclear antigen, Anti-neutrophil cytoplasmic antibody, rheumatoid factor

**respondents did not specify which other immunotherapies they would consider

5.5 Discussion

This national service evaluation of care for women/couples with RM and infertility demonstrates that while management mostly adhered to the relevant KPIs, there was variation in counselling, investigations and surgical treatments offered. While public providers responded well, the private provider responder rate was low.

There was wide range in the number of women seen annually with RM and infertility, from zero to 150. A recent audit of RM care in women with three miscarriages and infertility in a large Irish maternity unit estimated an average of 11 women attended per annum (622). Even when including women with two consecutive miscarriages, provided figures seem improbable. Potentially, this is due to more women seeking treatment in the private sector, possibly after two rather than three miscarriages, or a disparity between the provided estimations and the true number seen annually. This reiterates the need for better recording of miscarriage data, possibly through a national register or database, along with outcomes data from fertility services (43).

The availability of fertility specialists for consultations in the public sector was 39%, with 28% having access to fertility counsellors. Conversely, within fertility services access to a specialist experienced in RM care (75%) and to bereavement counselling (100%) was better. While access to these services within the public sector should improve with funding for fertility services nationally, efforts must be made to overcome the geographical limitations posed by centralisation of these services in larger cities. Although fertility clinics were in agreement on referring for RM care after three miscarriages, this is outdated guidance (21). Referral pathways from public hospitals for fertility care were mostly to larger public maternity hospitals, but a quarter were to private clinics or not defined. Surgical pathways were also unclear, with most referring to both public and private operators. How efficient these pathways are regarding waiting periods, and what additional burdens such as travel and costs they place on women/couples, merits exploration.

The time allocated to consultations was also variable, from 15-60 minutes. It is important that women/couples are allocated adequate time for in-depth counselling to address their concerns and to plan for future pregnancy (406,410). This is particularly important for women/couples with infertility who are highly motivated to conceive again and seek

fertility treatments. Certainly, information provided was variable, with less than half of women provided with information on all potential fertility treatment options. The risks and benefits of such treatments, including success rates, are important to relay to, and discuss with, women/couples (623). Notably, the 2011 RCOG guideline predominated as an educational resource, suggesting a possible reluctance to follow international guidelines, alongside the need for updated education and guidance. Interestingly, half of respondents indicated that they used national guidelines to inform practice, however there was neither a national RM nor fertility guideline available. An Irish guideline on RM has since been published (595), alongside updated ESHRE and RCOG guidelines; identifying this educational deficit regarding guidelines is important to secure resources and training supports for successful implementation. Details of continuing professional development attended or online resources employed were not provided by respondents, despite the opportunity to do so. There was limited awareness of available national resources for women/couples, with international sources cited more often. Awareness of these national educational and supportive resources must increase to direct women to the most relevant information and accessible supports, as online resources are not always reliable or wholly informative (477). Identifying women's/couples' needs could also inform more applicable resources.

Investigations routinely performed varied, similar to other studies (34,323,619,620). This may reflect the adaptation of practice in line with updated evidence, as some previously recommended investigations are not recommended in updated guidance, (e.g., thrombophilia screening) (26,29). Some investigations while demonstrating a clear association with RM, such as ANA and thyroid peroxidase antibodies, do not have subsequent evidence-based treatments, which may deter from inclusion in routine practice (234,306). Most respondents did not perform unorthodox immunological investigations routinely, in line with CPGs. While 25% of respondents were unsure of unorthodox immunological investigations, a considerable proportion were unsure of standard investigations (13%), e.g., anti-phospholipid antibodies, indicating a need for greater education, extended to all involved HCPs. Counselling women/couples on not performing unnecessary investigations such as HVS is important as almost half of couples with RM feel under-investigated (457). Endometrial scratch or biopsy was performed against CPGs by a proportion of respondents, in addition to unrecommended tests for

uterine natural killer cells and chronic endometritis. They would also treat chronic endometritis, which is not shown to be of benefit (268). As it was beyond the scope of this study, it is unknown what laboratories perform these immunological tests or what the parameters and subsequent treatment thresholds are. Such standardisation is important in determining a true clinical effect and the absence of protocols for immune profiling, particularly for natural killer cells, has been flagged in systematic reviews of immunological treatments (624). Immunological treatments employed such as intralipid therapy and LIT continue to not be recommended within updated guidance, despite some reported benefits, due to the heterogeneity of study populations and protocols, and methodological quality (625,626).

While sperm DNA fragmentation testing is to be considered (35), it is not widely available as our findings show, and implementation would require significant investment in andrology services within the ROI. In addition to structural constraints in ART provision, PGT-A remains a “code red” add-on due to a lack of high-quality evidence to demonstrate a benefit in RM treatment (206). Similarly, there is no strong evidence to support treatment for male factors in RM (627).

Surgical interventions were mostly performed in line with CPGs. Few respondents performed complex surgeries such as metroplasty. Again, the publication of outcomes data for women undergoing these surgeries would contribute to the limited available literature. Such treatments should be ideally within the context of a randomised control trial (26) and undertaken by a multi-disciplinary team (MDT)(628). Given the small numbers of women likely to experience a major Mullerian abnormality annually and the absence of an international guideline on management (629), consideration should be given to establishing such an MDT with clear protocols within the new public fertility framework.

Medical treatments for unexplained RM were not widely prescribed with most reserved for certain clinical circumstances. Greater consideration could be given to prescribing aspirin given the results of the EAGeR trial and the benefits in reducing pre-eclampsia and preterm birth (332,630) particularly in a cohort of women with infertility or of AMA. Similarly, there is evidence to suggest progesterone is of benefit in those with a history of miscarriage and bleeding (385) and it could be offered in the absence of bleeding as there

is a benefit, albeit not statistically significant (14). Again, a proportion of respondents were unsure of prescribing medications. This study identifies a clear need for a national clinical guideline with accompanying education, combined with adequate resources and supports for implementation among all HCPs.

5.5.1 Strengths and limitations

This is an original study using guideline based KPIs developed with a diverse stakeholder group to examine care provision nationally for women/couples with RM and infertility. This topic had not been covered previously nationally or internationally, and this work, like previous studies, provides insights on how current practice compares to current CPGs. CPGs are limited by the quality and currency of evidence underpinning recommendations, with a notable scarcity of high-quality randomised control trials in RM and infertility treatments (626,631). Moreover, the RCOG and ESHRE guidelines used for KPI development have been updated and an Irish guideline on RM published; these will need to be incorporated into revised KPIs for future audit.

This study is timely, providing evidence for service improvements in advance of the introduction of publicly-funded fertility treatment in the ROI (Women's Health Action Plan 2022 – 2023). The 73% response rate incorporates an excellent response rate from RM services (95%), but poor response rates from public (40%) and private (33%) fertility clinics. This was despite three reminders and efforts associated with higher response rates such as small sample size, personalisation and reworded reminders (632,633).

Potentially, this excludes meaningful insights into fertility structures and management practices. It is a potential limitation that just one clinic from each fertility group was surveyed as there may have been inter-responder/regional variation. A proportion of surveys were answered by CMS who may not have experience of ART and this may be a contributory factor in the not insignificant proportion of blank/don't know responses.

5.6 **Conclusions**

This national service evaluation identified practice largely in line with CPGs. However, staff education is required, especially regarding counselling, information provision and resources to better inform and support women. Care structures must improve to allow better access to fertility services and ameliorate referral processes. Investigations should

align with updated guidance. A small number of providers offer unorthodox investigations and treatments, which warrants further attention. There needs to be greater engagement from the private fertility sector and an onus to report outcomes data as well as treatments and interventions used. The lived experience of women/couples currently using RM and infertility services must be obtained to direct service improvements.

Chapter 6 – An examination of care received by women with recurrent miscarriage and infertility against guideline-based key performance indicators.

Linehan L, Hennessy M, O'Donoghue K. An examination of care received by women with recurrent miscarriage and infertility against guideline-based key performance indicators. Eur J Obstet Gynecol Reprod Biol. 2023 Mar;282:17-23. Doi: 10.1016/j.ejogrb.2023.01.002. Epub 2023 Jan 2. PMID: 36621261.

Chapter 6 – An examination of care received by women with recurrent miscarriage and infertility against guideline-based key performance indicators

6.1 Abstract

Objectives

International guidelines for the management of recurrent miscarriage (RM) do not provide detailed guidance for the care of women/couples with concurrent infertility. Research studies concerning the investigation and treatment of RM frequently omit this cohort. The aim of this study was to assess the care of women/couples with infertility attending a RM clinic in a large tertiary unit in the Republic of Ireland.

Study Design

We conducted an audit of women with RM and infertility attending our RM clinic from 2008-2020 against 110 established guideline-based key performance indicators (KPIs) for RM care, encompassing five categories: structure of care, counselling/supportive care, investigation, treatment and outcomes. Information was gathered from documentation from the RM clinic, hospital laboratory and electronic health records.

Results

We identified 128 women with infertility and RM. Information provision in RM clinics regarding modifiable risk factors (71%; 91/128) and unexplained RM (53%; 69/128) could be improved. Most women were investigated in line with KPIs, except for pelvic ultrasound (40%; 51/128), cytogenetic analysis (27%; 34/128) and 3D ultrasound (2%; 2/128). Immunotherapies were seldom prescribed (<1%); however, 98% (125/128) of women received aspirin, 48% LMWH (62/128) and 16% corticosteroids (21/128). Surgical interventions were uncommon (5%; 6/128)). The subsequent pregnancy rate was 70% (89/128), with 36% undergoing artificial reproductive technology (32/89). The livebirth rate was 63% (56/89); 37% had a further pregnancy loss (33/89), of which two were second-trimester miscarriages.

Conclusions

Women with RM and infertility received care largely in line with RM guideline-based KPIs. However, we identified areas for improvement, including the quality of information provision, and access to certain investigations. While guideline-based KPIs allow for internationally applicable and reproducible audit that can direct service improvements, the experiences and needs of service-users are not captured, meriting further qualitative research.

6.2 Introduction

Recurrent miscarriage (RM) is a reproductive medicine topic that has received increased attention of late. There is increasing recognition of its significance in subsequent pregnancies, as well as a need to improve care structures and psychological supports for women and couples (1,14). The 2021 Lancet Series on miscarriage proposed a graded approach to evidence-based care of women experiencing miscarriage and RM (14). This approach would surmount the debates within international guidelines on whether investigations should commence after two (28,35) or three miscarriages (603) or be confined to consecutive losses (35,603), and could synchronise clinical practice. It would also validate women's experiences of loss and better meet their individual needs (408) Updated draft guidelines have also (ESHRE, RCOG) incorporated these suggestions (35,603). This focus on RM is necessary; recent publications have shown inconsistencies in RM care structures, as well as disparities in investigation and treatment (34,323).

However, the Lancet Series and latest guidelines failed to issue any specific guidance for women with RM and a history of infertility (14); an omission previously noted in a systematic review of clinical guidelines (472). The guidelines reflect the wider literature; a narrative review demonstrated that women/couples with RM and infertility were seldom examined in high-quality research, providing little insight on their optimal care , with a sole qualitative piece exploring their experiences (437).

Although overlooked, RM and infertility are not uncommon reproductive health issues. Over one million artificial reproductive technology (ART) cycles took place in Europe in 2018 (42). Increasingly, women with RM undergo ART with pre-implantation testing for aneuploidy (PGT-A); RM accounted for 10% of PGT-A undertaken in 2016-2017 (634). RM is associated with secondary infertility and reciprocally, delayed time to conception is associated with miscarriage (621). Both RM and infertility are associated with adverse pregnancy outcomes such as preeclampsia, placental abruption and placenta praevia (1,5)

The care of women with RM and infertility is further complicated by the fact that Ireland is an outlier in Europe by not providing publicly funded IVF (41); the majority of IVF is undertaken in the private sector (43). The Irish government have recently announced increased availability of publicly funded ART (468). In advance of this implementation, we

sought to examine the care of women with RM and infertility to identify areas for improvement and resource allocation.

We aimed to evaluate the care received by women/couples with RM and infertility against RM guideline-based Key Performance Indicators (KPIs), to determine if care follows international best practice, to audit pregnancy outcomes and to identify potential areas for improvement.

6.3 Methods

Women who attended the RM Clinic in a large tertiary hospital between 2008 and 2020, with a history of RM and who had undergone investigation and/or treatment for infertility were audited. The RM clinic is a consultant-led clinic supported by Clinical Midwifery Specialists in Bereavement and Loss which sees approximately 70 women/couples annually.

Women with RM were identified from a cohort study of women with three consecutive miscarriages (n=748) (635). Women were identified as having a history of infertility if it was documented in their clinical records that they or their partner had undergone fertility investigations and/or treatments in either the public or private sector. Fertility investigations or treatments undertaken before or after attendance at the RM clinic were included, i.e., primary and secondary infertility was examined. For outcomes, the pregnancy after the most recent RM clinic attendance was audited.

As part of the RE:Current Study (636), 110 KPIs for RM care were developed through a six-stage process, including a systematic review of guidelines, Delphi surveys and consensus meetings with a Research Advisory Group (475). These KPIs were used for a national service evaluation of RM care in the 19 maternity units across Ireland (34).

KPIs were distributed across five categories – structure of care (n=20), counselling and supportive care (n=7), investigations (n=30), treatment (n=34) and outcomes (n=19) (34). Most KPIs for structure of care pertained to overall organisation of services rather than care of individuals and were assessed in the national service evaluation (34) (Supplementary File 6.1). Some KPIs were adapted to accommodate clinical audit (Supplementary file 6.2).

Clinical correspondence from the RM clinic was examined in detail in lieu of chart review for documentation of relevant risk factors and counselling, fertility care information and management plans. Laboratory and radiology applications and the Patient Information Management System (PIMS) were examined to assess whether RM and fertility investigations had been performed as well as pregnancy outcomes data. Electronic health records for women attending after 2016 were available for review. One researcher reviewed the data following in-depth discussion and agreement by all authors on the required criteria to meet each KPI.

Binary data for each KPI were entered into a Microsoft excel file for descriptive analysis. As this study came under the remit of clinical audit, ethical approval was not required.

6.4 Results

Overall, 128 women were included. Most women (100/128; 78%) had fertility care before attending the RM clinic, versus 22% (27/128) afterwards, (data unavailable, n=1). Fertility care provision was predominantly private (82/128; 64%) with 35% provided publicly (44/128) and 1% (2/128) received both public and private care.

6.4.1 Structure of care

Most structures for the RM clinic were in keeping with the KPIs (Supplementary File 6.1). Two KPIs in this section were included in the audit and confirmed that women received tailored investigation (126/128; 98%) and management plans (127/128; 99%) with a timeline for care.

Counselling and Supportive Care

Good practices were evident in counselling and supportive care (Table 6.1). Most women aged over 40 were advised of the increased risk of miscarriage (89%). Counselling regarding pre-conceptual folic acid (83%), behaviour/weight-related risk factors (71%), the risks and benefits of treatments (69%), and pregnancy success after unexplained RM (54%), was provided to most women, but could be improved.

Table 6. 1: Counselling and Supportive Care Key Performance Indicators

Counselling and Supportive Care Key Performance Indicators (n=9)	N (total)	Provided	n	Adherence %
Did the RM clinic provide information to women/couples about the increased risk of pregnancy loss with advancing age (>40)?	46	Yes	41	89
		No	5	
Did the RM clinic provide information to women/couples regarding changes on any of the following behavioural/weight-related risk factors as relevant: smoking cessation, weight management, healthy eating and physical activity (normal exercise pattern; not excessive), reducing alcohol and drug consumption?[a]	128	Yes	91	71
		No	37	
Did the RM clinic provide information on a) folic acid and	128	Yes	106	83
		No	22	
b) vitamin D supplementation?[a]	128	Yes	1	
		No	127	1
Did the RM clinic provide women/couples with unexplained RM with information about their individual chances for a future successful pregnancy?	128	Yes	69	54
		No	59	
Did the RM clinic provide information to women/couples about unorthodox investigations and treatments that are not supported by quality medical research?[a]	128	Yes	3	2
		No	125	
Did the RM clinic provide information about possible benefits and disadvantages of treatment to individuals/couples with RM?	128	Yes	88	69
		No	40	
Did the RM clinic provide information about clinical trials for which they may be eligible, and additional information if the individual/couple is interested in pursuing assessment for eligibility?	128	Yes	0	0
		No	128	
Did the RM clinic offer/provide access to genetic counselling to all individuals and couples with an abnormal parental karyotype result? [a]	5	Yes	3	60
		No	2	
Did the RM clinic offer/provide access to genetic counselling to individuals and couples with an abnormal fetal karyotype result?[a]	12	Yes	2	16
		No	10	

[a]adapted KPI

The denominator (N) represents the number of women to whom the KPI was applicable.

6.4.2 Investigations

There was 100% adherence to most KPIs where the recommendations were to *not* perform an investigation, such as natural killer cells testing and spermploidy/DNA fragmentation (Table 6.2). KPIs pertaining to fertility investigations performed less well, with 49% adherence to luteal phase testing and 88% to ovarian reserve testing . Most ovarian reserve testing (15/16; 94%), day 2-5 hormone profile testing (61/73; 84%), luteal phase testing (53/65; 82%) and androgen testing (9/12; 75%) were performed outside of the RM clinic.

Most women had investigations tailored to their history (98%), however documentation of behavioural/weight-related risk factors merits attention (68%). Most recommended investigations were performed such as thyroid function tests (99%), antiphospholipid antibodies (97%), anti-nuclear antibody testing (95%), diabetes screening (94%) and parental karyotyping (88%).

Areas for improvement in genetic testing include performance of cytogenetic testing (27%) and parental karyotyping after an atypical fetal karyotype was identified (76%). No array-CGH or genetic polymorphism studies were performed. Tests for spermploidy/DNA fragmentation were not undertaken as they are unavailable nationally.

Only 40% of women had anassessment of uterine anatomy with transvaginal ultrasound. Most women who had an ultrasound did so through fertility clinics (37/51;73%). Although 3D ultrasound was available, just two were performed for suspected Mullerian abnormalities. Both women with Mullerian abnormalities did not have additional assessment of the urinary tract (0/2; 0%) and underwent uterine septum resection (0/2; 0%).

Table 6. 2 Key Performance Indicators for Investigations

Investigations Key Performance Indicators (n=28)	N	Performed	n	Adherence %
General Investigations				
Did the RM clinic use medical, obstetric (for women) and family history to tailor diagnostic investigations in RM for women and men?	128	**Yes** No	**125** 3	98
Did the RM clinic collect information on relevant risk factors (smoking, alcohol consumption, exercise pattern, and body weight) for women and their partners?	128	**Yes** No	**87** 41	68
Was a full blood count taken?	128	**Yes** No	**91** 37	71
Were electrolytes and liver function tests taken?	128	**Yes** No	**33** 95	26
Anatomical Investigations				
Did the woman undergo assessment of uterine anatomy?[a]	128	**Yes** No	**51** 77	40
Was uterine anatomy assessed using transvaginal ultrasound?[a]	128	**Yes** No	**51** 77	40
Was a 3D ultrasound performed?[a]	128	**Yes** No	**2** 126	2
Did women with a uterine septum undergo a hysteroscopy?[a]	2	**Yes** No	**1** 1	50
Did women undergo investigation of the kidneys and urinary tract after diagnosis of a Müllerian uterine malformation?	2	**Yes** No	**0** 2	0
Immune Testing				
Were antinuclear antibodies performed for explanatory purposes?	128	**Yes** No	**121** 7	95
Was natural killer (NK) cell testing of either peripheral blood or endometrial tissue undertaken in women with RM?[b]	128	Yes **No**	0 **128**	100
Thrombophilia				
Was screening for hereditary thrombophilia undertaken in women with RM?[a,b]	128	Yes **No**	122 **6**	5
Was screening for antiphospholipid syndrome undertaken in women with RM?[a]	128	**Yes** No	**124** 4	97
Were plasma coagulation markers (D dimers, prothrombin fragments, etc.) undertaken during pregnancy in women with RM?[b]	128	Yes **No**	0 **128**	100
Endocrine				
Were levels of **a)** thyroid stimulating hormone (TSH) and thyroxine (T4) and	128	**Yes** No	**127** 1	99

b) thyroid peroxidase (TPO)-antibody tested in women with RM?		**Yes** No	**10** 118	6
Was screening for diabetes undertaken in women with RM?	128	**Yes** No	**118** 10	94
Was ovarian reserve testing undertaken in women with RM?[b]	128	Yes **No**	16 **112**	88
Was a 'day 2–5' hormone profile [Follicle stimulating hormone (FSH), oestradiol, FSH/luteinising hormone (LH) ratio] taken?	128	**Yes** No	**73** 55	57
Was luteal phase insufficiency testing undertaken in women with RM?[b]	128	Yes **No**	65 **63**	49
Was androgen testing undertaken in women with RM?[b]	127	Yes **No**	12 **115**	91
Was vitamin D measurement undertaken in women with RM?[b]	128	Yes **No**	0 **128**	100
Infectious				
Was infectious screening using vaginal swab specimens undertaken in asymptomatic women with RM?[b]	128	Yes No	1 **127**	99
Genetic testing				
Was cytogenetic analysis of the pregnancy tissue undertaken at the third early miscarriage?	128	**Yes** No	**34** 94	27
Was array-based comparative genomic hybridisation (array-CGH) undertaken for genetic analysis of the pregnancy tissue?	128	**Yes** No	**0**	0
Was a genetic polymorphism study undertaken in cases of unexplained RM?[b]	128	Yes **No**	0 **128**	100
Did parents undergo peripheral karyotyping after the third miscarriage, to detect any balanced structural chromosomal abnormalities?	128	**Yes** No	**113** 15	88
Was cytogenetic testing of both parents undertaken following detection of a structural chromosomal disorder in the pregnancy tissue?	21	**Yes** No	**16**	76
Was testing for spermploidy (e.g., fluorescence in situ hybridisation [FISH]) or DNA fragmentation undertaken in men with RM?[b]	128	Yes **No**	0 **128**	100

[a]adapted KPI

The denominator (N) represents the number of women to whom the KPI was applicable.

[b] KPI where the recommendation is to NOT perform the test

6.4.3 Treatments

KPIs for treatments are shown in table 6.3.

Unrecommended procedures were generally not performed, such as surgeries for Mullerian abnormalities and endometrial scratch (n=0, 100%). However, deviation from KPIs was noted for myomectomy (66%), septum resection and intrauterine adhesiolysis (0%).

Most KPIs regarding unapproved medications were fully adherent, particularly immunotherapies. Compliance was reduced for medications in unexplained RM such as prednisolone (86%), LMWH (54%) and aspirin (2%). Six women prescribed aspirin (6/125; 5%) and LMWH (6/62; 10%) had an inherited/acquired thrombophilia and 14% (3/21) of women prescribed prednisolone had autoimmune disease.

Several treatments were also instigated in this cohort by fertility services. One hysteroscopic septum resection (1/2; 50%), and all myomectomies (2/2; 100%) were performed through fertility services. Antibiotics (1/1), intravenous immunogloulin (1/1) HCG (1/1) and intralipid (2/2) were prescribed solely by fertility clinics. Fertility clinics prescribed a proportion of aspirin (3/125; 2%), LMWH (11/62; 18%), prednisolone (10/21; 48%) and progesterone (13/106; 12%).

Table 6. 3: Treatments Key Performance Indicators

Treatments Key Performance Indicators (n=32)	N	Received	n	Adherence %
Haematological Treatments				
Did the RM clinic refer women with RM and antiphospholipid syndrome to local haematology service?	1	**Yes** No	**1**	100
Did women with APLS receive ASA and LMWH?	1	**Yes** No	**1**	100
Did women with APLS receive IVIG?[b]	1	Yes **No**	0 **1**	100
Endocrine				
Did women with RM and subclinical hypothyroidism TSH level defined by population (range: >2.5-4.0 mIU/L)] receive treatment with levothyroxine?	10	**Yes** No	**9** 1	90
Did women with overt hypothyroidism receive treatment?	5	**Yes** No	**5** 0	100
Did women with thyroid autoimmunity and hypothyroidism receive levothyroxine in their next pregnancy?	1	**Yes** No	**1** 0	100
Did women receive human chorionic gonadotrophin supplementation in pregnancy?[b]	128	Yes **No**	1 **127**	99
Did women with RM and hyperprolactinemia receive bromocriptine?	3	**Yes** No	**0** 3	0
Did women with PCOS/insulin resistance receive a prescription for metformin?[b]	10	Yes **No**	9 **1**	10
Genetic Treatments				
Did couples with RM who have no familial chromosomal disorder and no monogenetic disease receive Pre-implantation genetic testing?[b]	123	Yes **No**	1 **122**	99
Did women/couples receive preimplantation genetic screening (PGS) with in vitro fertilisation treatment (IVF)?[b]	123	Yes **No**	1 **122**	99
Was oocyte donation discussed at a multidisciplinary meeting as an alternative treatment in women?	5	**Yes** No	**0** 5	0
Did couples with RM undergo sperm selection?[b]	128	Yes **No**	1 **127**	99
Anatomical Treatments				
Did women with fibroids and RM undergo myomectomy (laparoscopic or open)?[b]	6	Yes **No**	2 **4**	66
Did women with a uterine septum undergo a hysteroscopic septum resection?[b]	2	Yes **No**	2 **0**	0
Did women with RM and bicorporeal uterus/uterus didelphys and double cervix undergo metroplasty?[b]	0	Yes **No**	0 **0**	100

Was uterine reconstruction for hemi-uterus offered/performed in women with RM?[b]	0	Yes **No**	0 **0**	 100
Was patient selection and treatment for a *hysteroscopic metroplasty of a uterine septum* done by a multidisciplinary team including specialists in reproductive medicine, uterine imaging and hysteroscopic surgery?	2	**Yes** No	**0** 2	0 100
Did women with RM and intrauterine adhesions undergo surgical removal?[b]	2	Yes **No**	2 **0**	0
Unexplained RM				
Were antibiotics prescribed to women with RM as a treatment?[b]	128	Yes **No**	1 **127**	 99
Was low dose aspirin prescribed for women with unexplained RM (i.e. without thrombophilia)?[a,b]	122	Yes **No**	119 **3**	 2
Did women with unexplained RM and Infertility (i.e. without thrombophilia) receive prescriptions for LMWH?[a,b]	122	Yes **No**	56 **66**	 54
Did women with RM and Infertility receive a prescription for steroids?[b]	128	Yes **No**	21 **107**	 84
Did women with RM and Infertility without AI disease receive corticosteroids?[b]	125	Yes **No**	18 **107**	 86
Did women with RM and Infertility receive Intravenous Immunoglobulin?[b]	128	Yes **No**	1 **127**	 99
Did women with RM and Infertility receive empiric progesterone?	128	**Yes** No	**106** **22**	83
Did women with Infertility and RM receive intralipid therapy?[b]	128	Yes **No**	2 **126**	 98
Did women with RM and Infertility receive lymphocyte immunisation therapy?[b]	128	Yes **No**	0 **128**	 100
Did women with RM and Infertility receive Granulocyte-Colony Stimulating Factor?[b]	128	Yes **No**	0 **128**	 100
Did women with RM and Infertility receive Tumour Necrosis Factor alpha receptor blockers?[b]	128	Yes **No**	0 **128**	 100
Did women with RM and Infertility undergo an endometrial scratch?[b]	128	Yes **No**	1 **127**	 99
Was low dose folic acid (0.4 mg/day) pre-conceptually as a treatment for unexplained RM?	128	**Yes** No	**1** 127	1
Was 5mg folic acid prescribed to women with RM and infertility?	128	**Yes** No	**104**	81

[a]Adapted KPI

The denominator (N) represents the number of women to whom the KPI was applicable.

[b] KPI where the recommendation is to NOT perform the test

6.4.4 Outcomes

Outcome measures for future audit are included within the suite of RM KPIs and were examined for our cohort (table 4). However, there are no local or national audit results for comparison or specific parameters for these outcomes (bar high-risk ANC attendance and early pregnancy ultrasound). The livebirth rate was 63% (56/89) in those who conceived or 44% overall. The pregnancy loss rate was high at 37% (33/89), including two second-trimester miscarriages and two ectopic pregnancies. The rate of ART employed was notable at 36%, with a proportion of IVF with donor oocytes (30%).

Table 6. 4: Outcomes Key Performance Indicators

Outcomes Key Performance Indicators (n=20)	**N**	**Outcome**	**N**	**% Outcome**
Did the woman become pregnant again?	128	**Yes** No	**89** 39	70
Did the woman require artificial reproductive technology (ART) to conceive in subsequent pregnancy?	89	**Yes** No Missing	**32** 45 12	36
Did the woman require intra-uterine insemination or ovulation induction to achieve a new pregnancy?	89	**Yes** No	**6** 83	7
Did the woman/couple achieve a new pregnancy with IVF and/or IntraCytoplasmic Sperm Injection (ICSI)?[a]	89	**Yes** No	**26** 83	29
Did the woman/couple require donor gametes to achieve a new pregnancy?[a]	26	**Yes** No	**8** 18	30
Did the woman/couple achieve a new pregnancy with any use of Preimplantation Genetic Testing (PGT)?	26	**Yes** No	**2** 24	8
Did the woman/couple experience a subsequent first trimester miscarriage?[a]	89	**Yes** No	**29** 60	33
Did the woman/couple experience an ectopic pregnancy?[a]	89	**Yes** No	**2** 87	2
Did the woman/couple experience a subsequent second trimester miscarriage?[a]	58	**Yes** No	**2** 56	2
Did the woman develop fetal growth restriction in a subsequent pregnancy? [a]	56	**Yes** No	**0** 56	0
Did the woman experience a placental abruption in a subsequent pregnancy? [a]	56	**Yes** No	**0** 56	0
Did the woman develop pre-eclampsia in a subsequent pregnancy? [a]	56	**Yes** No	**3** 53	5

Did the women experience a preterm birth in a subsequent pregnancy? [a]	56	**Yes** No	**6** 50	11
Did the woman experience a stillbirth in a subsequent pregnancy? [a]	56	**Yes** No	**0** 56	0
Did the woman/couple experience a neonatal death? [a]	56	**Yes** No	**0** 56	0
Was the time interval to next pregnancy less than 6 months?	89	**Yes** No	**25** 64	28
Was the time interval to the next pregnancy 6-12 months?	89	**Yes** No	**17**	19
Was the time interval to the next pregnancy more than 12 months?	89	**Yes** No	**24**	27
Was the woman booked into a "high-risk" or perinatal medicine consultant-led clinic in a subsequent pregnancy?	56	**Yes** Private Missing	**41** 5 13	73
Did the woman receive an early pregnancy Ultrasound in a subsequent pregnancy?	89	**Yes** No	**66** 23	74

[a]adapted KPI

The denominator (N) represents the number of women to whom the KPI was applicable

6.5 Discussion

This examination of care of women with RM and infertility found that care provided was largely in line with KPIs for RM care. However, there were some notable deviations regarding counselling, investigations and treatments.

Structure of care was mostly adherent to KPIs (supplementary file 6.1). Treatment plans were unavailable in two cases due to absent clinical letters, which is an area for improvement as treatment plan provision matters to women experiencing RM and impacts on their overall care experience (410,457).

Counselling practices were mostly adherent, however, 60% of parents with an abnormal karyotype and 16% of those with an abnormal fetal karyotype received genetic counselling. While this reflects the predominance of aneuploidy due to maternal nondisjunction in fetal cytogenetics (204), parents with a translocation should have access to genetic expertise to aid decision-making regarding future pregnancy (637). Counselling regarding unorthodox treatments was poor (2%). However, the original KPI specified investigations and treatments that would never be prescribed in the RM clinic (supplementary file 6.2), potentially bypassing discussion. Alternative fertility treatments discussed and documented included, endometrial scratch (3/128; 2%), oocyte donation (14/128; 11%) and PGT-A (10/128; 8%). Given the array of add-on fertility treatments available, many without supporting evidence, counselling regarding unorthodox treatments is essential (638). Vitamin D supplementation was seldom discussed (1%); this merits improvement, as supplementation during pregnancy is beneficial (639). Notably, no RM clinical trials occurred in the hospital during the study period, reflecting the exclusion of pregnant women from clinical trials worldwide, and scarcity of robust trials in RM (621,640).

Regarding investigations, 95% of women had inherited thrombophilia testing against recommendations, as per protocols derived from RCOG guidance (21), a finding echoed in a UK study (323). Conversely, thyroid peroxidase antibodies were infrequently performed (6%), which requires improvement (35). Genetics investigations will change under new guidance which recommends that cytogenetics should be the primary genetics investigation, with parental karyotyping reserved for when pregnancy tissue is unavailable for testing (35,603). This reflects how fetal aneuploidy is a greater causative

factor in RM, especially in women over 35 (204). Poor access to 3D ultrasound was noted in the national service evaluation also and is highlighted as a barrier to implementation in the new Irish RM guideline (34,595). Prescription rates were higher than recommended in this cohort. Aspirin was not prescribed for miscarriage prevention, despite the per-protocol analysis from the EAGeR Trial providing some evidence that aspirin from preconception improved pregnancy and livebirth rates (332). Aspirin is shown to prevent hypertensive disease, preterm birth and growth restriction (641,642) as is LMWH (643), particularly in advanced maternal age and ART, which are both associated with pre-eclampsia. Progesterone supplementation was at 83%, which could be improved, particularly as new evidence suggests it may improve livebirth rates in RM (14).

Updated evidence suggests septum resection may reduce miscarriage (153), but clear patient selection pathways must be established. Our hospital does not have a complex gynaecology or reproductive medicine multi-disciplinary team (MDT) or meeting; the hysteroscopic resection and 3D ultrasounds were performed by one Consultant Gynaecologist. Similarly, women requiring oocyte donation are also not discussed at MDT level. Establishing a complex reproductive medicine MDT should be prioritised in the expansion of fertility services.

It must be acknowledged that high-quality data on management of recurrent pregnancy loss are limited and, therefore, therapeutic recommendations underpinning the KPIs are largely based upon clinical experience and data from observational studies (644). This has been highlighted as a barrier to guideline implementation (323).

Examining outcomes, women in the same RM cohort without infertility had a live-birth rate of 65% (635). This is lower than the 74-86% rates reported in international literature (381–384). Complications of pregnancy were low; however, the preterm birth rate was increased at 11%, versus 8% reported by Field and Murphy (388).

There is limited Irish data on women/couples experiencing RM and no national database/register of miscarriage in the ROI (381,388,645). While data is collected on fertility treatments through the Health Products Regulatory Authority's supervision of quality and safety standards in gamete and embryo treatment, they report on activity levels only and do not publish outcome data (43). Some outcome data is published by ESHRE, but several years following collection and is submitted voluntarily (42). Clinics are

not required to publish their annual outcomes and currently, this is done by a single fertility clinic operating in the ROI (646).Thus, there are no national data on women with RM who receive ART. The Assisted Human Reproduction Bill is to be written into legislation this year; enabling the establishment of an Assisted Human Reproduction Regulatory Authority whose duty it will be to collect and publish data on ART (43). Improved data collection and auditing of pregnancy outcomes would better identify the specific risks and subsequent obstetric care required by women undergoing ART in future pregnancy, including those with RM.

6.5.1 Strengths and limitations

This a is a novel audit, using guideline-based KPIs to assess RM care with a concurrent fertility history. While others have examined RM care, fertility status was not considered (323,620). These outcomes from a cohort of women with three consecutive miscarriages, verified by chart review, add to the limited data in the literature (635).

Documented fertility care received in the private sector was limited to clinical correspondence provided and patient knowledge. While we examined all pregnancies reported during the study period, this was limited to those who attended hospital for pregnancy or miscarriage care, potentially omitting some early pregnancies managed solely by fertility clinics. EHR allowed for greater information on subsequent pregnancy outcomes in those attending after 2016.

Audit was confined to documented clinical notes and correspondence; however, women may have been counselled on additional undocumented topics. There are no national sources of written information for RM and infertility, thus it was not provided as per clinic policy.

It is a limitation that we did not examine KPI adherence over time. Notably, no corticosteroids were prescribed from 2008-2011 with prescriptions increasing after the RCOG (21), and later ASRM and ESHRE (18,23), published guidelines explicitly discouraging this practice. This suggests that prescribing practices are not solely influenced by guidelines, and qualitative exploration is merited.

The KPIs were constructed prior to the publication of the latest ESHRE/RCOG guideline updates and Irish guideline on RM (32,35). Future revisions to KPIs and resultant audits must incorporate these changes.

6.6 Conclusion

This audit of care for women with RM and infertility demonstrates that alongside good clinical practice there are several areas for improvement. Counselling regarding risk factors and treatments, availability of genetic counselling, access to ultrasound and cytogenetic investigation should be improved. While guideline-based KPIs allow for internationally applicable and replicable audit that can direct service improvements, the experiences and needs of service-users are not captured, meriting further qualitative research.

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Linehan, L. A. 2024. Infertility and recurrent miscarriage: an examination of pregnancy outcomes, services and patient experience. PhD Thesis, University College Cork.

Please note that Chapter 7 (pp. 221-259) is unavailable due to a request by the author.

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Chapter 8 – Discussion

Chapter 8 – Thesis Discussion

8.1 Introduction

Miscarriage and infertility are significant reproductive health issues worldwide. Miscarriage is the most common adverse pregnancy outcome, estimated to affect 23 million women per year, with the pooled risk for all miscarriages placed at 15.3% (1). RM is estimated to have a prevalence of 1.9%, when defined as two miscarriages (1). Infertility is also a prevalent reproductive health issue, with 48.5 million couples estimated to be affected in 2010 (3), with lifetime prevalence calculated to be 17.5% or approximately one in six couples (41,91). Given that RM and infertility have shared risk factors and are independently associated with adverse obstetric and psychological sequelae, as well as being highly stigmatised, the dual experience merits greater study, receiving limited attention in research and practice to-date (1,2,433). Providing high-quality RM care and supports is known to be of benefit (386,420) but the supportive care needs of women and couples experiencing RM and infertility are unclear.

In order to address these deficits in knowledge, five research studies were conducted (Table 6.1) and a National Clinical Practice Guideline for RM was developed. These studies aimed to examine the dual experience of RM and infertility in the Republic of Ireland, encompassing a review of the relevant risk factors and associations, an examination of the evidence for current management of RM and associated fertility disorders with a comparison to current practice and an examination of reproductive outcomes, an evaluation of the current issues in RM and fertility service provision and how existing RM and infertility care services are viewed by women with lived experience and healthcare professionals working directly in these areas.

In this final chapter, I will present a summary of the findings from each chapter of my thesis and the contribution of my findings to the evidence base for RM and infertility as a dual experience and the resultant considerations for care. Additionally, the implications for policy, practice and future research areas will be considered. The strengths and limitations of this thesis will be outlined before concluding with the key findings and recommendations.

The main findings of each chapter are summarised in Table 8.1.

Table 8.1 : Key findings of each Chapter

Chapter / Title	Key findings
Chapter 2 **Infertility and subsequent recurrent miscarriage: current state of the literature and future considerations for practice and research** ***Published in HRB Open*** DOI:10.12688/hrbopenres.13397.1	There is an association between RM and infertility with shared risk factors
	The dual experience of RM and infertility is not recognised
	Women with RM and infertility feature indirectly in studies of costly investigations and treatments
	The experiences of women/couples with RM and infertility and their specific care needs are unknown
	It is unclear from current RM guidelines how best to manage and support this complex cohort.
Chapter 3 **National Clinical Practice Guideline: assessment and management of recurrent miscarriage** ***National Women and Infants Health Programme publication*** https://www.rcpi.ie/faculties/obstetricians-and-gynaecologists/national-clinical-guidelines-in-obstetrics-and-gynaecology/	Evidence for the management of RM is largely low-quality/consensus-based
	Women/couples with RM should have their fertility history and any current treatments considered in relation to investigations or treatments, and especially supports
	Implementation of the Guideline requires planning regarding education and dissemination as well as funding and resources
Chapter 4 **Reproductive outcomes following recurrent first-trimester miscarriage: a retrospective cohort study** ***Published in Human Reproduction Open*** *DOI: 10.1093/hropen/hoac045*	Women with RM and infertility or with RM and aged >40 years had lower live birth rates
	Risk factors such as maternal age, smoking and parental karyotype were negatively associated with having a subsequent pregnancy
	Investigations and treatments were not shown to be associated with subsequent livebirth, miscarriage or no further pregnancy

	Need for improved systems for data collection and reporting for RM and infertility locally and nationally
Chapter 5 **Recurrent miscarriage and infertility: a national service evaluation** ***Published in Journal of Obstetrics and Gynaecology*** *DOI: 10.1080/01443615.2023.2241916*	Deficits in health care professional (HCP) knowledge regarding RM guidance with regards to definitions and management
	Variation in investigations, treatments, referral criteria, counselling and time allocated to RM appointments nationally
	Deficits in HCP knowledge of fertility treatments
	Deficits in HCP awareness of information and support resources for RM and infertility
	Variation in access to services such as public fertility care, ultrasound and genetic counselling
	No standardised care pathways for women experiencing RM and infertility
	Need for improved data collection on RM and infertility and better engagement with audit of services and outcomes
Chapter 6 **An examination of care received by women with recurrent miscarriage and infertility against guideline-based key performance indicators** ***Published in the European Journal of Obstetrics and Gynaecology and Reproductive Biology*** *DOI: 10.1016/j.ejogrb.2023.01.002*	Deficits in counselling and information provision regarding RM, fertility and associated risk factors
	Limited access to investigations such as cytogenetics and 3D ultrasound
	Limited access to expertise such as genetic counselling or complex gynaecological surgery
	The availability of investigations and treatments that are not recommended
	Reduced livebirth rate and higher rate of miscarriage and preterm birth in women with RM and infertility
	Need for greater networking between private fertility clinics and maternity services to improve clinical communication and data collection

Chapter 7 **Recurrent miscarriage and infertility services and supports: a qualitative study of views and experiences in the Republic of Ireland** ***Under review Human Reproduction***	RM and infertility is a complex experience which impacted on all aspects of the lives of women/couples, with particular impacts on work, finances and psychological well-being
	Lack of recognition of dual experience by HCPs (within maternity services and wider health services) contributed to deficits in care
	Lack of recognition of dual experience within wider society added to isolation and stigmatisation
	Need for greater information provision regarding reproductive health throughout life course to facilitate agency
	Need for more equal access to RM and fertility care/services and supports across the ROI
	Need for better communication and networking between RM/maternity and private fertility services
	Need for greater transparency in private fertility services in addition to greater regulation, data collection and outcomes reporting
	Need for specialised staffing and significant resources within new fertility hubs with integrated bereavement care pathways

In consideration of the above findings, the following common themes were identified:

Table 8. 1: Common themes identified across the chapters within this thesis

	Themes	Sub-themes
1	The dual experience of RM and infertility needs greater recognition	There was a lack of recognition of the significance of RM and infertility
		The impact of the dual experience of RM and infertility
2	There is a need for equity and balance in the care provided to women with RM and infertility	A balance between standardised and individualised care is required
		There is a need for more equitable care for women/couples with RM and infertility
3	Information is central to improving care	There is a need for more information for both women and HCPS
		Data is needed to better inform care

These three themes are common to most of the studies, and they consolidate the conclusions drawn from this thesis. As well as exploring the main findings within each theme, the wider implications for practice, policy and future research are discussed below.

8.2 The dual experience of RM and infertility needs greater recognition

8.2.1 Main findings

RM and infertility are two distinct reproductive health issues that, while often having discrete aetiopathologies, share many common risk factors and association and increasingly, management plans such as assisted reproductive technologies (ART), including Pre-implantation Genetic Testing for Aneuploidy (PGT-A) (2). This thesis sought to examine the dual experience of RM and infertility however it was evident that this phenomenon was poorly recognised and overlooked within academic studies (the literature), among HCPs and in health policy, and within wider society (621).

There was a lack of recognition of the significance of RM and infertility (Chapters 2, 4-7)

Lack of recognition within academia

The literature review (chapter 2) set out the distinct gaps in the knowledge regarding RM and infertility that this doctoral work has since addressed (621). Women with RM and infertility did not appear in any specific cohort studies; women with RM who had undergone ART did appear within subgroups of investigations or treatments (392,525), with a few studies looking at reproductive outcomes after RM (381,382,384,388), and none examining outcomes after RM and infertility. Further, there were few qualitative studies examining the lived experience or the support needs of women/couples with RM and infertility (621). The resultant exclusion of the management of RM and infertility from international Clinical Practice Guidelines was therefore unsurprising (472,621). However, the studies within this thesis have since contributed to the knowledge base and additionally identified a number of reasons for this oversight. RM and infertility as a dual experience was often not examined in studies looking at investigations or treatments instead keeping study groups exclusive to a history of RM or fertility to avoid confounding cohorts (523,525). Other studies examining RM and infertility were focused on finding a common primary aetiology, such as with diminished ovarian reserve (DOR), or a relationship between very early pregnancy loss and infertility, therefore overlooking the experience itself (67,88).

While initially this thesis sought to examine the experience of RM after infertility, as it progressed it was evident that "RM and infertility" was a broader experience which also encompassed women with RM who experienced secondary infertility requiring treatment (497,675) and women with RM who sought out infertility treatment to try to improve their chances of successful pregnancy (chapters 2, 4 – 7) (621,622,649,676,677). This finding was an important factor in resultant care and was integrated and explored empirically within the qualitative study and service evaluation (649,676). This diversity of experience may also impede the recognition of RM and infertility as a phenomenon.

Lack of recognition within health services

The studies within this thesis (chapters 4-7) also highlight the lack of recognition of RM and infertility within the health service and among HCPs, identifying areas for improvement. For example, within the audit of care of women with RM and infertility (chapter 6), where women may have had appropriate investigations for infertility alongside RM investigations due to findings in her medical history, such tests were

contrary to the recommendations from the clinical guideline-based key performance indicators (KPIs) for RM care (622). This reflects how tailored care in the best interests of the individual may be outside of clinical guidance but requires clinical knowledge and awareness to recognise when this is appropriate. The service evaluation (chapter 5), also highlights areas for improvements; for example, there were often no established referral pathways or management plans for women with RM and concomitant or secondary infertility within the public service, and in some units, no local fertility services (649). Specific fertility supports were available in just five of the large/medium maternity units and therefore located in or near large cities (649). This geographical variation, which also been identified in miscarriage services, reflects the lack of recognition and planning for RM and infertility nationally (456,657).

The qualitative study (Chapter 7) has made an important contribution to the literature by capturing the lack of recognition of the dual experience by HCPs and within current care structures, and the subsequent impact on the lived experience(676). Women described the lack of recognition of the dual experience from HCPs at different stages in their care, be it at diagnosis of miscarriage, in seeking investigations or supports, or in subsequent pregnancy, which sometimes hindered accessing care or supports. Moreover, women found a lack of recognition and acknowledgement of their fertility treatment and their miscarriages to be hurtful, as previously established (648). The qualitative work identifies specific hurdles faced by the segregation of public and private services, which while mentioned in other studies of fertility care nationally and internationally, has not been previously explored in relation to RM (424,678,679). It illustrates the difficulty in navigating both public and private services within the ROI and how care between RM and fertility systems was disjointed (676). This is an additional stress which women/couples with RM and infertility face in the ROI, and potentially internationally where fertility care is conducted within private services. This study also outlines how the separation of these systems is responsible for additional administrative and travel burdens, further new findings which merit greater recognition (676). The qualitative study is also novel in capturing the views and concerns of HCPs regarding the lack of recognition of the dual experience in current national healthcare strategies and plans, such as the National Maternity Strategy and the Women's Health Action Plan (447,462). For example, HCPs highlighted the omission of miscarriage care pathways or supports in the new fertility

hubs, but also their concerns that the limited funding of ART will perpetuate the divisions in the system as the need for private fertility care remains. Women and HCPs reflected on how the lack of recognition of the dual experience was part of a wider phenomenon of unawareness regarding reproductive health and risk factors for RM and infertility which has been previously identified (680–682), and will be discussed in more depth in Section 8.4.

The impact of the dual experience of RM and infertility (Chapters 2, 4, 6, 7)

Impact on reproductive health

This work identified that having RM and an infertility history was associated with adverse reproductive outcomes in addition to psychological sequelae, which merit further recognition. Within the literature review (Chapter 2) the reciprocal relationship between RM and infertility was identified, i.e., women with RM were at increased risk of secondary infertility and women with a history of fertility were also likely to experience RM (621). This impact was demonstrated in the audit (Chapter 4) whereby a lower cumulative birthrate was seen in women with RM and infertility (54%), compared to those with RM alone (63%) (683). Poorer reproductive outcomes for women with RM and infertility were also seen in the audit of care for women with RM and infertility (Chapter 6) (622). While the live birth-rate for those who conceived was 63%, overall, just 43% of the women with RM and infertility in their first pregnancy after RM had a live birth. This lower birth rate than reported in other cohort studies of pregnancy after RM, 74– 86% (381–384), may also reflect that this cohort of women with first-trimester RM were older at an average age of 36 and included women with identified risk factors for RM such as thrombophilia and balanced translocations, whereas other cohorts focused on unexplained RM (381). As well as acknowledging the importance of a fertility history, the cohort study also confirmed the association between well-established risk factors for RM and infertility with pregnancy outcomes after RM, namely smoking, maternal age and parental karyotype (1). Chapter 6 also recognised RM and infertility as risk factors for reproductive outcomes, where alongside the mentioned overall lower birthrate, the rate of preterm birth (11%) was higher than quoted in a previous cohort of Irish women with RM (8%) (388).

The dual experience of RM and infertility has wide-reaching consequences for health beyond reproductive outcomes, which also merits greater recognition within health

services and associated health policies. The experience of RM and infertility has a profound impact on mental health, which is particularly clear in the qualitative study (Chapter 7). In keeping with other studies, women spoke of the deep grief after RM and infertility and the subsequent psychological impact with similar experiences of anxiety and depression (424,436,437,648). However, this work also highlights distinct challenging points in the journey, some of which are known, such as re-starting treatment, managing the first trimester in subsequent pregnancy (419,437), and original findings such as the difficulties faced in seeking information on treatments and supports (676). These findings can be used to raise awareness among HCPs and policymakers and should contribute to improved care experiences.

Additional impacts of RM and infertility

The studies conducted for this thesis also outline the significant additional burdens placed on women/couples with RM and infertility. Many of these are recognised within the international literature such as the financial cost, work pressures, social isolation and stigma (424,437,648). The PLACES (Pregnancy Loss in Workplaces: Informing policymakers on support mechanisms) project, commissioned by the Irish Department of Children, Equality, Disability, Integration and Youth in 2022, also recognised this burden on women and confirmed the impact of pregnancy loss on women's ability to work, the need for time off and the negative interactions experienced at work related to disclosing their loss (684). As mentioned previously, findings from the service evaluation (Chapter 5) and the qualitative work (Chapter 7) distinctly acknowledged that the current structure of care for fertility services in the ROI added to the administrative and travel burdens for women/couples with RM and infertility, and these burdens were often unrecognised (649,676). Moreover, the qualitative study captured how the separation of RM and fertility care sometimes impeded timely access to supports or services, and that the lack of recognition of the dual experience led to poor or inadequate provision of information and signposting of supports (676).

Thus, it is evident within this thesis that RM and infertility is an unrecognised phenomenon but given its association with adverse reproductive and psychological outcomes, it warrants greater attention to improve services and supports available.

8.2.2 Implications for practice and policy

In order to rectify the many issues identified for women/couples with RM and infertility, the dual experience and associated risk factors must be recognised in clinical practice and in wider health policy.

Increasing the recognition of RM and infertility in clinical practice to improve care

Addressing the lack of recognition of the dual experience of RM and infertility necessitates raising awareness, not just of the experience, but also of the associated risk factors and required supports. As well as enhancing the knowledge of HCPs in maternity services (such as obstetricians and gynaecologists, nurses and midwives), HCPs working in fertility clinics and in the wider community, such as GPs and mental health professionals, must be included in education efforts, so that all healthcare staff that women/couples encounter are adequately informed in order to provide suitable care.

Clinical Practice Guidelines are systematically developed resources, based on a thorough evaluation of the evidence, that can assist practitioner and patient decisions about appropriate healthcare for specific clinical circumstances, and are therefore important resources for providing a comprehensive, evidence-based guidance for the management of RM and infertility (685). Separate Clinical Practice Guidelines for the Management of RM and for Fertility Investigation and Management in Secondary Care were published in 2023 by NWIHP's Guideline Programme (469,595). These provide clinical knowledge and guidance for HCPs and aim to lead to standardisation of care for both conditions. The RM Guideline (Chapter 3) is the first RM Guideline published in the ROI and has set out clearly how RM care should be structured and managed, and what supports should be provided to women and their partners (595). Regarding RM and infertility, recommendation 21 of the RM Guideline specifically outlines the need for fertility investigations where a woman has a history suggestive of menstrual irregularities or infertility (595). Moreover, the RM Guideline expressly outlines in Section 4 the importance of capturing a history of fertility treatment in either the woman or a male partner. The need for additional support where a woman/couple has co-existing infertility or undergoing treatment is also addressed in Section 3 of the new Guideline (595). Within the RM Guideline, there is a plan for implementation, as well as a plain language summary and a new mobile-based application for easier access to Guidelines for HCPs (595,686). While there has been presentation and

discussion of the RM Guideline nationally and the national dissemination of an explanation of the guideline changes to GPs (686,687), further work is necessary to realise strategies, particularly around staff training and education, for full implementation (688). The Guideline on Fertility again covers shared risk factors which should be recognised in primary care and has a similar programme for implementation (469).

Alongside these new Guidelines, there is a need for more focused education and training for GPs, obstetricians and gynaecologists, nurses and midwives to better recognise risk factors for RM and/or fertility, such as maternal age, obesity, smoking and associated conditions such as endometriosis or PCOS. This could be delivered at under-graduate level to student doctors, nurses and midwives, but also integrated into post-graduate training and continuing professional development programmes with the Royal College of Physicians and the Irish College of General Practitioners. Raising awareness of RM and infertility among frontline staff will increase their clinical recognition of risk factors and may better enable women to access screening or earlier interventions, but also, raising awareness with individual women may facilitate informed choice and agency regarding reproductive health.

Moving beyond the current clinical guidelines, consideration could even be given to a more expansive approach to reproductive health within health services, such as the Swedish Reproductive Life Plan, whereby GPs and other frontline HCPs begin consultations for all women of reproductive age with screening for their intentions to become or not become pregnant in the short- and long-term and any factors which may affect their fertility (673). While such an approach may help to optimise use of the recently introduced free contraception to women under 31 (462), it would require training to ensure discussions are conducted sensitively without judgement or stigmatisation (689).

Returning to RM and infertility as a dual experience, education of HCPs in primary care, maternity and fertility services to recognise the significance of pregnancy loss with concurrent or previous fertility treatment could improve the care experience, which was noted in chapter 7 and in the RE:CURRENT study to be inconsistent (408,457,676). In addition to directing women/ couples to more appropriate supports and services, recognition among HCPs may also foster more empathic and supportive management, which women desire (406,593). It is also crucial that professionals working in supportive

roles, such as Bereavement and Loss Clinical Midwifery Specialists, Fertility Clinical Nurse Specialists, counsellors or other therapists, are also included in educational activities so as to improve their understanding of RM and infertility and the specific support and therapeutic needs required (690,691).

Recognition of RM and infertility within healthcare policy

In order to have a healthcare system which recognises and supports women and couples affected by RM and infertility, a number of issues must be addressed within healthcare policy and appropriate strategies adopted. These include the collection of data, the use of existing data to better guide healthcare policy and recognition of the impact of RM and infertility on society.

Development of a healthcare strategy to address the dual experience of RM and experience requires greater knowledge of the affected population, necessitating the collection of demographic data. This would not only help to delineate who was affected, but also where services are required. It would also identify the relevant risk factors which could also be addressed within health planning. However, as discussed within Chapter 1, data collection for miscarriage and fertility in the ROI is poor. There have been separate international calls for better collection of data on miscarriage and RM (Lancet Series) and fertility (Fertility Europe) and for national registers (1,692). The Assisted Human Reproduction Bill will enable the establishment of the Assisted Human Reproduction Authority, who will mandate some of this data collection within Irish fertility services, however it has yet to be passed by Government (43). Further data collection on miscarriage from maternity services is also needed to establish the extent of the issue within Ireland. A means of recording the numbers of women/couples seeking infertility treatment abroad is also required to fully illustrate the situation. Additionally, increased recognition of RM and infertility could influence how international data is reported. For example, ESHRE recently reported on PGT outcomes from 61 fertility centres across Europe; while RM is the second most common indication for PGT-A, the outcomes for PGT-A in this group were not specifically reported on (634).

Nonetheless, existing data illustrates current reproductive trends, which do not appear to be addressed within current health policy. Firstly, there is a clear pattern of rising maternal age; the average age of first-time mothers in Ireland was the highest ever in

2022 at 33.2 years, having been 31.9 in 2012 and 30.6 in 2003, and an increasing proportion of women are giving birth in their 40s (8.9% of total births in 2022, compared to 4.8% in 2012) (693,694). However, the birth rate has fallen by 20% since 2012 (72,225 to 57,540 which translates as a drop from 14.8 births/1000 of the population to 11.3/1000 of the population) and there has been a significant increase in the use of ART since 2009 (from 7,589 in 2009 to a peak of 11,359 in 2018) (43,693,694). Decreasing birth-rates are also indicative of advances for women in society, including increased educational attainment and increased reproductive autonomy through access to contraception and termination of pregnancy, which have facilitated women's increased participation in the workforce and important contribution to the economy (695).

However, despite these clear trends, there is no clear government policy on the impact of "delayed childbearing". Delayed childbearing refers to attempting to have a child at an older age, generally after 35, but it must be borne in mind that such decisions are not always wholly voluntary (696). While it is known that there is a lack of information regarding the impact of age on fertility and an over-estimation of the success of interventions such as oocyte freezing and IVF (697), it cannot be assumed that these are the sole factors in delayed childbearing (696). There are many other economic and social factors which deter couples from conceiving (485,696). These include economic stability, educational opportunities for women, career aspirations, academic and professional structures, financial considerations, changing cultural perspectives on motherhood, the influence of family values and societal pressure, modern media and culture, delayed marriage and misperceptions regarding the effectiveness of ART (695).

While the National Maternity Strategy recognises that increasing maternal age "adds to the complexity of maternity care required", there is no clarification as to how maternity services will adapt to manage this complexity (447). The Strategy also does not acknowledge the fall in birth rates or the rise in ART use, which particularly adds to the complexity of maternity care (379,447,698). Furthermore, there is no clear plan to address delayed childbearing within the Strategy, or an acknowledgement that this will potentially result in higher rates of miscarriage or infertility, increasing service demands and women's care needs (447). Similarly, the National Women's Health Action Plan, while supporting the development of fertility hubs, does not specifically acknowledge the rising

age of first-time mothers, the falling fertility rate or the drop in birth-rates (462). There is scope within Action 5B of the Action Plan – "Looking creatively at how women and girls can access better information in women's health at different ages and stages in life"– to develop a reproductive health awareness strategy (462). The Action Plan speaks strongly of gender equality in healthcare and advocates for change in Action 10 – "We will work within our organisations to model and lead the changes we want to see in our sector, our society and our economy"– which could open dialogue as to reasons for delayed childbearing in women and the impact of reproductive issues such as RM and infertility on women's working lives and careers (462). The PLACES report has also identified the need for statutory, protected, paid leave for women experiencing miscarriage, as well as other workplaces supports such as policies and guidance, training for management and staff, and flexible working arrangements (684).

This lack of recognition of both the experience of RM and infertility, and of the wider risk factors and contributory societal issues, within our current health policy is problematic. RM and infertility come at a cost, to women and their partners, but also wider society (10). The current policy has led to disjointed system which does not serve women with the dual experience and consequently, in addition to significant financial costs, women bear substantial personal costs, including physical and mental health, and potentially, involuntary childlessness (676,678). Failing to recognise RM and infertility and associated factors will not only lead to costs within health services, such as RM and fertility treatments, obstetric and mental health resources, but will also lead to long-term costs within society, namely the longer-term economic and social issues arising from reduced birth rates, as experienced globally (699).

8.2.3 Future Research

Prospective research efforts should be focused on enhancing the recognition of RM and infertility as a dual experience, improving the care received by women/couples across various services and addressing causative factors.

Recognition of RM and infertility requires a larger body of evidence across different geographic and demographic populations to corroborate the findings in this thesis. As well as enhancing data collection, women with RM and infertility must feature in more cohort studies, which would allow for greater analysis of demographic data and assessment of

reproductive outcomes. This would also allow for examination of the efficacy of existing investigations and treatments. Women with RM and infertility must be included in more high-quality interventional studies to provide a better evidence base for management, and to assess outcomes compared to those with RM or infertility alone. This is especially necessary for more costly interventions such as PGT-A and immune treatments. Women with RM who seek out ART also merit greater study; alongside further qualitative analysis of decision-making around pursuing ART, the ART protocols employed internationally for these circumstances merit scrutiny.

Care for women/couples with RM and infertility in the ROI must improve. In order to address the deficits identified in this work, consideration must be given to a more detailed examination of current care nationally, similar to the Maternity Bereavement Experience Survey (458). This could provide greater detail on the care received within private fertility clinics, which was not forthcoming from the service evaluation due to poor response rates from this sector (Chapter 5), and how care between services was/is delivered. This would also help to draw attention to the dual experience of RM and infertility. An important component of assessing care is clinical audit, in line with the National Standards for Safer Better Maternity Services (448), and audit is an important component of implementation of Clinical Guidelines (688). It is therefore important that audits are conducted to ensure that the recommendations laid out in the new National Clinical Practice Guidelines for RM and infertility are being applied. This will also aid the identification of areas for education, training and resource allocation.

There is a need for greater assessment of the societal trend for delayed childbearing and to identify the factors which contribute to this decision in Ireland. These results can then better inform future public health initiatives or inspire interventions which address the contributory factors.

8.3 There is a need for standardisation, individualisation and equity in the care provided to women with RM and infertility

8.3.1 Main findings

Across the studies in this thesis, it was evident that there needs to be a more consistent approach to caring for women with RM and infertility. Firstly, a balance must be struck between standardisation of care and individualised care in this difficult clinical scenario.

Additionally, there needs to be more balanced care across the ROI with more equitable distribution of resources and access to services.

A balance between standardised and individualised care is required (Chapters 4-7)

Care at opposite ends of the spectrum

Throughout this thesis, it is evident that the approaches to RM and infertility by HCPs across public and private services were sometimes contradictory. Within the service evaluation (Chapter 5) and the qualitative work (Chapter 7), it was apparent that some clinicians and other HCPs strictly followed RM guidelines, for example, denying access to investigations for RM unless women had three miscarriages (649,676). Within these studies and the audit (Chapter 6), there was evidence of Guideline recommendations being disregarded, with many examples of investigations or treatments being conducted against guideline recommendations, in public and private settings, an issue which had been previously identified by Manning et al. in a review of UK RM services (323,622,649,676). This was on a spectrum, ranging from empiric treatments such as aspirin or LMWH for women with more than three miscarriages, to more costly procedures such as PGT-A or lymphocyte immunotherapy. Within the qualitative study, (Chapter 7) there was further evidence to demonstrate that such approaches could be harmful. For women who were denied investigations or treatments on the basis that they had experienced “just two” miscarriages or were outside of evidence, they perceived HCPs to be uncaring and dismissive; this has previously been identified as a source of frustration for women (393,408). Women were upset at being denied supports based on the number of miscarriages experienced, particularly regarding scans in a subsequent pregnancy as in other studies (393,406,458). This approach also reduced their trust in maternity services.

The converse situation, where investigations and treatments outside of guidance were employed because an individual woman had RM and infertility was also shown to be harmful. As well as the significant financial cost of some of these unorthodox treatments, they hold the potential for serious side-effects, which women were aware of to varying degrees (32,310). While only small numbers of HCPs in the service evaluation indicated that they would use such investigations or treatments, within the qualitative study tests such as sperm DNA fragmentation and natural killer cell testing and treatments such as

PGT-A, intravenous immunoglobulin (IVIG) and Lymphocyte Immunization Therapy (LIT) were mentioned frequently by women and appeared to be in common use in fertility clinics. This is a novel finding and depicts greater use of unorthodox treatments than previous studies of RM care (323), and demonstrates the incongruence in RM and infertility care (649,676).

Factors which facilitate the imbalance

The qualitative study (Chapter 7) puts forward important insights as to why women take unorthodox treatments and highlighted the vulnerability of women at this time, as they grieve pregnancy loss and undergo stressful infertility treatment, as an important factor in decision-making around unorthodox treatments (676). Women desperately wanted to become pregnant and wanted to be sure they had tried everything to have a baby (676). Similarly, a survey of women undergoing IVF in Ireland examining the effect of the lack of legislation on their experience also captured how women were more focused on striving to have a baby than examining if treatments performed were within regulations, or fully understanding treatments (and potential risks) undertaken (679). This struggle between an individual woman's need to try everything to have a baby and the boundary set by the current evidence base is also uniquely captured in the qualitative study (676).

Clinicians have a responsibility to ensure that women understand the treatments available and the associated risks however, and within the audit, a stark finding was that counselling regarding unorthodox treatments was poor and infrequent (622). This perhaps reflects the lack of knowledge in wider maternity services regarding what treatments for RM may be used in fertility clinics, as shown in the lack of familiarity around treatments and clinical guidance in the service evaluation (649). This also underscores how the lack of recognition of RM and infertility and related issues in health services has implications for the quality of care received. International studies have also identified poor information provision and counselling as barriers to understanding fertility treatments, as well as sharing the finding that women want greater information of complex treatments and side-effects (424,700,701). It may also explain our finding that consultants or nurse practitioners in fertility with knowledge of the dual experience in Chapter 7 were keen to impart as much information as possible in consultations, as part of attempts to compensate for the wider lack of knowledge regarding unorthodox

treatments for RM and infertility (676). In this regard, it is evident that information provision plays an important role in ensuring that HCPs have the clinical knowledge and awareness to ensure standards for care within clinical guidance are met, but that individual needs are not constrained by guidance.

There is a need for more equitable care for women/couples with RM and infertility (Chapters 5,6,7)

Differences in services

Throughout this thesis, there is a strong theme of inequity in access to RM and fertility services. Within the service evaluation, there were clear variations in care and resources available, and this was further laid out by HCPs and women in the qualitative study. While it is to be expected that tertiary referral centres (larger maternity units) would have greater staffing levels and resources to meet the demands of greater patient numbers and complexity, this thesis demonstrates the degree of disparity with some smaller units unable to provide fundamental RM or fertility services. This was particularly evident in the structure of care for miscarriage and RM where just 50% of the participating units in the RE:CURRENT service evaluation had a specific RM clinic and 56% were able to accommodate women in separate spaces, which women and HCPs were acutely aware of, as outlined in the qualitative findings in Chapter 7 (657,676). Women described how the lack of separate spaces for ultrasound was difficult, but the absence of a designated private space in emergency waiting areas or in some maternity units, delivery areas, was undignified and distressing, echoing the findings of previous qualitative work on miscarriage (393,437,702). Notably, women attending private fertility services often attended public services for the first time when presenting with miscarriage or another medical emergency out of hours, with the unfamiliarity adding to their distress (676).

Importantly, the qualitative study also described how some units did not have a lead consultant for RM or fertility, and women were referred on to tertiary centres or had to seek private care as no referral system was in place (676). While these findings regarding RM were known (456,703), this inequity in care for women with RM and infertility has not previously been reported. There was also variation in the numbers of women with RM and infertility seen in each unit annually and in the time allocated (15-60 minutes), with few HCPs providing written resources or signposting to relevant information and support

(649). These are also new findings which again suggest a lack of recognition for the dual experience contributing to the imbalance in care. Access to more specialised services such as genetic counselling was also geographically restricted, as evidenced in chapters 5, 6 and 7, and previously demonstrated in the RE:CURRENT Study (622,649,676,703).

On the opposite end of the spectrum, the service evaluation and qualitative study revealed how some units had aspirational, high-quality care structures, which are also not described in the literature (649,676). For example, two large tertiary referral units had a multi-disciplinary team for reproductive genetics where women with complex RM and infertility were optimally managed. There were four large public fertility units where investigations were streamlined and conducted according to clear pathways and resources were available such that ovulation induction and intra-uterine insemination were able to be maximised within the public service. Many large and medium units had structured RM care where women were investigated and given a management plan with access to supports as needed. The service evaluation and qualitative study also demonstrated that the private clinics which did engage with the studies had better access to psychological supports such as counselling when compared with public services(649,676). While such findings are welcome, the contrast in care is jarring. This work is novel in identifying the highly variable nature of the care experience across the ROI and the marked geographic variation.

Difference in care for male partners

The imbalance in care and support for male partners was also evident throughout the chapters within this thesis. While some studies have been published in recent years which document the experience of men and miscarriage or RM (412,413,457), and there is increasing recognition of the contribution of male factors to RM and infertility (360,362,704), their care needs do not feature in international clinical guidelines for RM (472,621). Thus, the assessment of the care of the male partner was confined to sperm DNA fragmentation and spermploidy testing within the KPIs for the service evaluation and audit (Chapters 5 and 6). Within Chapter 7 however, women voiced the lack of supports for their partners and described how this was a further worry for them as they could see the toll the experience took on their partners (676).

While the impact of infertility and/or miscarriage on male partners is increasingly being recognised (412,413,429,431,702,705,706), the identification of the lack of male support in dealing with these issues as an additional worry for women is novel. Women noted the imbalance of care towards the female partner, and while they felt that the physical and emotional experience for women required this input, they also wanted their partners' psychological needs to be considered and acknowledged within support services. This was especially true for male partner infertility; similar to the findings of Hanna et al. in their review, women and HCPs described how men struggled with the impact of the diagnosis for their identity and plans for fatherhood but found it hard to discuss with others beyond their partner due to stigma (429). Outside of private fertility counselling services however, there was little support available for male partners which must be addressed, given the increasing awareness of both the contribution of male factors to RM and infertility and the impact on male mental health (352,413).

Inequity in access to fertility services

Across this thesis, there is evidence of the inequity in access to fertility services. Specifically in Chapters 6 and 7, the geographical inequity in public fertility services is clearly shown (649,676). Only a minority of units across the ROI have fertility specialists, therefore most smaller units can only offer basic investigations and women with RM and infertility must travel to access specialist care. Other units may have a fertility specialist but have limited resources for ART in comparison to the tertiary units in Dublin or Cork. The geographical variation also applies to private care with the result that women living in the northwest or southeast have a significant travel burden in accessing either public or private fertility care, a barrier also identified by Marshall in qualitative work around accessing fertility care in Ireland (678).

Geographical variation has previously been also identified as a barrier to fertility treatment internationally (92,424). However, the greatest obstacle in accessing fertility care identified in by women and HCPs in Chapter 7 was cost, as previously established in other qualitative studies (92,424,676). While the cost of a single round of IVF in 2017 was quoted at €4100 to €5900 (43), women in this study described spending many multiples of this on ART, disclosing additional costs such as travel, medications and alternative therapies, which were also identified by Marshall (678). Further costs were accrued with

unpaid leave taken, as identified by the PLACES Study (684). Women recognised the inequity of the access to ART and felt fortunate to be able to access such expensive treatment; a guilt that is not described in other qualitative studies on fertility treatment (676). Women and HCPs also recognised that these huge costs were beyond the capabilities of the health service and correctly assumed that the long-awaited public IVF would be limited, and voiced concerns that the inequity would remain, and echoed calls made by US women for more equal access to ART (424).

8.3.2 Implications for practice and policy

It is clear that there needs to be a more equitable approach to how RM and infertility care is delivered, individually and in combination. This will require changes to clinical practice and greater consideration of current health policy.

Addressing the imbalance in RM and infertility in clinical practice

Clinical practice must adapt to ensure that women with RM and infertility have equal access to high-quality RM and fertility care. Again, the implementation of the recently introduced Clinical Practice Guidelines for RM and Fertility will be an important step in improving clinical practice (595,707). In particular, the Clinical Practice Guideline for RM will help to standardise the definition of RM, as well as investigations and treatments (708). However, the RM Guideline has also incorporated a degree of flexibility to allow for individualisation of care for more complex cases, such as the prescription of empiric treatments, with the stipulation that women are appropriately counselled (708). The RM Guideline also outlines that psychological supports can be offered at any stage (708). A Clinical Practice Guideline for ART in tertiary centres is needed and will be a key step in standardising ART and make recommendations on the use of expensive add-ons and immunotherapies. The passing of the Assisted Human Reproduction Bill and the subsequent establishment of the relevant Regulatory Authority will also provide greater oversight to fertility treatment and ensure standardisation of care (466).

Considering the degree to which women and their partners were affected psychologically by the experience of RM and infertility, there is also a need to examine additional ways of providing more tailored care to women and couples, that are feasible, effective and crucially, acceptable to them. Moving away from a solely medical model of care and taking a more holistic approach may be beneficial. In chapter 7 and in other similar studies,

women found counselling and talking to others with similar experiences useful (424,437,676,709). Thus, assigning a specially trained counsellor to each maternity unit or fertility hub to which women have early access or having peer-to-peer supports may help. Alternatively, a more cost-effective approach may be to enable Clinical Midwifery Specialists in Bereavement and Loss could receive additional training in counselling and fertility care, to provide enhanced support. While early scans and supportive care in a subsequent pregnancy have been shown in this work and other studies to be helpful, managing the return to fertility treatment after pregnancy loss is more complex, requiring more tailored supports (393,419). To better include men in supports, there needs to be greater recognition of RM and infertility as an issue affecting both partners and increased training to relevant staff to help raise awareness and enhance skills to support inclusion (406,710,711). The RM Guideline has begun to address this imbalance in recognising the need for male partner support in its Section 3 and for recognition of male factors in its Section 4(595). Additionally, counselling services should be offered to both partners, and based on the experiences of women in Chapter 7, offered as couples counselling (676). There is a need nationally for male support groups for men experiencing infertility and miscarriage and other initiatives for peer-to-peer support, which must be developed with men not only to ensure that their support needs are identified and met, but also to foster engagement (412,413).

Clinical practice also needs to adapt to try to overcome the deficits within current services, particularly those due to geography. While the new fertility hub for the mid-west of the country, based in Limerick, will bolster fertility resources in the west of the country alongside the increased resources to Galway, this will not eradicate the need for substantial travel for many in the north-west. It is especially important that the hubs nation-wide incorporate bereavement supports and clear referral pathways for more localised supports and RM services to ensure women do not become caught or lost between both services. The hubs alone will also not be sufficient to equalise care across the country, particularly with regards to skilled workforce. While recruitment of more staff in the areas of pregnancy loss and fertility is the ideal solution to bridging this gap, alongside increased training, given the current recruitment issues within the HSE (712) and the time taken to gain the necessary clinical skillset in these areas, other solutions must be considered. The development of a reproductive medicine multi-disciplinary team

within each hub where complex cases, such as women with RM and infertility, could be considered. This could also involve clinical geneticists and gynaecologists specialised in management of uterine anomalies, allowing better access to this expertise. A less ideal, but more financially viable option, is better use of virtual resources as were employed during the pandemic (474,660,713). While face-to-face consultations are preferable for sensitive topics such as RM and infertility issues (474), there could be a limited role for virtual follow-up consultations to minimise travel requirements. This might work well if there was a local liaison team in each maternity unit who were directly contactable and could facilitate bloods and the necessary ultrasounds. While innovation and adaptability may help in bridging some of the current gaps in RM and infertility care, the core needs of skilled staff and adequate, suitable resources must be met.

Addressing imbalance in RM and infertility care through policy

The deficits identified in maternity services with regards to RM care are not new findings. As well as in the RE:CURRENT Service Evaluation and Care Experience survey (457,657), these inequities in both first and second-trimester miscarriage and RM have been highlighted in audits of the National Bereavement Standards for Pregnancy Loss and Perinatal Death and in the National Maternity Bereavement Experience Survey (456,458). The inequities in miscarriage care are known; in particular, the need for dedicated spaces, training in diagnosing and care of women experiencing miscarriage in early pregnancy, dedicated RM clinics and improved psychological supports have all been reiterated (456,458,657).

The 2016 National Maternity Strategy alludes to capital investment to provide the dedicated spaces required, which needs to be realised (447). The Women's Health Action Plan promises to fully fund the National Maternity Strategy and so it is important that the government bodies involved in conducting these assessments of care such as the Women's Health Taskforce (Department of Health), National Women and Infants Health Programme and Health Information and Quality Authority follow through in advocating for the required funding (462). Miscarriage and RM care also need to feature in the Women's Health Action Plan going forward, to better integrate these service needs into wider women's health policy. Significant work has been done to establish a framework for

providing high-quality miscarriage care within maternity services (449); this must be realised in order to effect change.

Inequities in fertility care identified in this thesis must be addressed to improve access to services (678). Access in healthcare can be assessed under five dimensions using the framework of Penchansky and Thomas – availability, accessibility, affordability, accommodation and acceptability (714) – with awareness added later by Saurman (715). Applying this framework to fertility care in the ROI, the degree of inequity is clear. Availability refers to the supply of resources (714); in the ROI fertility expertise is limited with much of the skilled workforce within private services , while public fertility resources are limited in both services and budget. Accessibility refers to the location of healthcare (714). As mentioned previously, fertility clinics are concentrated near larger cities in the ROI, increasing the need for transportation for access. Accommodation refers to how services are made available to healthcare users (714), for example in terms of opening hours; this thesis has found that out of hours support is lacking in private fertility services, particularly when miscarriage occurs. Acceptability refers to how willing healthcare providers are to supply a service (714); public IVF is unavailable to women with a BMI > 30, aged over 40 or experiencing secondary infertility(469). Exclusionary policies such as these have been contested and should be re-examined (105,108). Affordability is the cost of a healthcare service and the ability of the service user to pay (714); the costs of IVF are exceptionally high and unaffordable for many. Affordability is closely linked to ART utilisation (716). Awareness of many aspects of infertility and how they affect access are to be covered in the next theme. Ultimately, all of these dimensions are interlinked, and all need to be addressed to some degree to improve access.

Most of the above dimensions of access can be overcome with funding, however, simply funding fertility care is not necessarily the best solution. Conceptually, fertility is not straightforward and encompasses many complex societal and ethical issues. One could argue that it is discriminatory that infertility, classed as a disease by the WHO (39), is not allocated full treatment funding under public health services. From a reproductive justice perspective, it has been argued that “safe and dignified fertility management, childbirth, and parenting together constitute a fundamental human right” (717). Indeed, this argument forms part of a European campaign for equal access to fertility treatment across

Europe, a joint collaboration between Fertility Europe and the European Parliamentary Forum for Sexual and Reproductive Rights. The campaign includes the White Paper which aims to present accurate and up-to-date information on infertility, its prevalence and implications, as well as an Atlas of Fertility Treatment Policies in Europe which maps the discrepancies in the availability of and access to fertility treatments (692,718). It is notable that Ireland ranks second last with an access ranking of just 27%, above Albania at 13% (692). The White Paper also proposes necessary measures to ensure equal access to safe and efficient fertility treatments across Europe and calls for recognition of the right to try to have a child as a universal right across the EU, equal, fair and safe access to fertility treatments and public funding for all lines of fertility treatments (718).

Conversely, the significant costs involved for an already strained health service and the low pregnancy rates for ART treatment warrant caution. Funding and staffing wholly public ART services needs resources, such as skilled embryologists, andrologists, and laboratory spaces. These are so limited and expensive to obtain, that the initial public IVF service is being outsourced to private service providers (470). It is questionable that giving vast amounts of public money to private entities, who work for profit, in a largely unregulated system, is truly the best way to improve access to fertility care over a public health approach (719). Philosophically, there are further conflicting arguments; McTernan maintains it is not fair and just to fund ART over other "life-projects", while Brown et al., argue the harms of infertility and involuntary childlessness to the individual and society are sufficient to merit funding (720,721). In reality, the resources required in the ROI are so onerous that fully funded ART is implausible, but it is important to examine the debate around the issue in wider society. In the interim, it is vital that the optimal service that can be provided is made available and that relevant legislation is passed to ensure that women/couples, regardless of funding source, receive high-quality, regulated care.

In the absence of blanket funding for ART, other alternative options to give women/couples access to additional funds alongside the current public IVF allocations could be considered. This could include interest-free government loans, or access to previously paid taxes as per the Help-to-Buy Scheme for housing (722). The government could also mandate that fertility treatment is covered within insurance policies for a minimum number of IVF cycles, as done in some states in America (723). There is an

alternative argument that government policy should be aimed at reducing the need for IVF and as discussed in Section 8.2.3, focused on addressing issues which prevent women from having children earlier, such as gender equality in the workplace and childcare provision (721). It is critical that there is patient and public involvement in addressing RM and infertility and the associated issues in order to develop public health approaches and policies that are effective and make meaningful improvements (724).

In summary, it is important that RM and infertility care receives sufficient attention and resources to ensure that all maternity units are able to meet basic standards of care, but also that HCPs recognise that standardisation does not equate to uniformity, and that the needs of individuals are reasonably accommodated.

8.3.3 Future research

Potential research studies in RM and infertility care should examine why imbalances in care occur and how this can be addressed. Examining why women/couples receive unnecessary or unrecommended treatment, is also worthy of greater exploration to understand why the prescribing practices occur, such as a survey conducted on RM care in the UK which found that many unnecessary prescriptions were requested by women (323), or further qualitative work. There is a need to re-think traditional forms of psychological support to ensure better access and to align with how women want to access supports. Examining the feasibility and acceptability of online meetings, podcasts, local in-person and virtual support groups and peer-to-peer supports may be useful as suggested by the RE:CURRENT Study (474).

There is a requirement for greater qualitative research to detail the experiences of particular groups of women with RM and infertility in the ROI, and internationally. In particular, there is a need to capture the experiences of women for whom ART is unaffordable, including women/couples who are outside of the current criteria for public services and the women from within more marginalised groups, such as women of colour, women who are members of the Travelling community and women living in Direct Provision. Examining the dimensions of access in more detail for these groups would be insightful and would help to enhance and tailor supports. The RM and infertility experiences of lesbian, bisexual, gay, transgender and other sexual and gender minorities also need to be captured. There is a need to explore men's experience of miscarriage and

infertility as a dual experience and to identify how they would like to be supported. Additionally, the provision of public ART must be evaluated on an ongoing basis to ensure that it is being delivered in the most equitable way, with regards to access and economics, but also to ensure that outcomes are on a par with international standards.

8.4 Information is central to improving care

8.4.1 Main findings

Within this thesis, it is apparent there is a clear need for better information. This refers to the amount of information provision at every stage of the RM and infertility experience, the quality of information given and the overall information available about RM and infertility as a dual experience, which is hampered by a dearth of data collection in the ROI. In this section, the information needs identified across the studies in this thesis will be discussed, as will the data that is required to better inform care. How clinical practice and policy can be adapted to increase the knowledge and awareness of women and HCPs of RM and infertility and to improve data collection will also be discussed and areas for future research suggested.

There is a need for more information for both women and HCPs (chapters 2, 3, 4, 5)

Lack of knowledge and awareness

The paucity of information on RM and infertility as a dual experience was evident in every study across this thesis and overlaps with the other themes of a lack of recognition of RM and infertility and the lack of standardisation of care. For example, the dearth of high-quality literature in the literature review and Guideline (chapters 2 and 3) illustrates this dynamic; RM and infertility as an unrecognised phenomenon is understudied and thus, there is little information with which to inform standards of care or the women directly, which perpetrates the lack of recognition and poor care. More specifically, there was a lack of knowledge and awareness around many issues related to RM and infertility demonstrated in the service evaluation, audit and qualitative study (Chapters 5, 6 and 7) among both women and HCPs. Women identified having poor knowledge and awareness of their reproductive health prior to trying to conceive, and even those women who felt they had good knowledge, felt uninformed when facing RM and infertility. While some women knew miscarriage was common, they had less awareness of RM, as previously demonstrated in a study of the Irish general population (396). Similarly, women

understood that infertility was possible, but shared the wider misconception that it could be "fixed" with IVF, regardless of age (725,726). This lack of knowledge surrounding infertility, and risk factors, particularly maternal age, has been identified in many studies examining fertility awareness in different cohorts world-wide (397,680–682,725,727–735). It is notable that the additional risk of miscarriage alongside infertility was included in just a few of these studies (680–682,735). In Chapter 7, women expressed dismay that they were so uninformed about the possibility of these reproductive health issues occurring, and that the poor success rates of IVF, and costs, were not widely publicised. Further, women felt that their age, conditions such as endometriosis or PCOS or having a miscarriage, were not highlighted as risk factors for RM or infertility and that agency regarding opportunities for fertility optimisation were missed.

Ozturk et al. previously identified poor HCP awareness as a barrier to accessing fertility care (424), strengthening the argument that awareness is a dimension of access to healthcare (715). Women felt that they should have been informed about the age-related decline in fertility and about miscarriage as a reproductive outcome earlier in life, as standard and while in secondary school, which may have motivated earlier efforts to conceive, which has been suggested previously (732). However, in keeping with other studies with women trying to conceive after the age of 35 years, there was a similar concession that many other factors in this decision were out of their control (726,736). Nonetheless, greater awareness of this possibility of RM or infertility was still desired, which may have averted the shock of the experiences, and potentially mitigated the isolation and stigma experienced.

Deficits in information provision

Within the service evaluation and the audit (Chapters 5 and 6), it is seen how the inter-related lack of recognition of RM and infertility and the lack of information HCPs had on topics such as RM guidance, fertility treatments, unorthodox treatments for RM and infertility and supports available translated into inadequate counselling and information provision (622,649). Additionally, written information on RM or infertility was not always provided and signposting to other resources, such as websites, was poor among HCPs; this meant women missed further opportunities for information and support (649). In chapter 7, it was clear that miscarriage and fertility information in both the community

and maternity services was also lacking, which contributed to negative miscarriage experiences and delays in seeking or escalating medical attention. There was also a lack of awareness around sensitivity in imparting information, which was also contributory to negative experiences, a finding common to other studies (407). As in other qualitative work, women valued and wanted information on what to expect with the diagnosis of miscarriage or fertility, clear information on the significance of RM for future fertility, as well as clear explanations on investigations and treatments and alternatives (393,593). Women also wanted recognition of the major life event they were experiencing and appreciated empathy and supportive care (593).

Seeking out information

Even where women received high-quality information from HCPs on their journey, almost all women who participated in the qualitative study admitted to engaging in information-seeking behaviour, predominantly online. This information often identified new potential investigations or treatments to be pursued. However, women who had positive interactions and in-depth counselling from informed HCPs stated that they were less likely to undertake unorthodox treatments discovered online. As well as seeking information, women went online in search of support and emotional relief as identified in other studies of women with miscarriage and infertility (737–739). In their online communities they were able to express difficult emotions that they struggled to share with family and friends. Biosociality is the notion that people with shared biological conditions come together to form social networks, and it was evident that this occurred with RM and infertility (740). This connection through shared illness is generally regarded as a positive experience where mutual understanding and support can be obtained (740). However, many HCPs expressed concern at the sharing of misinformation and anecdotal evidence regarding unorthodox treatments on these forums, a finding previously shared by Lin et al. (738), which led to clinic confrontations regarding evidence-based medicine. This work therefore identifies unique insights into the online support and information needs of women with RM and infertility, but also the caveats that should be considered in developing future online information resources.

Data is needed to better inform care (chapters 2,4,5)

Underpinning the three themes — a lack of recognition, a need for balance and equity and a need for information — is the dearth of data available on RM and infertility highlighted throughout this thesis and the need for data collection has been highlighted in Section 8.2.2. As the numbers of women with the dual experience of RM and infertility, with RM before or after treatments, are not published annually in the ROI, the experience remains unrecognised, and the care and information needs of affected women continue to go unmet (43,451,452). There is also limited information available on the demographics of women with RM and/or infertility, thereby precluding the identification of public health issues which may be contributory (43,452). In this way, the cohort study of women with RM in chapter 4 makes a meaningful contribution to the literature, providing a large cohort of women verified as having had three or more consecutive miscarriages with delineation of primary and secondary RM (677). The regression analysis also confirms maternal age, smoking and parental karyotype to be associated with outcomes, which allows for these risk factors to be identified and targeted in both RM management, wider health policy and resource allocation (677). Similarly, the cohort study identified that women with the combined experience of RM and infertility had lower livebirth rates (677).

Identification of these cohorts is difficult, given these data on RM or fertility are not collected routinely and as the service evaluation has shown, audit is infrequently conducted (649). While the service evaluation gave some indication as to how many women attend fertility clinics with RM and the qualitative study confirmed this practice, there are no other data available on women with RM and infertility aside from the limited fertility data published by the Health Products Regulatory Authority (HPRA) (43,464). The service evaluation (Chapter 5) demonstrates how HCPs in public services currently have poor knowledge of the numbers of women with the dual experiences and the investigations and treatment they may be undergoing, and there was insufficient engagement from private clinics to provide meaningful insights on practices (649). Data collection on women with RM and infertility for the audit and cohort study was complicated by the reliance on clinical documentation and records, rather than a formal database for miscarriage, which has previously been called for (451).

Miscarriage data is known to be hard to collate, as demonstrated by the variation in miscarriage data at hospital level (451), in addition to the difficulties in initiating a miscarriage register (741). While large-scale population registers have provided much of the valuable demographic data on miscarriage (53,450,453,742–744), these registers have their own issues with miscarriage data accuracy, including false diagnoses, confusion with termination of pregnancy, exclusion of earlier miscarriages managed outside of hospital and the wider issue of confidentiality in health records (450,743). Registers however facilitate long-term follow-up, which is becoming more important as RM is associated with cardiovascular disease and thromboembolism in later life (1). Thus, data collection is an area that requires greater focus.

8.4.2 Implications for clinical practice and policy

Improvements in the care for women with RM and infertility can be brought about by increasing knowledge and awareness of both women and HCPs through better information provision, and by better data collection in miscarriage and fertility services, which can be facilitated through progressive clinical practice and policy.

Addressing the need for greater information in clinical practice

In order to increase the quantity and quality of information provided to women with RM and infertility within public maternity and fertility services, there is a need for improved training and education for HCPs on this topic. Many Clinical Midwifery and Nurse Specialists who participated in the qualitative study (Chapter 7) voiced how fertility and the various treatments were not included in their training as undergraduates and that they had limited clinical experience during training. This highlights a clear gap in education that should be addressed. Moreover, with the advent of the fertility hubs in Ireland, there is now a specific clinical placement opportunity to address the training deficit. This training and education could also be extended to medical students. Furthermore, previous studies have indicated that fertility information is just as poor among medical and non-medical university students (397,727,728), meaning this training can also empower the students regarding their own fertility.

Focused training would be required to increase the knowledge and awareness of existing staff. This could be delivered as part of the implementation efforts of Fertility in Secondary Care Guideline (469), with additional training on fertility risk factors, concomitant RM and

treatment challenges, to HCPs in obstetrics, midwifery and GP. Online training through the online HSE training portal (HSEland.ie) could also be considered, as has been rolled out with termination of pregnancy training (745). Workshops on miscarriage and RM care, with discussion of the dual experience of RM and infertility could also be developed and rolled-out, as have been done successfully for stillbirth (746).

Standard information leaflets on miscarriage and RM should be available, which include the experience of women undergoing fertility treatment. Work has begun has translating the knowledge available on miscarriage and RM into accessible formats following on from the RE:CURRENT study and the publication of the RM guideline and other studies from this thesis (636). These leaflets should be available nationally and distributed to every woman with such an experience, to ensure a baseline standard of information is received. Such a leaflet should not replace time and appropriate counselling by HCPs, however.

Alongside information leaflets, there needs to be increased HCP awareness of informative websites such as the Health Service Executive (HSE) mychild.ie, the pregnancyandinfantloss.ie, corkmiscarriage.com and the many support websites for miscarriage and infertility, to better direct women/couples. It is important that these websites have all of the relevant and clinically up to date information and present information in accessible and engaging formats. A study is currently underway assessing the quality of miscarriage and RM information available online nationally, as has previously been done for stillbirth (477,747). Again, ongoing patient and public involvement should be central to the development of new or updated information resources to facilitate maximum engagement and practicability (724).

Improved knowledge and awareness is dependent on informed healthcare policy

There is need for greater emphasis within public health policy on RM and infertility as reproductive health issues and new initiatives to enhance the knowledge and awareness of the general public. Improved data collection regarding miscarriage and fertility is also required to identify service deficits and required resources.

In 2019, ESHRE launched a poster campaign, at the European Parliament during Fertility Europe's 2019 European Fertility Week, which aimed to increase awareness of the need for fertility education (748). The poster targeted the general public of all ages, with the aim of facilitating the conversation around fertility education and was to be displayed in

doctors' and gynaecology surgeries, family planning clinics, and schools (748). The campaign for 2023 was psychological support in infertility with a focus on reducing stigma (749). An additional goal of the ESHRE fertility education campaign was for every country to have a fertility education website and provide fertility education in schools and beyond, in keeping with the goals of the White Paper mentioned previously (718,748). It is known that topics such as miscarriage and endometriosis are missing from curricula (750). Subsequently, a group of global experts have founded the International Fertility Education Initiative (IFEI), which aims to improve fertility and reproductive health awareness through education, reduce the prevalence of infertility and improve the health of future children (751). Engagement with these types of campaigns offers Ireland an opportunity to improve public awareness with shared resources using international best evidence and policy and would also allow for integration of these resources into existing reproductive education in schools. Alternatively, they provide an excellent starting point of development of a more customised campaign. The reproductive health education programme in Irish schools is undergoing a curriculum change, and while international practice in New Zealand and Ontario has been taken into consideration, the above European resources and the concepts of miscarriage, fertility and fertility decline, have not (752). Therefore, the reproductive health information offered in schools is an area for targeted improvement.

Data collection needs to be integrated into healthcare policy to better delineate the numbers of women/couples with infertility and RM and their reproductive outcomes, so as to allocate fertility and obstetric resources. As discussed previously, the establishment of the Assisted Human Reproduction Regulatory Authority and the mandated collection and publication of fertility treatments and outcomes will provide better data and greater insights on the number of women experiencing miscarriage while undergoing fertility treatment (43,466). Introduction of the electronic health record nationwide, with robust coding and clinical audit appears to be the most pragmatic solution for miscarriage data collection in Irish hospitals – in line with the plans within the Health Information Bill 2023 – but will require substantial input of resources (753). Another consideration for policy with regards to data collection for miscarriage is voluntary registration. As mentioned in the introduction to this thesis, Scotland and the United Kingdom have introduced a baby loss certificate, which allows women/couples who have experienced a pregnancy loss

before 24 weeks to have formal acknowledgement (754,755). As this certification is voluntary it may not provide wholly representative data, but it could provide new insights into miscarriage incidence alongside important validation for parents.

It is important to note that collection and reporting of information on its own is not enough to generate substantive change (756). The social determinants of health, according to the definition of the World Health Organization (WHO), are "the non-medical factors that influence health outcomes…the conditions in which people are born, grow, work, live, and age, and the wider set of forces and systems shaping the conditions of daily life" (757). It is important that the systems within healthcare are considered (such as general practice, maternity service, fertility service etc.) alongside the social determinants of health for the targeted population in considering how best to provide information and to implement change (756). It is critical that data collected on RM and infertility captures these differences and that adequate resources are provided to help women/couples overcome the identified inequities in accessing treatment, and also that information across healthcare systems is accessible to all who require it (756).

8.4.3 Future research

To enable better information provision on reproductive health across the health service, there needs to be further assessment of the knowledge and awareness of HCPs who do not work directly in RM or fertility services, such as general obstetricians and gynaecologists and GPs. This would identify and target areas for knowledge improvement and training, with the overall aim of enabling better recognition of reproductive health issues and information provision. Future research could examine the quality of the online information that is available on websites accessed by women seeking support or advice on investigation and treatment of RM and infertility, as has been done for stillbirth (747). Not only would this identify gaps in the knowledge currently provided, but it would also allow the various sources of information to be differentiated and may identify potential conflicts of interest. This would be useful in tackling misinformation as women could be directed to reliable resources. Another important aspect of information provision is how best to distribute information on reproductive health to women of various ages. While in Chapter 7, women voiced a desire for information on miscarriage and infertility from secondary school age, these are topics that must be broached with sensitivity. It would

be important to conduct research, such as surveys or qualitative studies, with teachers and teenagers on how this information should be delivered and to explore whether this should form part of the current sexual health education programme or be delivered separately, in a different format.

8.5 Strengths and limitations

This doctoral work on RM and infertility drew on many different methods to explore this topic in the ROI. This included quantitative analysis of existing data within the RM database of a tertiary hospital, as well as newly generated data from a national service evaluation and qualitative interviews with women and HCPs nationally. This thesis contributes substantially to what is an under-researched and under-served area within the literature as well as to a wider body of work conducted by clinical and non-clinical professionals and researchers in an effort to improve miscarriage and RM care in the ROI (34,473,475).

Some limitations should be noted. This work was limited by the quality of routine RM data collection within the tertiary hospital, which will hopefully improve with the awareness gained from this work and progressive use of the electronic health record in the ROI. The limited engagement from the private sector in the service evaluation and the qualitative study restricted the information and insights available on care structures and management. While this work provides important insights into the experiences of male partners, many aspects of their lived experience remain unexplored and merits further research. The qualitative work was also limited by the homogeneous socio-demographics of the women who participated, and – as noted above – more work is needed with women of varying social circumstances, such as migrant women, women who are members of the Travelling community and women living in direct provision. Environmental factors contributing to RM and infertility were not explored in the introduction and subsequent studies, due to the existing breadth of this thesis. Such factors are increasingly recognised as important issues within public health and sexual and reproductive health, including pregnancy loss (1,719). More focused work is needed to determine what impact deteriorating air and water quality is having on reproductive health, alongside more complex issues such as the hormonal effects of plastic pollution (719).

8.6 Conclusion

RM and infertility is a difficult experience for women/couples which impacts on every aspect of the lives of those affected. This doctoral work has examined the dual experience of RM and infertility in the ROI across and has provided meaningful insights into the issues with current service provision and the management of RM and infertility, the reproductive outcomes following this experience and the lived experiences of women with the dual experience and relevant HCPs. This thesis has critically analysed the findings of the included studies alongside the available literature to generate areas for improvement. It has identified that there is a lack of recognition of RM and infertility as a dual experience – by individuals, HCPs and within services – which contributes to isolation, poor care and disjointed management. These issues contribute negatively to what is already an emotionally complex and burdensome situation for women/couples. A need for greater equity in care for RM and infertility was also evident within this work, alongside the need for more standardised clinical care that can also meet the individual care needs of women/couples. To address these issues, there is a need for greater information dissemination on reproductive health issues to women/couples affected, to HCPs working directly and indirectly in these areas and to the general public. It is crucial that this information is supplemented with adequate resources so that it is accessible to those who need it. It is imperative that individuals with lived experience are involved in targeting these barriers to accessing RM and infertility care, as well as the progression of public fertility care, to ensure that the necessary funding and policy reforms are appropriately directed and effective. Moreover, this must be bolstered by improved data on RM and fertility care in the ROI, implementation of updated (and awaited) Clinical Practice Guidelines and greater regulation within the fertility sector. By addressing these areas, we can strive towards a more compassionate, informed, and equitable approach to reproductive healthcare for women and their partners dealing with RM and infertility.

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Supporting materials

Supplementary file 3.1 – Clinical practice guidelines for recurrent miscarriage in high-income countries: a systematic review

RBMO

ELSEVIER



REVIEW

Clinical practice guidelines for recurrent miscarriage in high-income countries: a systematic review



BIOGRAPHY

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KEY MESSAGE

Thirty-two clinical practice guidelines (CPG) for recurrent miscarriage were identified. Levels of consensus across the CPG varied, with some conflicting recommendations. Greater efforts are required to improve the quality of evidence underpinning CPG, the rigour of their development and the inclusion of multi-disciplinary perspectives, including those with lived experience of recurrent miscarriage.

ABSTRACT

Recurrent miscarriage affects 1–2% of women of reproductive age, depending on the definition used. A systematic review was conducted to identify, appraise and describe clinical practice guidelines (CPG) published since 2000 for the investigation, management, and/or follow-up of recurrent miscarriage within high-income countries. Six major databases, eight guideline repositories and the websites of 11 professional organizations were searched to identify potentially eligible studies. The quality of eligible CPG was assessed using the Appraisal of Guidelines for Research and Evaluation (AGREE II) Tool. A narrative synthesis was conducted to describe, compare and contrast the CPG and recommendations therein. Thirty-two CPG were included, from which 373 recommendations concerning first-trimester recurrent miscarriage were identified across four sub-categories: structure of care (42 recommendations, nine CPG), investigations (134 recommendations, 23 CPG), treatment (153 recommendations, 24 CPG), and counselling and supportive care (46 recommendations, nine CPG). Most CPG scored 'poor' on applicability (84%) and editorial independence (69%); and to a lesser extent stakeholder involvement (38%) and rigour of development (31%). Varying levels of consensus were found across CPG, with some conflicting recommendations. Greater efforts are required to improve the quality of evidence underpinning CPG, the rigour of their development and the inclusion of multi-disciplinary perspectives, including those with lived experience of recurrent miscarriage.

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KEYWORDS
AGREE II
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Declaration: KOD and RR were involved in the development of one of the clinical practice guidelines appraised in this paper (Health Service Executive, 2016); KOD is National Lead within Ireland for its implementation. Neither KOD nor RR were involved in the quality assessment of this CPG. The authors report no financial or commercial conflicts of interest.

INTRODUCTION

Recurrent miscarriage is estimated to affect 1–2% of women of reproductive age, depending on the definition used, and with the caveat that the actual prevalence is difficult to obtain owing to difficulty accessing data (*Hemminki and Forssas, 1999*; *Oliver-Williams and Steer, 2015*; *European Society of Human Reproduction and Embryology [ESHRE] Early Pregnancy Guideline Development Group, 2017*; *Rasmark Roepke et al., 2017*; *Woolner, et al., 2020*). The term used to describe the condition varies between countries and professional bodies (Youssef *et al.*, 2020); for example, ESHRE uses the term 'recurrent pregnancy loss' (*ESHRE Early Pregnancy Guideline Development Group, 2017*), whereas the Royal College of Obstetricians and Gynaecologists (RCOG) in the UK uses the term 'recurrent miscarriage' (*RCOG, 2011*). For the purposes of reporting within this paper, the latter term is used throughout, and the focus is on recurrent first-trimester miscarriage given that this should be treated differently to second-trimester miscarriage (*McPherson, 2016*; *Shields et al., 2020*). Some professional bodies or organizations, such as ESHRE (*ESHRE Early Pregnancy Guideline Development Group, 2017*) and the American Society for Reproductive Medicine (ASRM) in the USA (*Practice Committee of the ASRM, 2012*) now define recurrent miscarriage as the loss of two or more consecutive pregnancies for investigations; however, the previous definition of three or more consecutive pregnancy losses remains in use by others, such as the *RCOG (2011)*, the Health Service Executive (HSE) in Ireland (*HSE, 2016*) and the French College of Gynaecologists and Obstetricians (*Huchon et al., 2016*). As the revised definition of recurrent miscarriage is used across more countries and regions, more women and/or couples will be accessing services for investigation and management.

Evidence-based, up-to-date clinical practice guidelines (CPG) are required to inform the effective management of recurrent miscarriage (*Van den Berg et al., 2014*; *Gibbins and Porter, 2016*). About 70% of women who have experienced two recurrent losses will conceive a subsequent pregnancy, with a 70% success rate (*Clifford et al., 1997*; *Brigham et al., 1999*; *Habayeb and Konje, 2004*). The risk of further miscarriage increases after each successive pregnancy loss, reaching about 40% after three consecutive pregnancy losses; a previous live birth does not prevent a woman experiencing recurrent miscarriage, and the prognosis worsens with increasing maternal age (*Clifford et al., 1997*; *Nybo Andersen et al., 2000*).

The suggested causes of recurrent miscarriage include uterine anomalies (inclusive of common acquired anomalies, such as fibroids, and more uncommon anatomical defects, such as uterine septae), endocrine disorders (such as thyroid disease), autoimmune diseases (such as lupus), acquired thrombophilia and genetic causes, in particular balanced translocations (*Toth et al., 2010*; *RCOG, 2011*; *El Hachem et al., 2017*; *van Dijk et al., 2020*). Others, such as chronic endometritis, infectious diseases, inherited thrombophilia, luteal phase deficiency, high sperm DNA fragmentation levels, polycystic ovary syndrome and high body mass index, have been proposed, but remain debated (*RCOG, 2011*; *El Hachem et al., 2017*; *ESHRE Early Pregnancy Guideline Development Group, 2017*; *Matjila et al., 2017*). Most investigations and treatments offered also remain controversial, with lack of consensus among professionals and/or groups (*Tzioras et al., 2009*; *Matthiesen et al., 2012*; *Branch and Silver, 2016*; *Scott, 2016*; *Bruno, et al., 2019*). Nevertheless, standard investigations for recurrent miscarriage continue to be important in evaluating potential factors responsible for pregnancy loss (*Clifford et al., 1994*).

It is also important that the provision of care meets the needs of those who experience recurrent miscarriage. The psychological wellbeing of women and men who experience recurrent miscarriage can be negatively affected in the medium- to long-term (*Klock et al., 1997*; *Lok and Neugebauer, 2007*; *Kolte et al., 2014*; *2015*; *McCarthy et al., 2015*; *Tavoli et al., 2018*). In addition, women and men report gaps in their perceived needs and their care experience after recurrent miscarriage, highlighting the need for more information, psychological support, the inclusion of partners in consultations, and follow-up care (*Musters et al., 2011*; *2013*; *van den Berg et al., 2017*; *Koert et al., 2018*).

Clinical practice guidelines synthesize the best available evidence to guide clinician and patient decision-making, with the aim of improving care quality and patient outcomes (*Lugtenberg et al., 2009*; *Graham et al., 2011*). They are 'statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options' (*Institute of Medicine, 2011*). The identification, appraisal and description of published CPG in high-income countries would be a valuable first step in informing efforts to promote the optimization and standardization of recurrent miscarriage care. Given the large discrepancies in pregnancy outcomes and care structures between high, low and middle-income countries (*Goldenberg et al., 2018*; *Gage et al., 2019*), this systematic review focuses on high-income countries, as defined by the *World Bank (2020)*. Some attempts have been made to do this already. *Youssef et al. (2019)* recently conducted a comparison and appraisal of the ESHRE, ASRM and RCOG recurrent miscarriage CPG using the Appraisal of Guidelines, Research and Evaluation version 2 (AGREE II) criteria, an accepted and validated tool for assessing the methodological quality of CPG (*Siering et al., 2013*). *Hong Li and Marren (2018)* also provide an overview of these three CPG, without any quality appraisal. *Khalife et al. (2019)* review and compare the ASRM and ESHRE CPG, noting the lack of consensus on standard evaluation of recurrent pregnancy loss. Each of these studies focused on a select group of CPG. Therefore, a more systematic approach to identifying CPG concerning recurrent miscarriage would add to the body of evidence.

The aim of the present systematic review was to identify, appraise and describe published CPG for the investigation, management, and/or follow-up of first-trimester recurrent miscarriage within high-income countries. The specific objectives were to identify published CPG for the investigation, management, and/or follow-up of recurrent miscarriage within high-income countries; appraise the quality of included CPG using the AGREE II instrument; and describe recommendations from the included CPG concerning first-trimester recurrent miscarriage.

MATERIALS AND METHODS

This systematic review is reported following PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidance. The protocol for the review was published in advance (*Hennessy et al., 2020*) and pre-registered on PROSPERO, the International Prospective Register of Systematic Reviews (CRD42020173881; registered 28 April 2020).

Eligibility criteria

Inclusion and exclusion criteria were developed according to the 'PICAR' (population and clinical areas, interventions, comparators, attributes of CPG and recommendation characteristics) framework (TABLE 1). For this review, CPG were defined as 'systematically developed statements to assist practitioners about appropriate health care for specific clinical circumstances'; an adaptation of the

TABLE 1 ELIGIBILITY CRITERIA PERTAINING TO THE POPULATION AND CLINICAL AREAS, INTERVENTIONS, COMPARATORS, ATTRIBUTES OF CLINICAL PRACTICE GUIDELINES AND RECOMMENDATION CHARACTERISTICS (PICAR) STATEMENT

PICAR framework	Eligibility criteria
Population, clinical indication(s), and condition(s)	Study population • Women or couples experiencing recurrent miscarriage. • Humans only. Clinical indication • Investigation, management and/or follow-up of women and/or or couples with recurrent miscarriage, specifically first-trimester recurrent miscarriage. Clinical condition • Recurrent miscarriage is defined by the review team as the loss of two or more consecutive pregnancies (*ESHRE Early Pregnancy Guideline Development Group, 2017*), with a specific focus on first-trimester recurrent miscarriage. For the purposes of this review, all clinical practice guidelines (CPG) that focus on recurrent miscarriage, regardless of the definition used, will be included. The definition applied by each included CPG will be extracted and considered when synthesizing and interpreting the review findings.
Interventions	• Any intervention focusing on the investigation, management and/or follow-up of recurrent miscarriage.
Comparator(s), Comparison(s), and (key) Content	• Any comparator or comparison. • No 'key' CPG content is of interest, unless CPG are broader in scope; in such instances, content specific to recurrent miscarriage is only of interest.
Attributes of eligible CPGs	Language • Available in English. • CPG in which summaries are available in English, but full text is not, will be excluded. Year of publication • 2000 onwards. • In Ireland, the National Clinical Effectiveness Committee, requires a full guideline update within 3 years (*National Clinical Effectiveness Committee, 2019*); however, The Scottish Intercollegiate Guidelines Network also specifies 3 years, but also includes those over 3 years old and revalidated (*Scottish Intercollegiate Guidelines Network (SIGN), 2019*). The World Health Organization does not have a defined period for guideline updates (*World Health Organization, 2014*). To be comprehensive, CPG published within the last 20 years (January 2000 to date) will be eligible for inclusion given that international CPG concerning recurrent miscarriage can fall well outside the 3-year period (*American College of Obstetricians and Gynecologists, 2002; Association of Early Pregnancy Units, 2007*). A good-quality older guideline could be a good base on which to develop a new guideline (*The ADAPTE Collaboration, 2010*). Developing or publishing organization • Only CPG issued or endorsed by national or international scientific societies, professional colleges, charitable organizations and government organizations will be included. Country of publication • High-income countries, as defined by the World Bank (*World Bank, 2020*) as large discrepancies exist in pregnancy outcomes and care structures between high, low and middle-income countries (*Goldenberg et al., 2018; Gage et al., 2019*) Version • Latest version only. Development process • Evidence-based, consensus-based, or both. System of rating evidence • Use of a system to rate the level of evidence within CPG is not an eligibility criterion; however, such data will be extracted to inform synthesis and interpretation of findings. Quality of evidence • The eligibility of CPG will not be based on a specific minimum quality cut-off score based on the AGREE II criteria. • We are interested in all guidance generated regardless of quality, e.g. because CPG determined to be of 'high quality' may not necessarily report recommendations that are highly valid and implementable (Johnston *et al.*, 2019); this will, however, be taken into consideration when synthesizing and interpreting the review findings. Scope • Must have a primary or secondary focus on the investigation and treatment of recurrent miscarriage. Must be national or international in scope. • Covers any aspect of recurrent miscarriage care and its organization, including the provision of dedicated pregnancy loss clinics, treatment and management of recurrent miscarriage, investigations carried out after recurrent miscarriage to inform prognosis of future pregnancy outcomes and counselling of parents after recurrent miscarriage. • Must be clearly identified as a CPG. • Must be published. Unpublished CPG, conference papers, discussion papers, drafts and opinions will be excluded.
Recommendations	Must have 'recommendations' concerning the identification, management and/or follow-up of recurrent miscarriage (either explicitly highlighted as such within the document or noted within the body of the document, but not explicitly identified as a recommendation). To be eligible, recommendations need not be accompanied by an explicit level of confidence (and quality assessment criteria system used specified); however, these data will be extracted (where available) and considered during the synthesis and interpretation of findings.

definitions used by the *National Clinical Effectiveness Committee (2019)* and *Scottish Intercollegiate Guidelines Network (SIGN) (2020)*.

Information sources and search strategy

The following databases were systematically searched to identify eligible CPG, published between January 2000 and March 2020: *CINAHL Plus* (EBSCOhost; 1994), *Embase*® (Elsevier; 1980), *MEDLINE* (Ovid®; 1946), *Open Grey* (INIST-CNRS; 2011), *Scopus* (Elsevier; 2004), and *Web of Science*™ (Thomson Reuters). Guideline repositories (n = 8) and the websites of professional organizations and associations from around the world (n = 11) were also searched. The search strategy was developed with the assistance of a specialist librarian. Key word searches, using combinations of key words and Medical Subject Headings (or equivalent), were used across two concepts using the AND Boolean operator: clinical guidelines; recurrent miscarriage. Within each of the categories, keywords were combined using the 'AND' or 'OR' Boolean operators. Information sources and search terms applied are detailed in Supplementary Table 1.

Study selection

Retrieved records were imported firstly into EndNote X9 and de-duplicated using the 'remove duplicates' function, as well as manually screening results for accuracy. They were then imported into Rayyan and screened again for duplicates. Two independent reviewers (MH and RD) subsequently screened titles and abstracts of retrieved records against the inclusion criteria; this process was repeated for full texts. Any disagreements were discussed and resolved via consensus, with the input of a third reviewer (SM/KOD), where necessary.

Data collection process

To ensure that the most up-to-date versions of CPG were included in the final results, MH conducted searches and contacted authors where necessary. Once the final set of included CPG was agreed, MH retrieved all documents related to the CPG (such as supplemental documents, methodology papers and others) before data extraction or quality assessment was undertaken. RD independently verified all documents collected to confirm the completeness and ensure that companion documents were matched appropriately.

Data extraction

Key features of CPG and the documented recommendations were extracted using a structured data extraction form in Microsoft Excel (Microsoft Corporation, Redmond, WA, USA) (*Hennessy et al., 2020*), which was piloted in advance. Data were extracted by MH and verified for accuracy and completeness by RD. Discrepancies were resolved through consensus and, where agreement could not be reached, SM/KOD reviewed and made a final decision. To facilitate data synthesis, reviewers assigned categories and sub-categories to each recommendation during data extraction; some were pre-defined whereas others were generated iteratively. Details on the level of evidence (and strength, if provided) associated with each recommendation were also extracted.

Quality assessment

The quality of included CPG was assessed using the AGREE II criteria (*Brouwers et al., 2010*). The criteria encompass 23 items, over six domains, rated on a seven-point Likert scale: scope and purpose of the guideline; stakeholder involvement in the development of the guidelines; rigour of development and formulation of the recommendations within the guideline; clarity of presentation of the guideline; applicability of the guideline; and editorial independence in the formulation of recommendations within the guideline. As part of the overall assessment, two global ratings are included: a rating on the overall quality of the guideline; and whether the guideline would be recommended for use in practice. Three reviewers with methodological, clinical expertise, or both (MH, LL and SM), conducted an independent quality assessment of the CPG. Major discrepancies in the scores (where assigned scores differed by more than two points) were discussed and independently reassessed and consensus reached. Domain scores were calculated by summing up all the scores of the individual items in a domain and by scaling the total as a percentage of the maximum possible score for that domain, as per the AGREE II User Manual. To make the scores more relevant to readers and enable fair comparison, the AGREE II outcomes are reported categorically using the five-point Likert scale described by other reviews (*Eady et al., 2017*; *Daley et al., 2019*): excellent (>80%), good (>60–80%), average (>40–60%), fair (>20–40%) and poor (≤20%).

Data synthesis

A narrative synthesis is used to describe, compare and contrast CPG and the recommendations therein, taking account of quality appraisal (using the AGREE II tool) and recency of publication. The levels of evidence associated with the recommendations within each CPG is reported, and quality assessment rating system used; no attempt was made to standardize evidence ratings across CPG.

Patient and public involvement

The protocol for this systematic review was developed in conjunction with a pregnancy loss parent advocate (RR) and through consultations with Specialist Bereavement and Loss Midwives. This work is part of a broader project evaluating current services for recurrent miscarriage in the Republic of Ireland. The RE:CURRENT project Research Advisory Group includes representation from healthcare and allied health professionals, advocacy and support organizations, those involved in the administration, governance and management of maternity services, academics, and women and men who have experienced recurrent miscarriage. RR is a member of this group and was involved in discussions and decisions concerning the conduct, findings and outputs of the review.

RESULTS

Guideline selection

A total of 6065 records from the planned searches of databases (n = 5536), guideline repositories (n = 395) and websites of professional bodies and organizations (n = 134) were retrieved; the PRISMA flow chart is presented in FIGURE 1.

After removing duplicates, the titles and abstracts of 4108 records were screened and, subsequently, 170 full texts were assessed. Thirty-two CPG were included in the final synthesis (TABLE 2); the original data extraction file (containing CPG characteristics and recommendations) is available in an open access repository

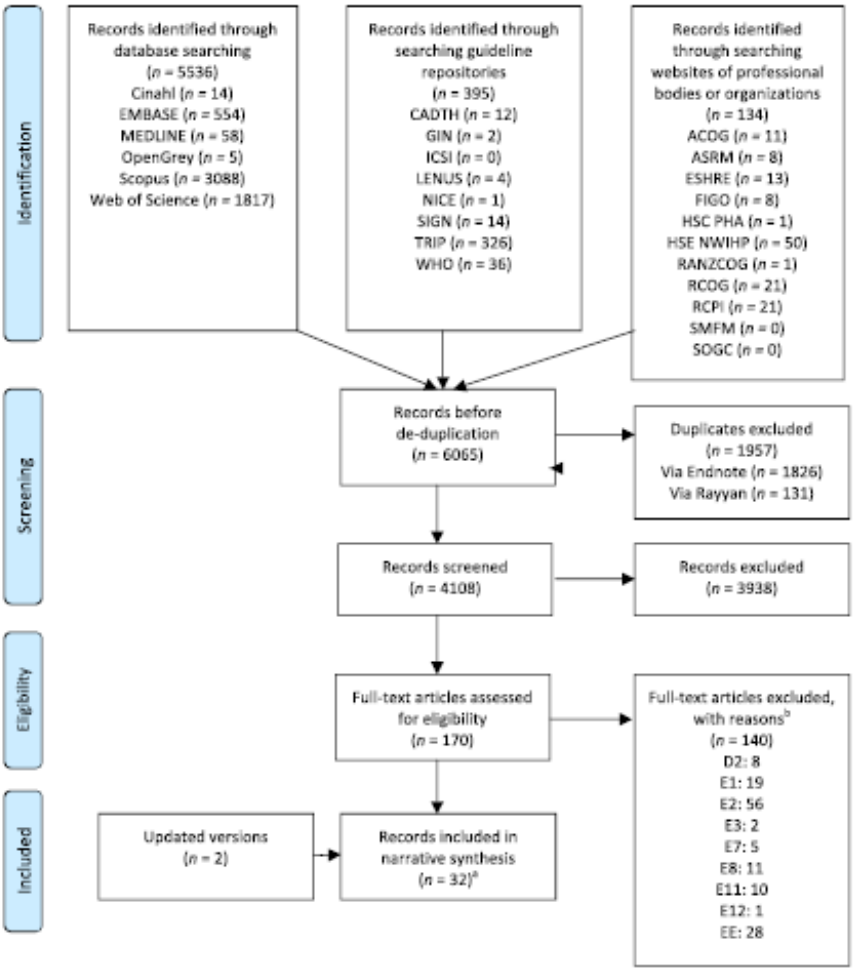


FIGURE 1 PRISMA flow diagram. [a]Plus two addenda (Arachchillage, 2020; Bashford, 2020). [b]D2, duplicate; E1, not a clinical practice guideline; E2, not focused (primary/secondary) on the investigation, management and/or follow-up of recurrent miscarriage; E3, not issued, endorsed, or both, by national or international scientific societies, professional colleges, charitable organizations and/or government organisations; E7, not published in English; E8, not latest version; E11, withdrawn or no longer available; E12, cannot access full text; EE, meets two or more exclusion criteria.

(*Hennessy et al., 2021*). Details of records excluded at the full-text review stage are presented in Supplementary Table 2.

Guideline characteristics

Most of the included CPG were described by their authors as guideline(s) (*n* = 9 [28%]), clinical practice guideline(s)/clinical guidelines (*n* = 9 [28%]), or practice guideline(s) (*n* = 3 [9%]) (TABLE 1). Seven (22%) CPG focused specifically on recurrent miscarriage, recurrent pregnancy loss (RPL), or both (including one focused on a specific procedure) (*RCOG, 2011*; *Practice Committee of the ASRM, 2012*; *National Institute for Health and Care Excellence [NICE], 2015*; *ESHRE Early Pregnancy Guideline Development Group, 2017*; *Toth et al., 2018*; *Arab et al., 2019*; *Northern Ireland Public Health Agency, 2020*), two (6%) focused on early pregnancy loss (*American College of Obstetrics and Gynaecology [ACOG], 2018*; *Queensland Clinical Guidelines, 2018*) and two (6%) on pregnancy loss, perinatal death, or both (*HSE, 2016*; *Huchon et al., 2016*). The remaining 21 (66%) CPG were broader in focus: uterine and/or genital anomalies (*American Association of Gynecologic Laparoscopists [AAGL], 2012*; *Grimbizis et al., 2016*; *Practice Committee of the ASRM, 2016*; *2017*), infertility (*Practice Committee of the ASRM, 2015*; *Agarwal et al., 2017*; *Wall et al., 2020*), thyroid disease during pregnancy and the postpartum (*De Groot et al., 2012*; *Alexander et al., 2017*) and more generally (*Garber et al., 2012*), genetic testing and/or prenatal diagnosis (*Armour et al., 2018*; *Practice Committees of the ASRM and the Society for Assisted Reproductive Technology, 2018*; *Wilson, 2018*; ESHRE Preimplantation Genetic Testing [PGT] *Consortium Steering Committee et al., 2020*), venous thromboembolism, and thrombophilia and/or antiphospholipid syndrome (*Bates et al., 2012*; *Keeling et al., 2012*; *Hickey et al., 2013*; *Institute of Obstetricians and Gynaecologists Royal College of Physicians of Ireland [RCPI], HSE Clinical Care Programme in Obstetrics and*

TABLE 2 SUMMARY OF INCLUDED CLNICAL PRACTICE GUIDELINES

Title	Author, year	Developing or publishing organization, or authors	Country or countries of publication	Description provided by authors (e.g. guideline or algorithm)	Type of guideline (formulated, adapted, updated or revised)	Topic addressed (recurrent miscarriage, RPL or broader)	Number of recommendations specific to recurrent miscarriage	Development process (evidence-based, consensus-based, or both)	System of rating evidence or quality instrument used during guideline development (GRADE, Oxford, not mentioned, or other)	Funding
American Association of Gynecologic Laparoscopists (AAGL) practice report: practice guidelines for the diagnosis and management of submucous leiomyomas	AAGL, 2012	Practice Committee of the AAGL	Global	Practice guidelines	Not specified; formulated	Broader: submucous leiomyomas	3	Evidence-based; expert consensus-based	Modified method outlined by the US Preventive Services Task Force [USPSTF]; criteria described in the Report of the Canadian Task Force on the Periodic Health Examination	Not specified
American College of Obstetrics and Gynaecology (ACOG) practice bulletin number 200: early pregnancy loss	ACOG, 2018	ACOG	USA	Practice Bulletin/clinical management guidelines	Update	Broader: early pregnancy loss	2	Evidence-based; expert opinion	USPSTF	Not specified
The Society for Translational Medicine: clinical practice guidelines for sperm DNA fragmentation testing in male infertility	Agarwal, 2017	The Society for Translational Medicine	Global	Clinical practice guidelines	Not specified	Broader: male infertility	2	Not specified	Modified from Oxford Centre for Evidence-Based Medicine (http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/)	Not specified
Guidelines of the American Thyroid Association (ATA) for the diagnosis and management of thyroid disease during pregnancy and the postpartum	Alexander, 2017	ATA	USA	Guidelines	Revised	Broader: thyroid disease during pregnancy and the postpartum	2	Evidence-based; expert consensus-based	American College of Physicians Guideline Grading System	ATA without support from any commercial sources
Saudi guidelines for threatened and recurrent miscarriage management; the role of progestogens in threatened and idiopathic recurrent miscarriage	Arab, 2019	Saudi Society of Obstetrics and Gynecology	Saudi Arabia	Guidelines	Updated	Recurrent miscarriage	9	Evidence-based; expert consensus-based	Not mentioned	Abbott, Saudi Arabia provided funding for medical writing assistance, & sponsored the two consensus meetings
Practice guideline: Joint Society of Obstetricians and Gynaecologists of Canada (SOGC)-Canadian College of Medical Geneticists (CCMG) recommendations for the use of chromosomal microarray analysis for prenatal diagnosis and assessment of fetal loss in Canada	Armour, 2018	SOGC–CCMG	Canada	Practice guideline	Updated	Broader: use of chromosomal microarray analysis for prenatal diagnosis and assessment of fetal loss	1	Evidence-based	Modified criteria described in the Report of the Canadian Task Force on Preventive Healthcare	The Hospital for Sick Children Centre for Genetic Medicine and the University of Toronto McLaughlin Centre
Evaluation and treatment of recurrent pregnancy loss: a committee opinion	American Society for Reproductive Medicine (ASRM), 2012	ASRM	USA	Committee opinion	Not specified	Recurrent pregnancy loss	26	Not specified	None/not mentioned	Not specified

TABLE 2 *(continued)*

Title	Author, year	Developing or publishing organization, or authors	Country or countries of publication	Description provided by authors (e.g. guideline or algorithm)	Type of guideline (formulated, adapted, updated or revised)	Topic addressed (recurrent miscarriage, RPL or broader)	Number of recommendations specific to recurrent miscarriage	Development process (evidence-based, consensus-based, or both)	System of rating evidence or quality instrument used during guideline development (GRADE, Oxford, not mentioned, or other)	Funding
Subclinical hypothyroidism in the infertile female population: a guideline	ASRM, 2015	ASRM	USA	Guideline	Not specified; formulated	Broader: treating subclinical hypothyroidism in female patients with a history of infertility and miscarriage	3	Evidence-based; expert consensus-based	Described, but system name not mentioned	Not specified
Uterine septum: a guideline	ASRM, 2016	ASRM	USA	Guideline	Formulated	Broader: treatment of septate uterus	2	Evidence-based	Described, but system name not mentioned	Not specified
Removal of myomas in asymptomatic patients to improve fertility and/or reduce miscarriage rate: a guideline	ASRM, 2017	ASRM	USA	Clinical practice guideline	Formulated	Broader: removal of myomas in asymptomatic patients to improve fertility/ reduce miscarriage rate	2	Evidence-based	Described, but system name not mentioned	Not specified
The use of preimplantation genetic testing for aneuploidy (PGT-A): a committee opinion	ASRM, 2018	ASRM and the Society for Assisted Reproductive Technology (SART)	USA	Committee opinion	Formulated	Broader: use of preimplantation genetic testing for aneuploidy	1	Evidence-based	None/not mentioned	Not specified
Venous thromboembolism (VTE), thrombophilia, antithrombotic therapy, and pregnancy: antithrombotic therapy and prevention of thrombosis, 9th edn: American College of Chest Physicians evidence-based clinical practice guidelines	Bates, 2012	American College of Chest Physicians	USA	Clinical practice guidelines	Updated/ revised	Broader: VTE disease; this section is specifically on the management of VTE and thrombophilia as well as the use of antithrombotic agents during pregnancy	5	Evidence-based	GRADE	National Heart, Lung, and Blood Institute (R13 HL104758) and Bayer Schering Pharma AG. Educational grants provided by Bristol-Myers Squibb; Pfizer, Inc; Canyon Pharmaceuticals; Sanofi-Aventis USA.
Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society clinical practice guideline	De Groot, 2012	Endocrine Society. Co-Sponsoring Associations: Asia and Oceania Thyroid Association, European Thyroid Association, and Latin American Thyroid Society	Global	Clinical practice guideline	Update	Broader: management of thyroid dysfunction during pregnancy and postpartum	3	Evidence-based	GRADE and USPSTF	Co-Sponsoring Associations: Asia and Oceania Thyroid Association, European Thyroid Association, and Latin American Thyroid Society

TABLE 2 *(continued)*

Title	Author, year	Developing or publishing organization, or authors	Country or countries of publication	Description provided by authors (e.g. guideline or algorithm)	Type of guideline (formulated, adapted, updated or revised)	Topic addressed (recurrent miscarriage, RPL or broader)	Number of recommendations specific to recurrent miscarriage	Development process (evidence-based, consensus-based, or both)	System of rating evidence or quality instrument used during guideline development (GRADE, Oxford, not mentioned, or other)	Funding
Recurrent pregnancy loss: guideline of the European Society of Human Reproduction and Embryology (ESHRE)	ESHRE, 2017	ESHRE	Europe	Guideline	Formulated, although previous version existed	Recurrent pregnancy loss	92	Evidence-based; expert consensus-based	GRADE	ESHRE
ESHRE PGT Consortium good practice recommendations for the organization of PGT	ESHRE, 2020	ESHRE	Europe	Good Practice Recommendations	Updated	Broader: preimplantation genetic testing	3	Expert consensus-based	None	ESHRE
Clinical practice guidelines for hypothyroidism in adults	Garber, 2012	American Association of Clinical Endocrinologists (AACE) in association with ATA	USA	Clinical practice guidelines	Updated	Broader: clinical management of hypothyroidism in ambulatory patients	1	Evidence-based; expert consensus-based	Approach outlined in the AACE's Protocol for Standardized Production of Clinical Guidelines: 2010 update	Not specified
The Thessaloniki ESHRE/ESGE consensus on diagnosis of female genital anomalies	Grimbizis, 2016	ESHRE/European Society for Gynaecological Endoscopy (ESGE)	Europe	Consensus	Formulated	Broader: diagnosis of female genital anomalies	6	Evidence-based; expert consensus-based	None/not mentioned	ESHRE and ESGE
American College of Medical Genetics and Genomics (ACMG) practice guideline: lack of evidence for *MTHFR* polymorphism testing	Hickey, 2013 (Addendum: Bashford, 2020)	ACMG	USA	Clinical practice resource (practice guideline until 27 April 2020)	Unclear/not specified	Broader: *MTHFR* polymorphism testing	1	Not specified	Not mentioned	Not specified
Clinical practice guideline: venous thromboprophylaxis in pregnancy	Health Service Executive (HSE), 2013	Institute of Obstetricians and Gynaecologists, Royal College of Physicians of Ireland; HSE Clinical Care Programme in Obstetrics and Gynaecology	Ireland	Clinical practice guideline	Formulated	Broader: venous thromboprophylaxis in pregnancy	4	Consensus-based	None/not mentioned	Not specified
National standards for bereavement care following pregnancy loss and perinatal death	HSE, 2016	HSE	Ireland	Standards	Formulated	Broader: bereavement care following pregnancy loss and perinatal death	2	Evidence-based; expert consensus-based	None/not mentioned	Not specified
Pregnancy loss: French clinical practice guidelines	Huchon, 2016	College National des Gynecologues Obstetriciens Francais (CNGOF)	France	Clinical practice guidelines	Formulated	Broader: pregnancy loss	24	Evidence-based; expert consensus-based	Rating scheme developed by the Haute Autorite de Sante (French National Authority for Health)	Not specified

TABLE 2 *(continued)*

Title	Author, year	Developing or publishing organization, or authors	Country or countries of publication	Description provided by authors (e.g. guideline or algorithm)	Type of guideline (formulated, adapted, updated or revised)	Topic addressed (recurrent miscarriage, RPL or broader)	Number of recommendations specific to recurrent miscarriage	Development process (evidence-based, consensus-based, or both)	System of rating evidence or quality instrument used during guideline development (GRADE, Oxford, not mentioned, or other)	Funding
Guidelines on the investigation and management of antiphospholipid syndrome	Keeling, 2012 (Addendum: Arachchillage, 2020)	British Society for Haematology	UK	Guideline	Update	Broader: investigation and management of APS	6	Evidence-based; expert consensus-based	GRADE	Not specified
Hysteroscopic metroplasty of a uterine septum for recurrent miscarriage: Interventional procedures guidance	National Institute for Health and Care Excellence (NICE), 2015	NICE. Endorsed by: Healthcare Improvement Scotland	UK	Interventional procedures guidance	Formulated (note: updated before publication)	Recurrent miscarriage: hysteroscopic metroplasty of a uterine septum	3	Evidence-based; expert consensus-based	Not mentioned	Not specified
Recurrent pregnancy loss care pathway for Northern Ireland	Public Health Agency, 2020	Public Health Agency (Northern Ireland)	Northern Ireland	Care pathway	Formulated	Recurrent pregnancy loss	64	Evidence-based	None/not mentioned	Not specified
Maternity and neonatal clinical guideline: early pregnancy loss	Queensland Clinical Guidelines, 2018	Queensland Clinical Guidelines	Australia	Clinical Guideline	Update	Broader: early pregnancy loss	19	Evidence-based; expert consensus-based. Best described as 'evidence informed consensus guidelines'	National Health and Medical Research Council (NHMRC, 2009). Note: the 'consensus' definition is different from that proposed by the NHMRC. Instead, it relates to forms of evidence that are not identified by the NHMRC/that arise from the clinical experience of the guideline's clinical lead and working party	Healthcare Improvement Unit, Queensland Health
Green-top guideline number 17: the investigation and treatment of couples with recurrent first-trimester and second-trimester miscarriage	Royal College of Obstetrics and Gynaecology (RCOG), 2011	RCOG	UK	Guideline	Not specified (updated/revised)	Recurrent miscarriage	19	Evidence-based	Scottish Intercollegiate Guidelines Network (SIGN)	Not specified
The role of natural killer cells in human fertility: scientific impact paper number 53	RCOG, 2016	RCOG	UK	Scientific impact paper	Formulated	Broader: role of natural killer cells in human fertility	1	Not described	None/not mentioned	Not specified
SIGN 129: antithrombotics: indications and management	SIGN, 2013	SIGN	UK	Clinical guideline	Update	Broader: antithrombotics	5	Evidence-based	SIGN	NHS Quality Improvement Scotland

(continued on next page)

TABLE 2 *(continued)*

Title	Author, year	Developing or publishing organization, or authors	Country or countries of publication	Description provided by authors (e.g. guideline or algorithm)	Type of guideline (formulated, adapted, updated or revised)	Topic addressed (recurrent miscarriage, RPL or broader)	Number of recommendations specific to recurrent miscarriage	Development process (evidence-based, consensus-based, or both)	System of rating evidence or quality instrument used during guideline development (GRADE, Oxford, not mentioned, or other)	Funding
Intravenous immunoglobulin G in women with reproductive failure: The Korean Society for Reproductive Immunology practice guidelines	Sung, 2017	Korean Society for Reproductive Immunology	Korea	Practice guidelines	Formulated	Broader: intravenous immuno-globulin G in women with reproductive failure	6	Evidence-based; expert consensus-based	System used by Fauser et al. (2012); available at https://www.fertstert.org/article/S0015-0282(11)02552-0/fulltext#appsec1	Partially supported by a grant from the Korean Health Technology R&D Project, Ministry of Health and Welfare, Republic of Korea
Recurrent miscarriage: diagnostic and therapeutic procedures. Guideline of the German Society of Gynecology and Obstetrics (DGGG), Austrian Society of Gynecology and Obstetrics (OEGGG) and the Swiss Society of Gynecology and Obstetrics (SGGG) (S2k-Level, AWMF Registry Number 015/050)	Toth, 2018	DGGG, ÖGGG and SGGG	Germany, Austria, Switzerland	Guideline	Update	Recurrent miscarriage	45	Evidence-based (though no systematic search); expert consensus-based	Guideline does not discuss levels of evidence. The recommendations are graded according to their own instrument, described but name not mentioned	Not specified
American College of Radiology (ACR) appropriateness criteria infertility	Wall, 2020	ACR	USA	Guidelines	Revised	Broader: infertility	2	Evidence-based	RAND/UCLA Appropriateness Method and ACR's own criteria for Study Quality and Strength of Evidence, using concepts from GRADE (https://www.acr.org/-/media/ACR/Files/Appropriateness-Criteria/EvidenceTableDevelopment.pdf)	Not specified
Woman's pre-conception evaluation: genetic and fetal risk considerations for counselling and informed choice	Wilson, 2018	Genetics Committee of The SOGC	Canada	Consideration for Care Statement	Not specified (an update is implied however)	Broader: pre-conception evaluation	9	Evidence-based	GRADE	None

MTHFR, methylenetetrahydrofolate reductase; PGT, preimplantation genetic testing; Rand/UCLA, Rand Corporation and University of California at Los Angeles; RPL, recurrent pregnancy loss.

Gynaecology, and Irish Haematology Society, 2013), thrombosis (*SIGN, 2013*), immunology (*Sung et al., 2017*) and natural killer cells (*RCOG, 2016*).

The CPG were predominantly country-specific, with most originating in the USA (*n* = 11 [34%]), with others from Australia (*n* = 1 [3%]), Canada (*n* = 2 [6%]), France (*n* = 1 [3%]), Ireland (*n* = 2 [6%]), Korea (*n* = 1 [3%]), Northern Ireland (*n* = 1 [3%]), Saudi Arabia (*n* = 1 [3%]), and the UK (*n* = 5 [16%]). Seven CPG (22%) focused on more than one country, with one CPG from Germany, Austria and Switzerland (3%), three European (9%) and three global (9%) CPG. The CPG were published between 2011 and 2020: 2011 (*n* = 1 [3%]), 2012 (*n* = 6 [19%]), 2013 (*n* = 3 [9%]), 2015 (*n* = 2 [6%]), 2016 (*n* = 5 [16%]), 2017 (*n* = 5 [16%]), 2018 (*n* = 6 [19%]), 2019 (*n* = 1 [3%]) and 2020 (*n* = 3 [9%]). Seventeen (53%) CPG specifically mentioned a system of rating evidence and/or quality instrument used during CPG development, four (13%) described a system but did not specifically mention a name, whereas 11 (34%) did not report or use any. Of the 17 that specifically mentioned a system of rating the evidence, a variety were mentioned, with GRADE (Grading of Recommendations, Assessment, Development and Evaluations) being the most common, mentioned by five CPG (29%).

The terms used to describe recurrent miscarriage within the included CPG, as well as the definitions provided, are presented in TABLE 3. Most CPG used the term RPL (*n* = 15 [47%]), whereas others used recurrent miscarriage (*n* = 8 [25%]), a combination of terms such as RPL, recurrent miscarriage or other (*n* = 7 [22%]); two CPG (6%) did not specify a term. Definitions of these terms also varied. Of the 17 CPG that provided a description of recurrent miscarriage, RPL or other, nine referred to three or more losses (53%), seven referred to two or more losses (41%) and one referred to two consecutive spontaneous losses or three or more spontaneous losses (6%). Fifteen CPG did not provide a definition (47%); however, two of these referred to three losses within their texts.

Quality assessment findings (AGREE II evaluations)

The quality assessment scores for the 32 included CPG are presented in FIGURE 2 and TABLE 4; the original data file, with individual reviewer scores, is available in an open access repository (*Hennessy et al., 2021*). Only two of the CPG were recommended for use in their current form (6%) (*Bates et al., 2012*; *ESHRE Early Pregnancy Guideline Development Group, 2017*); most CPG were recommended for use with modification (*n* = 29 [91%]), whereas one (3%) was not recommended (*Hickey et al., 2013*). The overall quality of most included CPG was fair (*n* = 14 [44%]) or average (*n* = 11 [34%]); only one (3%) scored excellent (*Bates et al., 2012*). Applicability and editorial independence were the two domains in which CPG scored most poorly; 84% and 69% of CPG rated these domains as poor, respectively.

Synthesis of recommendations

Each included recommendation was assigned to one of the following categories: structure of care; investigations; treatment; and counselling and/or supportive care, with further sub-categories assigned. The number of recommendations by category and sub-category are presented in TABLE 5. Given the diversity of the CPG included, and the varying quality of CPG and evidence underpinning recommendations therein, the recommendations were not synthesized further. Instead, a narrative description is provided, comparing and contrasting the recommendations under each category and sub-category.

Structure of care

Forty-two recommendations from nine CPG were categorized under 'Structure of care' (Supplementary Table 3 and Supplementary Table 4). Two of these recommendations were categorized under two or more sub-categories. Forty recommendations within this category did not have associated strength of recommendation, quality of evidence ratings, or both, primarily because they were statements, good practice points, or both, within the relevant CPG. Ten recommendations from six CPG (*RCOG, 2011*; *NICE, 2015*; *ESHRE Early Pregnancy Guideline Development Group, 2017*; *Queensland Clinical Guidelines, 2018*; *Toth et al., 2018*; *Northern Ireland Public Health Agency, 2020*) related to 'clinician knowledge/skills/expertise' referring to individual clinicians and/or multi-disciplinary teams that should be involved in the care of those who experience recurrent miscarriage, either within specialist clinics, elsewhere, or both. A further 10 recommendations from three CPG (*RCOG, 2011*; *ESHRE Early Pregnancy Guideline Development Group, 2017*; *Northern Ireland Public Health Agency, 2020*) related to 'specialist clinic', specifically around how women who experience recurrent miscarriage should be referred to and/or seen in a specialist clinic, with two of the CPG including recommendations about the location of the clinic, and one CPG making recommendations around what should happen at the first visit, and the equipment and facilities needed.

Seven recommendations from two CPG (*ESHRE Early Pregnancy Guideline Development Group, 2017*; *Northern Ireland Public Health Agency, 2020*) related to 'counselling (psychological and/or emotional), recognizing the effect of recurrent miscarriage on those who experience recurrent miscarriage, as well as the provision of appropriate support services, referral to these services, or both. Five recommendations from two CPG (*HSE, 2016*; *Northern Ireland Public Health Agency, 2020*) related to 'referral'. One CPG contained one recommendation to ensure that those who experience recurrent miscarriage are referred to a pregnancy loss or gynaecological clinic (*HSE, 2016*). Another CPG included recommendations on referral criteria, information to be provided on referral and information about referrals outside of a particular jurisdiction (*Northern Ireland Public Health Agency, 2020*). Four recommendations from three CPG (*Practice Committee of the ASRM, 2012*; *ACOG, 2018*; *Northern Ireland Public Health Agency, 2020*) related to 'investigations'. Two of these recommendations related to proceeding with investigations for recurrent miscarriage after two consecutive clinical pregnancy losses (*Practice Committee of the ASRM, 2012*; *ACOG, 2018*), one recommendation concerned the tailoring of investigation plans, i.e. matching an intervention or components to previously measured characteristics of the participant (*Northern Ireland Public Health Agency, 2020*), whereas one related to experimental tests and how they should not take place outside of research settings (*Northern Ireland Public Health Agency, 2020*).

Four recommendations from two CPG (*ESHRE Early Pregnancy Guideline Development Group, 2017*; *Northern Ireland Public Health Agency, 2020*)

TABLE 3 DEFINITION OF RECURRENT MISCARRIAGE USED WITHIN CLINICAL PRACTICE GUIDELINES

Title	Author, year	Terminology used	Definition provided
AAGL practice report: practice guidelines for the diagnosis and management of submucous leiomyomas	AAGL, 2012	Recurrent pregnancy loss	None.
ACOG practice bulletin number 200: early pregnancy loss	ACOG, 2018	None	None; however, they refer to 'women who have experienced three prior pregnancy losses'. Early pregnancy loss is defined as loss of an intrauterine pregnancy in the first trimester.
The Society for Translational Medicine: clinical practice guidelines for sperm DNA fragmentation testing in male infertility	Agarwal, 2017	Recurrent pregnancy loss	Three consecutive pregnancy losses before 20-week gestation.
Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum	Alexander, 2017	Recurrent pregnancy loss	Two consecutive spontaneous losses or three or more spontaneous losses.
Saudi guidelines for threatened and recurrent miscarriage management; the role of progestogens in threatened and idiopathic recurrent miscarriage	Arab, 2019	Recurrent miscarriage	The loss of two or more pregnancies (biochemical/ultrasound confirmation). Note: draw on ESHRE guidelines
Practice guideline: joint CCMG-SOGC recommendations for the use of chromosomal microarray analysis for prenatal diagnosis and assessment of fetal loss in Canada	Armour, 2018	None	None. They refer to 'third pregnancy loss'
Evaluation and treatment of recurrent pregnancy loss: a committee opinion	ASRM, 2012	Recurrent pregnancy loss	Two or more failed clinical pregnancies; pregnancy is defined as a clinical pregnancy documented by ultrasonography or histopathological examination. Ideally, a threshold of three or more losses should be used for epidemiological studies while clinical evaluation may proceed following two first-trimester pregnancy losses.
Subclinical hypothyroidism in the infertile female population: a guideline	ASRM, 2015	Recurrent miscarriage; recurrent pregnancy loss	None.
Uterine septum: a guideline	ASRM, 2016	Recurrent pregnancy loss	None.
Removal of myomas in asymptomatic patients to improve fertility, reduce miscarriage rate, or both: a guideline	ASRM, 2017	Recurrent pregnancy Loss	None (note: one of the included studies defines as two or more miscarriages).
The use of PGT-A: a committee opinion	ASRM, 2018	Recurrent pregnancy loss	None.
VTE, thrombophilia, antithrombotic therapy, and pregnancy; antithrombotic therapy and prevention of thrombosis, 9th edn. American College of Chest Physicians evidence-based clinical practice guidelines	Bates 2012	Recurrent pregnancy loss; recurrent first trimester loss; recurrent early pregnancy loss	Recurrent early pregnancy loss: three or more miscarriages before 10 weeks of gestation. Note: In TABLE 1, defined as 'Preferred as defined by three early losses before 12 weeks; if not able to extract by this definition'.
Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society clinical practice guideline	DeGroot, 2012	Recurrent miscarriage; recurrent abortion; recurrent pregnancy loss	None.
Recurrent pregnancy loss: guideline of the European Society of Human Reproduction an Embryology	ESHRE, 2017	Recurrent pregnancy loss	The loss of two or more pregnancies. It excludes ectopic pregnancy and molar pregnancy. A pregnancy loss (miscarriage) is defined as the spontaneous demise of a pregnancy before the fetus reaches viability. The term, therefore, includes all pregnancy losses from the time of conception until 24 weeks of gestation. Primary RPL is described as RPL without a previous ongoing pregnancy (viable pregnancy) beyond 24 weeks' gestation, while secondary RPL is defined as an episode of RPL after one or more previous pregnancies progressing beyond 24 weeks' gestation. A pregnancy in the definition is confirmed at least by either serum or urine beta-HCG, i.e. including non-visualized pregnancy losses (biochemical pregnancy losses, resolved and treated pregnancies of unknown location, or both). Recurrent 'early' pregnancy loss is the loss of two or more pregnancies before 10 weeks of gestational age. Recommend the use of 'recurrent pregnancy loss' to describe repeated pregnancy demise and to reserve 'recurrent miscarriage' to describe cases where all pregnancy losses have been confirmed as intrauterine miscarriages.
ESHRE PGT Consortium good practice recommendations for the organisation of PGT	ESHRE, 2020	Recurrent miscarriage	Two or more pregnancy losses before 24 weeks of gestation (including chemical pregnancy).
Clinical practice guidelines for hypothyroidism in adults	Garber, 2012	Recurrent miscarriage	None.

(continued on next page)

TABLE 3 *(continued)*

Title	Author, year	Terminology used	Definition provided
The Thessaloniki ESHRE/ESGE consensus on diagnosis of female genital anomalies	Grimbizis, 2016	Recurrent pregnancy loss	None.
ACMG practice guideline: lack of evidence for MTHFR polymorphism testing	Hickey, 2013	Recurrent pregnancy loss	None.
Clinical practice guideline: venous thromboprophylaxis in pregnancy	HSE, 2013	Recurrent miscarriage	None.
National standards for bereavement care following pregnancy loss and perinatal death	HSE, 2016	Recurrent miscarriage	The loss of three or more consecutive pregnancies before 24 weeks' gestation.
Pregnancy loss: French clinical practice guidelines	Huchon, 2016	Recurrent pregnancy loss (also known as repeated miscarriages)	The experience of three or more consecutive miscarriages before 14 weeks' gestation.
Guidelines on the investigation and management of antiphospholipid syndrome	Keeling, 2012	Recurrent pregnancy loss; recurrent fetal loss	Three or more pregnancy losses, before 10 weeks' gestation.
Hysteroscopic metroplasty of a uterine septum for recurrent miscarriage: interventional procedures guidance	NICE, 2015	Recurrent miscarriage	Usually defined as three or more miscarriages in a row
Recurrent pregnancy loss care pathway for Northern Ireland	Public Health Agency, 2020	Recurrent pregnancy loss	A diagnosis of RPL could be considered after the loss of two or more pregnancies (ESHRE). Pregnancy loss is defined as the spontaneous loss of a pregnancy before the fetus reaches viability. It therefore includes all pregnancy losses from the time of conception until 24 weeks of gestation.
Maternity and neonatal clinical guideline: early pregnancy loss	Queensland Clinical Guidelines, 2018	Recurrent miscarriage	Three or more consecutive miscarriages. There is no specific term for non-consecutive pregnancy losses. Note: scope of document is women experiencing pregnancy loss before 20 weeks' gestation.
Green-top guideline number 17: the investigation and treatment of couples with recurrent first-trimester and second-trimester miscarriage	RCOG, 2011	Recurrent first-trimester and second-trimester miscarriage	Three or more first-trimester miscarriages, or one or more second-trimester miscarriages. Includes all pregnancy losses from the time of conception until 24 weeks of gestation.
The role of natural killer cells in human fertility: scientific impact paper number 53	RCOG, 2016	Recurrent miscarriage; recurrent spontaneous pregnancy loss	None.
SIGN 129: antithrombotics: indications and management	SIGN, 2013	Recurrent pregnancy failure; recurrent miscarriage; recurrent pregnancy loss	None.
Intravenous immunoglobulin G in women with reproductive failure: The Korean Society for Reproductive Immunology practice guidelines	Sung, 2017	Recurrent pregnancy loss	State recurrent pregnancy loss traditionally defined as three or more consecutive miscarriages, but ASRM define as two or more failed pregnancies, based on the risk of recurrence and the prevalence of etiologies.
Recurrent miscarriage: diagnostic and therapeutic procedures. Guideline of the DGGG, OEGGG and SGGG (S2k-Level, AWMF Registry Number 015/050)	Toth, 2018	Recurrent miscarriage	Three or more consecutive recurrent miscarriages (WHO definition).
ACR appropriateness criteria infertility	Wall, 2020	Recurrent pregnancy loss	Two or more consecutive early pregnancy losses (ASRM definition).
Woman's pre-conception evaluation: genetic and fetal risk considerations for counselling and informed choice	Wilson, 2018	Recurrent pregnancy loss	None.

AAGL, American Association of Gynecologic Laparoscopists; ACMG, American College of Medical Genetics and Genomics; ACOG, American College of Obstetrics and Gynaecology; ACR, American College of Radiology; ASRM, American Society for Reproductive Medicine; CCMG, Canadian College of Medical Geneticists; DGGG, German Society of Gynecology and Obstetrics; ESGE, European Society for Gynaecological Endoscopy; ESHRE, European Society of Human Reproduction and Embryology; HSE, Health Service Executive; MTHFR, methylenetetrahydrofolate reductase; NICE, National Institute for Health and Care Excellence; OEGGG, Austrian Society of Gynecology and Obstetrics; PGT-A, preimplantation genetic testing for aneuploidy; RCOG, Royal College of Obstetrics and Gynaecology; RPL, recurrent pregnancy loss; SGGG, Swiss Society of Gynecology and Obstetrics; SIGN, Scottish Intercollegiate Guidelines Network; SOGC, Society of Obstetricians and Gynaecologists of Canada; VTE, Venous thromboembolism; WHO, World Health Organization.

related to 'treatment' and concerned tailored treatment plans, including plans for future pregnancies; one CPG referred to experimental treatments and how they should not take place outside of research settings (*Northern Ireland Public Health Agency, 2020*). Three recommendations from two CPG (*ESHRE Early Pregnancy Guideline Development Group, 2017*; *Northern Ireland Public Health Agency, 2020*) related to 'informational support' and concerned information (written, spoken, or both) that should be provided to those who experience recurrent miscarriage at



FIGURE 2 AGREE II Domain scores for the 32 guidelines, percentage (%). Excellent (>80%), good (>60–80%), average (>40–60%), fair (>20–40%) and poor (≤20%)

the outset, including information about what will happen, sources of support, or both. Two recommendations from one CPG (*Northern Ireland Public Health Agency, 2020*) related to 'research'; these related to experimental investigations and treatments mentioned earlier under those sub-categories, as well as travel funding requests for assessment of trial eligibility.

Investigations

One hundred and thirty-four recommendations from 23 CPG were categorized under 'Investigations' (Supplementary Table 5 and Supplementary Table 6). Nine of these recommendations were categorized under two or more sub-categories. Fifty-six recommendations did not have the strength of recommendation, quality of evidence ratings, or both, to accompany them, as they were statements, good practice points, or both, within the relevant CPG, or were not specified.

Thirty recommendations from nine CPG related to 'metabolic and endocrinologic factors'. No clear agreement was reached, with some conflicting recommendations. Thyroid-stimulating hormone (TSH) was recommended by three CPG (*Practice Committee of the ASRM, 2012*; *ESHRE Early Pregnancy Guideline Development Group, 2017*; *Toth et al., 2018*). Thyroid peroxidase antibody testing was recommended only in the event of abnormal TSH by two of the three CPG (*Practice Committee of the ASRM, 2012*; *Toth et al., 2018*), whereas they were recommended as standard tests by three CPG (*Huchon et al., 2016*; *ESHRE Early Pregnancy Guideline Development Group, 2017*; *Northern Ireland Public Health Agency, 2020*). Prolactin level testing was recommended as standard by two CPG (*Practice Committee of the ASRM, 2012*; *Huchon et al., 2016*). Two CPG (*Huchon et al., 2016*; and *ESHRE Early Pregnancy Guideline Development Group, 2017*) directly contradicted each other's recommendations in the investigations required. Three CPG recommended a screen for diabetes (*Practice Committee of the ASRM, 2012*; *Huchon et al., 2016*; *Queensland Clinical Guidelines, 2018*). *Wilson (2018)* recommended an overall endocrine assessment, but no evidence for any particular investigation or test.

Twenty-nine recommendations from 12 CPG related to 'thrombophilia screening'. Greater consensus was reached in this section with 10 CPG recommending antiphospholipid antibodies (APLA) after two or three miscarriages as standard (*RCOG, 2011*; *Bates et al., 2012*; *Keeling et al., 2012*; *Practice Committee of the ASRM, 2012*; *Institute of Obstetricians and Gynaecologists RCPI et al., 2013*; *Huchon et al., 2016*; *ESHRE Early Pregnancy Guideline Development Group, 2017*; *Queensland Clinical Guidelines, 2018*; *Toth et al., 2018*; *Northern Ireland Public Health Agency, 2020*), two of which had caveats (*Practice Committee of the ASRM, 2012*; *Toth et al., 2018*). Four specified repeating APLA after 12 weeks (*RCOG, 2011*; *Keeling et al., 2012*; *Institute of Obstetricians and Gynaecologists RCPI et al., 2013*; *Northern Ireland Public Health Agency, 2020*). The remaining CPG requested APLA testing on meeting certain conditions, i.e. not as standard after two or three miscarriages. Only the *Queensland Clinical Guidelines (2018)* recommended an inherited thrombophilia screen as standard. Only *Hickey et al. (2013)* suggested methylenetetrahydrofolate reductase (*MTHFR*) genetic screening and did not recommend it as standard.

Twenty-six recommendations from 12 CPG concerned 'anatomical investigations'. It was generally agreed that uterine anatomy should be assessed as part of the routine investigation of recurrent miscarriage. Opinions differed, however, on what the most appropriate investigation was, with little supporting evidence. Many CPG agreed that ultrasound is a suitable primary investigation for assessing pelvic anatomy (*RCOG, 2011*; *Grimbizis et al., 2016*; *Huchon et al., 2016*; *ESHRE Early Pregnancy Guideline Development Group, 2017*; *Queensland Clinical Guidelines, 2018*; *Wall et al., 2020*). No consensus, however, was reached on what second-line investigations were more appropriate, with saline infusion sonohysterogram, hysterosalpingography (HSG), hysterosalpingo-contrast-sonography, three-dimensional ultrasound and magnetic resonance imaging all suggested. Some CPG recommended the use of HSG (*Practice Committee of the ASRM, 2012*), others did not (*Huchon et al., 2016*; *ESHRE Early Pregnancy Guideline Development Group, 2017*); similarly, one recommended magnetic resonance imaging (*Wall et al., 2020*),

TABLE 4 AGREE II QUALITY ASSESSMENT RATINGS, BY DOMAIN (% CLINICAL PRACTICE GUIDELINES)

Title	Author, year	Domain 1: scope and purpose (%)	Domain 2: stakeholder involvement (%)	Domain 3: rigour of development (%)	Domain 4: clarity of presentation (%)	Domain 5: applicability (%)	Domain 6: editorial independence (%)	Overall quality of the guideline (%)	Recommend for use
AAGL practice report: practice guidelines for the diagnosis and management of submucous leiomyomas	AAGL, 2012	Average (43)	Poor (9)	Fair (35)	Good (67)	Poor (6)	Poor (17)	Average (56)	YWM
ACOG practice bulletin number 200: early pregnancy loss	ACOG, 2018	Average (57)	Fair (24)	Poor (20)	Good (63)	Poor (4)	Poor (8)	Average (50)	YWM
The Society for Translational Medicine: clinical practice guidelines for sperm DNA fragmentation testing in male infertility	Agarwal, 2017	Average (46)	Poor (17)	Poor (13)	Average (48)	Poor (0)	Poor (6)	Fair (33)	YWM
Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum	Alexander, 2017	Good (67)	Average (44)	Average (42)	Good (69)	Poor (7)	Good (67)	Good (67)	YWM
Saudi guidelines for threatened and recurrent miscarriage management; the role of progestogens in threatened and idiopathic recurrent miscarriage	Arab, 2019	Average (50)	Fair (37)	Fair (21)	Average (54)	Poor (0)	Poor (19)	Fair (39)	YWM
Practice guideline: joint CCMG-SOGC recommendations for the use of chromosomal microarray analysis for prenatal diagnosis and assessment of fetal loss in Canada	Armour, 2018	Average (54)	Average (48)	Fair (28)	Good (72)	Poor (15)	Poor (17)	Average (56)	YWM
Evaluation and treatment of recurrent pregnancy loss: a committee opinion	ASRM, 2012	Average (41)	Poor (9)	Poor (16)	Average (41)	Poor (3)	Fair (22)	Fair (39)	YWM
Subclinical hypothyroidism in the infertile female population: a guideline	ASRM, 2015	Average (50)	Poor (11)	Fair (27)	Average (56)	Poor (4)	Fair (22)	Average (44)	YWM
	Author, Year	Domain 1: scope and purpose	Domain 2: stakeholder involvement	Domain 3: rigour of development	Domain 4: clarity of presentation	Domain 5: applicability	Domain 6: editorial independence	Overall quality of the guideline	Recommend for use
Uterine septum: a guideline	ASRM, 2016	Average (44)	Poor (17)	Average (41)	Average (57)	Poor (0)	Poor (17)	Average (44)	YWM
Removal of myomas in asymptomatic patients to improve fertility and/or reduce miscarriage rate: a guideline	ASRM, 2017	Fair (31)	Poor (15)	Fair (34)	Average (54)	Poor (1)	Poor (19)	Fair (33)	YWM
The use of PGT-A: a committee opinion	ASRM, 2018	Fair (26)	Poor (15)	Fair (31)	Fair (37)	Poor (8)	Fair (22)	Fair (33)	YWM
VTE, thrombophilia, antithrombotic therapy, and pregnancy; Antithrombotic therapy and prevention of thrombosis, 9th edn: American College of Chest Physicians evidence-based clinical practice guidelines	Bates, 2012	Good (76)	Average (57)	Good (65)	Good (76)	Fair (22)	Good (72)	Excellent (83)	Yes
Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society clinical practice guideline	DeGroot, 2012	Average (57)	Fair (28)	Fair (38)	Good (74)	Poor (3)	Fair (22)	Average (56)	YWM
Recurrent pregnancy loss: guideline of the European Society of Human Reproduction and Embryology	ESHRE, 2017	Good (74)	Good (61)	Good (66)	Excellent (81)	Poor (19)	Average (50)	Good (72)	Yes
ESHRE PGT Consortium good practice recommendations for the organization of PGT	ESHRE, 2020	Average (46)	Average (41)	Poor (20)	Average (52)	Poor (7)	Poor (14)	Fair (33)	YWM
Clinical practice guidelines for hypothyroidism in adults	Garber, 2012	Good (61)	Fair (30)	Fair (37)	Good (70)	Poor (6)	Poor (14)	Average (50)	YWM
The Thessaloniki ESHRE/ESGE consensus on diagnosis of female genital anomalies	Grimbizis, 2016	Fair (39)	Fair (30)	Poor (20)	Average (48)	Poor (11)	Poor (14)	Fair (33)	YWM
ACMG practice guideline: lack of evidence for *MTHFR* polymorphism testing	Hickey, 2013	Poor (15)	Poor (13)	Poor (9)	Average (44)	Poor (0)	Poor (6)	Poor (11)	No

(continued on next page)

TABLE 4 *(continued)*

Title	Author, year	Domain 1: scope and purpose (%)	Domain 2: stakeholder involvement (%)	Domain 3: rigour of development (%)	Domain 4: clarity of presentation (%)	Domain 5: applicability (%)	Domain 6: editorial independence (%)	Overall quality of the guideline (%)	Recommend for use
Clinical practice guideline: Venous thromboprophylaxis in pregnancy	HSE, 2013	Average (54)	Average (41)	Fair (26)	Good (72)	Poor (15)	Poor (0)	Average (44)	YWM
National standards for bereavement care following pregnancy loss and perinatal death	HSE, 2016	Average (50)	Good (65)	Poor (10)	Average (54)	Fair (22)	Poor (0)	Fair (33)	YWM
Pregnancy loss: French clinical practice guidelines	Huchon, 2016	Poor (17)	Fair (26)	Poor (16)	Average (48)	Poor (10)	Poor (0)	Fair (33)	YWM
Guidelines on the investigation and management of antiphospholipid syndrome	Keeling, 2012	Average (43)	Fair (28)	Fair (35)	Average (54)	Poor (0)	Poor (8)	Fair (50)	YWM
Hysteroscopic metroplasty of a uterine septum for recurrent miscarriage: interventional procedures guidance	NICE, 2015	Average (44)	Poor (13)	Average (58)	Good (70)	Poor (18)	Poor (14)	Average (50)	YWM
Recurrent pregnancy loss care pathway for Northern Ireland	Public Health Agency, 2020	Average (54)	Average (48)	Poor (7)	Average (56)	Fair (21)	Poor (0)	Fair (22)	YWM
Maternity and neonatal clinical guideline: early pregnancy loss	Queensland Clinical Guidelines, 2018	Good (63)	Average (48)	Fair (33)	Excellent (81)	Fair (40)	Fair (36)	Good (61)	YWM
Green-top guideline number 17: the investigation and treatment of couples with recurrent first-trimester and second-trimester miscarriage	RCOG, 2011	Average (57)	Fair (22)	Average (42)	Good (76)	Poor (8)	Poor (6)	Average (50)	YWM
The role of natural killer cells in human fertility: scientific impact paper number 53	RCOG, 2016	Fair (28)	Poor (20)	Poor (17)	Average (54)	Poor (0)	Poor (9)	Fair (22)	YWM
SIGN 129: antithrombotics: indications and management	SIGN, 2013	Average (54)	Good (70)	Average (56)	Good (72)	Fair (26)	Fair (25)	Good (61)	YWM
Intravenous immunoglobulin G in women with reproductive failure: The Korean Society for Reproductive Immunology practice guidelines	Sung, 2017	Fair (30)	Poor (13)	Fair (22)	Average (43)	Poor (0)	Poor (14)	Fair (33)	YWM
	Author, Year	Domain 1: Scope & purpose	Domain 2: Stakeholder involvement	Domain 3: Rigour of development	Domain 4: Clarity of presentation	Domain 5: Applicability	Domain 6: Editorial independence	Overall quality of the guideline	Recommend for use
Recurrent miscarriage: diagnostic and therapeutic procedures. Guideline of the DGGG, OEGGG 7 SGGG (S2k-level, AWMF registry number 015/050)	Toth, 2018	Fair (39)	Fair (35)	Fair (31)	Average (59)	Poor (7)	Poor (14)	Fair (33)	YWM
ACR appropriateness criteria infertility	Wall, 2020	Average (52)	Fair (31)	Average (56)	Good (67)	Poor (3)	Poor (6)	Average (50)	YWM
Woman's pre-conception evaluation: Genetic and fetal risk considerations for counselling and informed choice	Wilson, 2018	Average (44)	Poor (19)	Fair (24)	Average (54)	Poor (10)	Fair (22)	Poor (17)	YWM

Excellent (>80%), good (>60–80%), average (>40–60%), fair (>20–40%), poor (≤20%).

AAGL, American Association of Gynecologic Laparoscopists; ACMG, American College of Medical Genetics and Genomics; ACOG, American College of Obstetrics and Gynaecology; ACR, American College of Radiology; ASRM, American Society for Reproductive Medicine; CCMG, Canadian College of Medical Geneticists; DGGG, German Society of Gynecology and Obstetrics; ESGE, European Society for Gynaecological Endoscopy; ESHRE, European Society of Human Reproduction and Embryology; HSE, Health Service Executive; MTHFR, methylenetetrahydrofolate reductase; NICE, National Institute for Health and Care Excellence; OEGGG, Austrian Society of Gynecology and Obstetrics; PGT-A, preimplantation genetic testing for aneuploidy; RCOG, Royal College of Obstetrics and Gynaecology; SGGG, Swiss Society of Gynecology and Obstetrics; SIGN, Scottish Intercollegiate Guidelines Network; SOGC, Society of Obstetricians and Gynaecologists of Canada; VTE, Venous thromboembolism; YWM, yes with modifications.

TABLE 5 NUMBER OF RECOMMENDATIONS BY CATEGORY AND SUB-CATEGORY

Category	Sub-category	Number of recommendations[a]	Number of clinical practice guidelines[b]
Structure of care (n = 42)	Clinician knowledge/skills/expertise	10	6
	Counselling	7	2
	Informational support	3	2
	Investigations	4	3
	Referral	5	2
	Research	2	1
	Specialist clinic	10	3
	Treatment	4	2
	Sub-total	**45**	**9**
Investigations (n = 134)	Anatomical investigations	26	12
	Haematology	2	1
	Immunological screening	13	7
	Male factors	5	4
	Medical and family history	5	3
	Metabolic and endocrinologic factors	30	9
	Microbiological factors	4	3
	Risk factors[c]	4	4
	Screening for genetic factors	22	9
	Tailoring	4	3
	Thrombophilia screening	29	12
	Unexplained recurrent miscarriage	2	2
	Sub-total	**146**	**23**
Treatment (n = 153)	Antiphospholipid syndrome	18	10
	Assisted reproductive technology	1	1
	Genetic factors	11	6
	Immunotherapy	15	6
	Male factors	4	2
	Metabolic or endocrinologic factors	44	12
	Microbiological factors	2	2
	Prognosis	1	1
	Risk factors	1	1
	Tailoring	1	1
	Thrombophilia	12	7
	Unexplained recurrent miscarriage	21	6
	Uterine factors	22	10
	Vitamins	4	3
	Sub-total	**157**	**24**
Counselling and/or supportive care (n = 46)	Clinician knowledge/skills/expertise	1	1
	Genetic counselling	4	4
	Informational support	3	2
	Investigations	4	3
	Prognosis	6	5
	Psychological and/or emotional counselling	11	5
	Research	2	2
	Risk factors[c]	13	5
	Tailoring	2	1
	Treatment	1	1
	Sub-total	**47**	**9**
Total (n = 373)		**375**	**32**

[a] Sub-total of the number of recommendations may be higher than the number of recommendations highlighted under the category as some recommendations were categorized under more than one sub-category.

[b] Sub-total of the number of clinical practice guidelines (CPG) is not the sum of the number of CPG; it is the total number of CPG with recommendations within the particular category.

[c] Risk factors mentioned could include the following: age; successive pregnancy losses; anatomical, endocrine/metabolic and genetic factors; smoking; drug, alcohol use, or both; obesity or underweight; diet (including caffeine consumption); and physical inactivity.

whereas one did not recommend it as a first-line option (*ESHRE Early Pregnancy Guideline Development Group, 2017*). *Toth et al. (2018)* and the *Practice Committee of the ASRM (2016)* suggested hysteroscopy as more appropriate for uterine septae or adhesions. The *ESHRE Early Pregnancy Guideline Development Group (2017)* and *Huchon et al. (2016)* both stated that HSG is not an appropriate first-line investigation for uterine anomalies.

Twenty-two recommendations from nine CPG related to 'screening for genetic factors'. Five CPG recommended karyotyping of pregnancy tissue as standard (*Practice Committee of the ASRM, 2012*; *Huchon et al., 2016*; *Queensland Clinical Guidelines, 2018*; *Toth et al., 2018*; *Wilson, 2018*); two did not routinely recommend, but on an individual basis as an explanatory investigation (*ESHRE Early Pregnancy Guideline Development Group, 2017*; *Northern Ireland Public Health Agency, 2020*); a further one stated that, in cases of congenital anomalies, intrauterine growth restriction, or both, in any fetal loss before 20 weeks' gestation, if quantitative fluorescent polymerase chain reaction methodologies, other-directed diagnostic inquiries, or both, did not provide a diagnosis and further cytogenetic analysis is intended, karyotype should be replaced with chromosomal microarray analysis (*Armour et al., 2018*). Parental karyotyping was suggested as a standard investigation by three CPG if pregnancy tissue was not available (*Huchon et al., 2016*; *Queensland Clinical Guidelines, 2018*; *Toth et al., 2018*); two CPG suggested it if the pregnancy tissue testing reported an abnormality (*Practice Committee of the ASRM, 2012*; *Toth et al., 2018*). Two CPG mentioned other genetic tests on women and men (*Huchon et al., 2016*; *Toth et al., 2018*).

Thirteen recommendations from seven CPG related to 'immunological screening'. Five of these CPG made recommendations around natural killer cell testing: four did not recommend such testing (*Practice Committee of the ASRM, 2012*; *RCOG, 2016*; *ESHRE Early Pregnancy Guideline Development Group, 2017*; *Toth et al., 2018*), whereas one did (*Sung et al., 2017*). The consensus amongst CPG in relation to immunological screening was that human leukocyte antigen analysis, peripheral and uterine natural killer cell analysis, T helper type 1 and type 2 measurements were all experimental, with the exception of the guidelines from *Sung et al. (2017)*, which recommended them all as standard. The *ESHRE Early Pregnancy Guideline Development Group (2017)* cited an exception for one disorder in which women had miscarriages after one previous male child.

Five recommendations from four CPG related to 'male factors', with one of these relating to risk factors (mentioned later also). Four of the recommendations concerning male factors related to sperm testing: three recommended sperm testing, with two specifically recommending sperm DNA fragmentation (*Agarwal et al., 2017*; *ESHRE Early Pregnancy Guideline Development Group, 2017*), whereas one recommended against routine testing for spermploidy or sperm DNA fragmentation (*Practice Committee of the ASRM, 2012*); the strength of recommendation, quality of evidence, or both, was not assessed, i.e. they were statements, or was low for these. Five recommendations from three CPG related to 'medical and family history', i.e. the need to take such a history, and four of these related to tailoring investigations accordingly (mentioned later also) (*ESHRE Early Pregnancy Guideline Development Group, 2017*; *Queensland Clinical Guidelines, 2018*; *Northern Ireland Public Health Agency, 2020*). Four recommendations from three CPG related to 'microbiological factors'. Two of these CPG recommended against routinely screening for infections (*Practice Committee of the ASRM, 2012*; *Toth et al., 2018*), with one of these recommending that endometrial biopsy may be carried out to rule out chronic endometritis (*Toth et al., 2018*); another CPG recommended testing for Rubella immune status (*Northern Ireland Public Health Agency, 2020*); only two had the strength of recommendation, quality of evidence ratings (expert consensus), or both. Four recommendations from three CPG related to 'tailoring' investigations to each woman or couple (*ESHRE Early Pregnancy Guideline Development Group, 2017*; *Queensland Clinical Guidelines, 2018*; *Northern Ireland Public Health Agency, 2020*). Four recommendations from four CPG related to 'risk factors', e.g. alcohol, smoking, caffeine, weight status, physical activity, and the need to evaluate these (*Practice Committee of the ASRM, 2012*; *ESHRE Early Pregnancy Guideline Development Group, 2017*; *Wilson, 2018*; *Northern Ireland Public Health Agency, 2020*), with two of the CPG explicitly stating the inclusion of males or partners (*ESHRE Early Pregnancy Guideline Development Group, 2017*; *Northern Ireland Public Health Agency, 2020*). Two recommendations from one CPG related to 'haematology' and stated that full blood count and electrolytes and liver function tests should be standard investigations (*Queensland Clinical Guidelines, 2018*). Two recommendations from two CPG related to 'unexplained recurrent miscarriage' and how this diagnosis can be made when investigations have been conducted, and no cause of recurrent miscarriage found (*Toth et al., 2018*; *Arab et al., 2019*).

Treatment

One hundred and fifty-three recommendations from 24 CPG were categorized under 'Treatment' (Supplementary Table 7 and Supplementary Table 8). Three of these recommendations were categorized under two or more sub-categories. Sixty-two recommendations did not have the strength of recommendation, quality of evidence ratings, or both, to accompany them, as they were statements, good practice points, or both, within the relevant CPG, or were not specified.

Forty-four recommendations from 12 CPG related to 'metabolic or endocrinologic factors'. Three CPG recommended that overt hypothyroidism is treated in recurrent miscarriage (*Practice Committee of the ASRM, 2015*; *ESHRE Early Pregnancy Guideline Development Group, 2017*; *Toth et al., 2018*). Two CPG stated that subclinical hypothyroidism (TSH >4.0 mIU/l as per ASRM) should be treated in the presence of recurrent miscarriage (*Huchon et al., 2016*; *Toth et al., 2018*). Three CPG recommended that treatment of subclinical hypothyroidism in recurrent miscarriage should be considered as benefits may outweigh risks (*Alexander et al., 2017*; *ESHRE Early Pregnancy Guideline Development Group, 2017*; *Northern Ireland Public Health Agency, 2020*). The recommendations were less clear on treatment if women were euthyroid and had antibodies: *Huchon et al. (2016)* and *Toth et al. (2018)* recommended treatment; *De Groot et al. (2012)* recommended treatment if other autoimmune disease was present;

Alexander et al. (2017) stated that the benefits might outweigh the risks; and the *Northern Ireland Public Health Agency (2020)* did not recommend treatment. Two CPG stated that progesterone treatment had insufficient evidence demonstrating benefit (*RCOG, 2011*; *ESHRE Early Pregnancy Guideline Development Group, 2017*), whereas three suggested it may be of help (*Practice Committee of the ASRM, 2012*; *ACOG, 2018*; *Northern Ireland Public Health Agency, 2020*). Three CPG recommended bromocriptine for hyperprolactinaemia (*Huchon et al., 2016*; *ESHRE Early Pregnancy Guideline Development Group, 2017*; *Northern Ireland Public Health Agency, 2020*). According to two CPG, HCG, metformin and growth factors were not recommended (*ESHRE Early Pregnancy Guideline Development Group, 2017*; *Northern Ireland Public Health Agency, 2020*).

Twenty-two recommendations from 10 CPG related to 'uterine factors'. Three CPG stated that the evidence for any of the mentioned procedures in recurrent miscarriage was insufficient (*RCOG, 2011*; *ESHRE Early Pregnancy Guideline Development Group, 2017*; *Northern Ireland Public Health Agency, 2020*). Two CPG recommended surgical correction of any anomaly after three miscarriages (*Huchon et al., 2016*; *Toth et al., 2018*). *The American Association of Gynecologic Laparoscopists (AAGL) (2012)* recommended submucosal myomectomy. The *Practice Committee of the ASRM (2016)* suggested septal incision. The *Practice Committee of the ASRM (2017)* stated that myomectomy makes no difference to live birth rates after assisted reproductive technology but that it also does not reduce the miscarriage rate. *NICE (2015)* stated that some evidence suggested that uterine surgery may be of some efficacy but with rare serious side-effects. Overall, the evidence seems insufficient to merit advising procedures on anything but an individual basis.

Twenty-one recommendations from six CPG related to 'unexplained recurrent miscarriage'. Two CPG recommended reassurance of excellent prognosis for future pregnancy and supportive care (*RCOG, 2011*; *ESHRE Early Pregnancy Guideline Development Group, 2017*). One CPG recommended that early IVF or intracytoplasmic sperm injection as a potential alternative treatment (*Agarwal et al., 2017*). Three CPG recommended against intravenous immunoglobulin (IVIG) for unexplained recurrent miscarriage (*Huchon et al., 2016*; *ESHRE Early Pregnancy Guideline Development Group, 2017*; *Sung et al., 2017*); two recommended against aspirin (*Huchon et al., 2016*; *ESHRE Early Pregnancy Guideline Development Group, 2017*), low molecular weight heparin (*Huchon et al., 2016*; *ESHRE Early Pregnancy Guideline Development Group, 2017*), progesterone and natural micronized progesterone in the first trimester (*ESHRE Early Pregnancy Guideline Development Group, 2017*; *Toth et al., 2018*), and the administration of granulocyte-colony stimulating factor (*ESHRE Early Pregnancy Guideline Development Group, 2017*; *Toth et al., 2018*). One CPG recommended against acetylsalicylic acid with or without additional heparin (*Toth et al., 2018*); lymphocyte immunization therapy (*ESHRE Early Pregnancy Guideline Development Group, 2017*); this CPG also recommended against glucocorticoids in recurrent miscarriage with selected immunological biomarkers, folic acid for treatment of unexplained recurrent miscarriage, progesterone, intralipid therapy and endometrial scratching (*ESHRE Early Pregnancy Guideline Development Group, 2017*).

Eighteen recommendations from 10 CPG related to 'antiphospholipid syndrome'. The CPG consistently recommended that antiphospholipid syndrome requires treatment with aspirin and heparin (*RCOG, 2011*; *Bates et al., 2012*; *Keeling et al., 2012*; *Practice Committee of the American Society for Reproductive Medicine, 2012*; *Institute of Obstetricians and Gynaecologists RCPI et al., 2013*; *SIGN, 2013*; *Queensland Clinical Guidelines, 2018*; *Toth et al., 2018*; *Northern Ireland Public Health Agency, 2020*). Recommendations for dose of aspirin, and unfractionated heparin (*Bates et al., 2012*; *Practice Committee of the ASRM, 2012*) compared with low-molecular-weight heparin, and whether a prophylactic or intermediate dose was required, were inconsistent. Some also recommended treatment with the caveat that they fulfilled clinical and laboratory criteria for antiphospholipid syndrome (*Bates et al., 2012*; *Practice Committee of the ASRM, 2012*; *SIGN, 2013*; *Northern Ireland Public Health Agency, 2020*), whereas *Toth et al. (2018)* recommended treatment in all cases. *Huchon et al. (2016)* specified that antiphospholipid syndrome and recurrent miscarriage only warranted aspirin and heparin if there was a history of venous thromboembolism.

Fifteen recommendations from six CPG related to 'immunotherapy'. All CPG were in agreement that immunotherapies were not recommended outside of clinical trials or in specific autoimmune diseases (*RCOG, 2011*; *Practice Committee of the ASRM, 2012*; *Alexander et al., 2017*; *Toth et al., 2018*; *Northern Ireland Public Health Agency, 2020*), except for *Sung et al. (2017)*, which recommended IVIG for recurrent miscarriage and cellular immune abnormalities. One recommendation from one CPG related to 'non-conventional treatments' and how intralipid therapy should not be recommended (*Northern Ireland Public Health Agency, 2020*).

Twelve recommendations from seven CPG related to 'thrombophilia' (*RCOG, 2011*; *Bates et al., 2012*; *Institute of Obstetricians and Gynaecologists RCPI et al., 2013*; *ESHRE Early Pregnancy Guideline Development Group, 2017*; *Sung et al., 2017*; *Queensland Clinical Guidelines, 2018*; *Toth et al., 2018*). Most were in agreement that inherited thrombophilia and a history of recurrent miscarriage are insufficient to warrant aspirin and heparin prophylaxis in the absence of thrombotic events or risk factors. *Sung et al. (2017)* suggested IVIG as an alternative if heparin, aspirin, or both, were not tolerated. *Toth et al. (2018)* stated that aspirin should not be given for recurrent miscarriage.

Eleven recommendations from six CPG related to 'genetic factors'. Two CPG stated that PGT should not be undertaken routinely (*Practice Committee of the ASRM, 2012*; *Toth et al., 2018*). Preimplantation genetic diagnosis (PGD) and PGT are the terms used within the respective guidelines. For consistency in reporting, the term PGT is used; furthermore, PGT has replaced PGD and preimplantation genetic screening (PGS) after changes to terminology in infertility care (ESHRE PGT *Consortium Steering Committee et al., 2020*). One CPG stated that the value of PGT for aneuploidy (PGT-A) as a universal screening test for all IVF patients has yet to be determined (*Practice Committees of the ASRM and the Society for Assisted Reproductive Technology, 2018*). ESHRE PGT

Consortium Steering Committee et al. (2020) recommended against PGT-A for recurrent miscarriage without a genetic cause. The *RCOG (2011)* and *Practice Committee of the ASRM (2012)* also made a point of declaring that PGT and IVF do not lead to a higher live birth rate in women who experience recurrent miscarriage, whereas the *RCOG (2011)* and *ESHRE Early Pregnancy Guideline Development Group (2017)* clearly stated the natural live birth rate in this cohort is, in fact, higher than with PGT and IVF.

Four recommendations from two CPG related to 'male factors'. Two CPG recommended against sperm selection (*ESHRE Early Pregnancy Guideline Development Group, 2017*; *Northern Ireland Public Health Agency, 2020*), one recommended against antioxidants for men (*ESHRE Early Pregnancy Guideline Development Group, 2017*) and another recommended smoking cessation, normal body weight, limited alcohol consumption and a normal exercise pattern in couples who have experienced recurrent miscarriage (*ESHRE Early Pregnancy Guideline Development Group, 2017*); this recommendation was also categorized under 'risk factors' (the only recommendation in this sub-category).

Four recommendations from three CPG related to 'vitamins'. One CPG recommended pre-conceptual folic acid supplementation, and pre-conceptual vitamin B6 and vitamin B9 (and during pregnancy, if occurs), in women who had experienced recurrent miscarriage and a diagnosis of B9 deficiency, hyperhomocysteinaemia, or both (*Huchon et al., 2016*). Two CPG recommended advising on multi-vitamins that are safe during pregnancy, if asked (*ESHRE Early Pregnancy Guideline Development Group, 2017*; *Northern Ireland Public Health Agency, 2020*).

Two recommendations from two CPG related to 'microbiological factors': one consensus-based CPG recommended that antibiotics may be administered to women who had experienced recurrent miscarriage and chronic endometritis (*Toth et al., 2018*); however, another stated that any use of antibiotics was not supported by the evidence (*Practice Committee of the ASRM, 2012*).

One recommendation from one CPG related to 'prognosis', including basing prognosis on the number of preceding losses and female age (*ESHRE Early Pregnancy Guideline Development Group, 2017*). One recommendation from one CPG related to assisted reproductive technology and how oocyte donation could be discussed as an alternative treatment in women with low ovarian reserve who have experienced recurrent miscarriage (*Huchon et al., 2016*). One recommendation from one CPG related to 'tailoring' treatment to individual clinical circumstances (*Queensland Clinical Guidelines, 2018*).

Counselling and/or supportive care

Forty-six recommendations from nine CPG were categorized under 'Counselling/supportive care', which includes anything from general supportive care, informational support, to psychological counselling and genetic counselling (Supplementary Table 9 and Supplementary Table 10). Three of these recommendations were categorized under two sub-categories. Thirty-six recommendations did not have the strength of recommendation, quality of evidence ratings, or both, to accompany them, as they were statements, good practice points, or both, within the relevant CPG, or were not specified.

Thirteen recommendations in five CPG (*Practice Committee of the ASRM, 2012*; *ESHRE Early Pregnancy Guideline Development Group, 2017*; *Queensland Clinical Guidelines, 2018*; *Toth et al., 2018*; *Northern Ireland Public Health Agency, 2020*) related to 'risk factors' and providing information, discussing risk factors for recurrent miscarriage with patients, or both. Risk factors primarily included age, successive pregnancy losses and anatomical, endocrine or metabolic and genetic factors, as well as smoking, drug and/or alcohol use, obesity or underweight, diet (including caffeine consumption) and physical inactivity. Eleven recommendations in five CPG (*Practice Committee of the ASRM, 2012*; *HSE, 2016*; *Huchon et al., 2016*; *Toth et al., 2018*; *Northern Ireland Public Health Agency, 2020*) related to 'psychological and/or emotional counselling'. These included acknowledging the emotional effect of pregnancy loss; offering (or highlighting the availability of) counselling and support (psychological and/or emotional) to couples who had experienced recurrent miscarriage, including exploring which support might be best for the woman or couple; and offering access or referral to the Bereavement Specialist Teams and others. Recommendations in this sub-category also encompassed reassurance with repeated consultations with ultrasounds in women who had experienced recurrent miscarriage and the provision of 'tender loving care' for psychological support, despite its efficacy for recurrent miscarriage being unproven. Discussion to identify preferred language or terminology to be used in discussions, and offering additional emotional support if necessary in future pregnancies, were also recommended.

Six recommendations from five CPG (*Practice Committee of the ASRM, 2012*; *ESHRE Early Pregnancy Guideline Development Group, 2017*; *Queensland Clinical Guidelines, 2018*; *Wilson, 2018*; *Northern Ireland Public Health Agency, 2020*) related to 'prognosis' and covered potential for unexplained recurrent miscarriage; emphasising chance for a future successful pregnancy in unexplained recurrent miscarriage; lack of evidence-based treatments for recurrent miscarriage; and the use of prognostic tools to provide an estimate of the subsequent chance of live birth or prognostic information.

Four recommendations from three CPG (*ESHRE Early Pregnancy Guideline Development Group, 2017*; *Wilson, 2018*; *Northern Ireland Public Health Agency, 2020*) related to 'investigations': The *Northern Ireland Public Health Agency (2020)* recommended advising women to not become pregnant before a second blood sample at 12 weeks if a second antiphospholipid test is indicated, whereas *Wilson (2018)* advised cautioning women and couples about investigations (and treatments) that are not evidence-based. The *ESHRE Early Pregnancy Guideline Development Group (2017)* highlighted how it should be made clear from the beginning that investigations do not necessarily lead to treatment options, and that the wishes and views of those who experience recurrent miscarriage should be taken into consideration when discussing investigation options, as well as providing the timeframe for the results and discussion of the results.

Three recommendations from two CPG (*ESHRE Early Pregnancy Guideline Development Group, 2017*; *Northern Ireland Public Health Agency, 2020*) related to 'informational support' and

provision of a regional information leaflet; appropriate information on available support services; and information about benefits and disadvantages of conditions for which treatment is uncertain. Four recommendations from four CPG (*RCOG, 2011*; *Practice Committee of the ASRM, 2012*; *ESHRE Early Pregnancy Guideline Development Group, 2017*; *Northern Ireland Public Health Agency, 2020*) related to 'genetic counselling' and how it should be provided when a genetic factor is identified during investigations.

Two recommendations from two CPG (*ESHRE Early Pregnancy Guideline Development Group, 2017*; *Northern Ireland Public Health Agency, 2020*) related to 'research' and informing those who experience recurrent miscarriage about relevant clinical trials and research. Two recommendations from one CPG (*Northern Ireland Public Health Agency, 2020*) related to 'tailoring' and how supportive care and emotional support should be tailored to each individual or couple. One recommendation from one CPG (*Wilson, 2018*) related to 'treatment' and cautioned against non-evidence-based treatments (covered previously in this section under 'investigations'). One recommendation concerned 'clinician knowledge, skills and expertise' in caring for those who have experienced recurrent miscarriage. It stated the need for individual care, time for discussions, respect, clear and sensitive language, honesty, shared planning kindness and supportive care in the next pregnancy (*ESHRE Early Pregnancy Guideline Development Group, 2017*).

DISCUSSION

We identified 32 CPG for the management, investigation and/or follow-up of recurrent miscarriage within high-income countries, most of which were from the USA. Seven of the identified CPG focused specifically on recurrent miscarriage, recurrent pregnancy loss, or both (including one focused on a specific procedure). Seventeen CPG specifically mentioned a system of rating evidence or quality instrument, or both, used during CPG development, with various systems mentioned; four described a system but did not specifically mention a name. We extracted 373 recommendations, under four categories: structure of care (42), investigations (134), treatment (153), and counselling and/or supportive care (46); with two recommendations classified under two categories. There were varying levels of consensus across the CPG, with some conflicting recommendations, particularly relating to investigations and treatments. Conflicting recommendations across CPG has been noted elsewhere in maternity care (*Zheng et al., 2019*) and in recurrent miscarriage, specifically (*Khalife et al., 2019*).

Of the 17 CPG that defined recurrent miscarriage and/or RPL, nine referred to three or more losses, seven referred to two or more losses, and one referred to two consecutive spontaneous losses or three or more spontaneous losses. This is also reflected in the recent ESHRE CPG, which suggests a definition of two or more, but notes that consensus was not achieved on this within the CPG development group (*ESHRE Early Pregnancy Guideline Development Group, 2017*). The results of a recent systematic review of the current evidence on the prevalence of abnormal test results for recurrent miscarriage among patients with two versus three or more pregnancy losses, were supportive of investigations after two pregnancy losses in couples who had experienced recurrent miscarriage, but the authors stressed the need for additional studies on the prognostic value of test results used in the recurrent miscarriage population (*van Dijk et al., 2020*). The findings of our review also support such calls for more research to inform the development of consensus on both the definition of recurrent miscarriage, including when investigations should be conducted, and terminology used to describe the condition.

Only two of the CPG in our review were recommended for use in their current form (*Bates et al., 2012*; *ESHRE Early Pregnancy Guideline Development Group, 2017*); 29 were recommended for use with modification, whereas one was not recommended. The quality of CPG was quite poor overall, with applicability and editorial independence scoring most poorly. Other reviews, across different topics, have noted poor reporting within domain five (applicability), which addresses factors that may affect a CPG's implementation, the potential effect on resources, and strategies to improve uptake (*Lei et al., 2017*; *Johnston et al., 2018*; *Dans et al., 2020*). To enhance the translation of CPG into practice, more consideration needs to be given to these factors during the development process. Use of the validated ADAPTE framework (*The ADAPTE Collaboration, 2010*) could assist in this regard. Issues with inadequate reporting of conflicts of interest or editorial independence have been noted in many reviews of CPG, in general (*Dans et al., 2020*; *Elder et al., 2020*) as well as in areas such as the prevention and treatment of pregnancy-associated venous thromboembolism (*Zheng et al., 2019*).

Other AGREE II domains, such as stakeholder involvement and rigour of development, also scored quite poorly in our review. A recent review of the methodological quality of local CPG on the identification and management of gestational diabetes highlighted issues with the reporting of those who have undertaken development of the CPG, user involvement, an assessment of resource implications, a listing of conflicts of interests, and external review (*Daley et al., 2019*). In their review, *van de Bovenkamp and Zuiderent-Jerak (2015)* found that Dutch CPG generally scored low on patient participation. Follow-up interviews highlighted that, although some felt that patient participation was beneficial, many felt that it was difficult in practice to accommodate patient experiences within the traditional evidence-based medicine structure of CPG development; when patients became experienced in this area, it often resulted in them losing their credibility as patient representatives (*van de Bovenkamp and Zuiderent-Jerak, 2015*). Lack of patient involvement in CPG development, from a conduct and reporting perspective, potentially limits the relevance, use and beneficial impact of CPG (*Blackwood et al., 2020*). Similar to our review, in a review of CPG in the Philippines (*Dans et al., 2020*), the involvement of a range of relevant external stakeholders, and the incorporation of patient views and preferences was lacking or poorly documented. The involvement and incorporation of the perspectives of a multidisciplinary team in CPG development, and in the formulation of recommendations, will enhance their acceptability and applicability. More significant efforts should be made to incorporate multi-disciplinary perspectives, including the involvement of patients and/or experts by experience, in CPG development.

Other reviews have also highlighted issues concerning rigour of development, e.g. CPG for the management of pregnant women with obesity (*Simon et al., 2020*) and the prevention and treatment of pregnancy-associated venous thromboembolism (*Zheng et al., 2019*). There have been calls to improve the quality of evidence underpinning CPG and the rigour of CPG development, as well as efforts to enhance CPG implementation (*Heneghan et al., 2017*). Our review illustrates that there are clear gaps in the evidence base in relation to many aspects of recurrent miscarriage and emphasizes the need for more research in the area to better inform CPG development and, ultimately, practice. This has also been highlighted by *Vlaanderen (2014)* who argues that evidence underpinning recurrent miscarriage CPG is 'meagre or even absent' and should be addressed to inform better CPG, which in turn will influence their implementation and, ultimately, the care of women and men who experience recurrent miscarriage. Future research and CPG should also consider the needs of those who have multiple medical conditions, a topic that is often neglected within CPG (*Shekelle et al., 2012*). Furthermore, despite tools such as AGREE II to assist with the development process, concerns about quality and reporting of CPG persist. The consistent use of CPG development standards will improve the quality of CPG (*Simon et al., 2020*); these should be incorporated into the routine development and updating of CPG. Our findings are relevant to those involved in the development or updating of CPG, including professional organizations such as the RCOG, whose CPG for recurrent miscarriage was published in 2011. Our findings will also inform the development of a CPG for recurrent miscarriage in the Republic of Ireland, which will be undertaken by members of the research team.

Although CPG are promising and effective tools for improving the quality of care, many are not implemented fully in practice after dissemination; this is also the case for recurrent miscarriage (*Franssen et al., 2007; Poddar et al., 2011; Van den Boogaard et al., 2011; 2013; Parry, 2018; Manning et al, 2020*) and pregnancy loss (*Le Gouic et al., 2017; Ijaz et al., 2019*) and reproductive CPG more broadly (*Gameiro et al., 2019*). Barriers to recurrent miscarriage CPG implementation occur at four levels: the CPG; professionals; patients; and organizations (*Van Den Boogaard et al., 2011*). Several barriers and facilitators to CPG implementation have been documented (*Francke et al., 2008*) across a variety of areas, including cancer treatment (*Bierbaum et al., 2020*) and recurrent miscarriage (*Van Den Boogaard et al., 2011*). Barriers can include concern over CPG content and currency, concern about the evidence underpinning CPG (*Gameiro et al., 2019; Bierbaum et al., 2020*) and perceptions that the CPG is too complicated for use in practice (*Gameiro et al., 2019*). Others include difficulties complying with patient wishes when they diverge with CPG recommendations (*Van Den Boogaard et al., 2011*); clinician uncertainty and negative perceptions of CPG (*Bierbaum et al., 2020*); organizational and environmental factors, including lack of peer or managerial support and insufficient time and resources (*Francke et al., 2008; Bierbaum et al., 2020*); and patient factors, such as cases of co-morbidity (*Francke et al., 2008; Bierbaum et al., 2020*). Facilitators of CPG implementation include CPG that are accessible, easy to understand and use and do not require specific resources (*Francke et al., 2008; Bierbaum et al., 2020*); endorsement and dissemination of CPG and adequate access to treatment facilities and resources (*Bierbaum et al., 2020*); awareness of CPG and belief in their relevance; belief that CPG support decision making, improve patient care, reduce clinical variation and reduce costs (*Bierbaum et al., 2020*). Effective CPG implementation strategies often have multiple components; the use of one single strategy, such as reminders only or an educational intervention, is less effective (*Francke et al., 2008*). In a recent review of the effectiveness of CPG dissemination and implementation strategies on the behaviour of healthcare professionals and patient outcomes in the context of cancer care, however, the number of strategies used per intervention was not associated with positive outcomes (*Tomasone et al., 2020*).

The present review has several strengths. We conducted a rigorous systematic review of CPG for the investigation treatment and/or follow-up of recurrent miscarriage. One of the strengths of is the rigorous and transparent search strategy used to ensure that all published and unpublished CPG concerning recurrent miscarriage were identified. We evaluated the quality of CPG using AGREE II, a validated international CPG quality assessment tool. Assessments were conducted by three independent reviewers, with methodological, clinical expertise, or both. Several limitations should be acknowledged. First, only CPG published in English were eligible for inclusion. Those written in other languages may exist, e.g. we excluded five full-texts as they were not published in English, which may have otherwise been relevant CPG. Second, the appraisal of CPG was merely based on the information reported by the authors in the CPG or any other material referenced alongside the CPG, e.g. manuals and patient booklets. Furthermore, we categorized guidelines as evidence-based, consensus-based, or both, depending on how the CPG developers described them. We recognize that such distinction is not advised given that both require interpretation of the evidence and consensus (*Djulbegovic and Guyatt, 2019*). Some items in AGREE II maybe have been assigned a low score as the authors did not report the necessary information in their CPG or related documentation to inform the scoring, even though they could have undertaken the required processes during CPG development. Third, AGREE II is a tool used to access the quality of the CPG development instead of the quality of the evidence. Recommendations from high-score CPG might be based on weak evidence and *vice versa*. The AGREE II focuses primarily on methodological quality and internal validity of CPG, with limited attention on the external validity of the recommendations (*Brouwers et al., 2020*). We did not assess the quality of CPG recommendations within this systematic review. *Brouwers et al. (2020)* recently developed the Appraisal of Guidelines Research and Evaluation–Recommendations Excellence (AGREE-REX) tool to appraise the quality of CPG; future work could apply this tool to the identified CPG.

In conclusion, we identified 32 CPG for recurrent miscarriage in high-income countries. There is a need to build the evidence base for recurrent miscarriage, develop consensus on the definition of recurrent miscarriage and terminology used to describe the condition, and to improve the quality

of evidence underpinning CPG and the rigour of their development. This will influence CPG implementation and, ultimately, the care of women and men who experience recurrent miscarriage. More significant efforts should also be made to incorporate multi-disciplinary perspectives, including the involvement of those who experience recurrent miscarriage, in CPG development.

DATA AVAILABILITY STATEMENT

In the protocol, we stated that we would search CINAHL Complete (EBSCOhost; 1994); we searched Cinahl Plus With Full Text, due to access issues. We also searched the websites of two additional professional bodies: HSC Public Health Agency and Health Service Executive National Women and Infants Health Programme.

The data underlying this article are available on Open Science Framework (*Hennessy et al., 2021*).

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.rbmo.2021.02.014.

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Supplementary file 3.2 – Developing guideline-based key performance indicators for recurrent miscarriage care: lessons from a multi-stage consensus process with a diverse stakeholder group

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Developing guideline-based key performance indicators for recurrent miscarriage care: lessons from a multi-stage consensus process with a diverse stakeholder group

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Abstract

Background: Standardised care pathways tailored to women/couples who experience recurrent miscarriage are needed; however, clinical practice is inconsistent and poorly organised. In this paper, we outline our processes and experiences of developing guideline-based key performance indicators (KPIs) for recurrent miscarriage care with a diverse stakeholder group which will be used to evaluate national services. To date, such exercises have generally only involved clinicians, with the need for greater stakeholder involvement highlighted.

Methods: Our study involved six stages: (i) identification and synthesis of recommendations for recurrent miscarriage care through a systematic review of clinical practice guidelines; (ii) a two-round modified e-Delphi survey with stakeholders to develop consensus on recommendations and outcomes; (iii) four virtual meetings to develop this consensus further; (iv) development of a list of candidate KPIs; (v) survey to achieve consensus on the final suite of KPIs and a (vi) virtual meeting to agree on the final set of KPIs. Through participatory methods, participants provided feedback on the process of KPI development.

Results: From an initial list of 373 recommendations and 14 outcomes, 110 indicators were prioritised for inclusion in the final suite of KPIs: (i) structure of care (n = 20); (ii) counselling and supportive care (n = 7); (iii) investigations (n = 30); treatment (n = 34); outcomes (n = 19). Participants' feedback on the process comprised three main themes: accessibility, richness in diversity, streamlining the development process.

Conclusions: It is important and feasible to develop guideline-based KPIs with a diverse stakeholder group. One hundred and ten KPIs were prioritised for inclusion in a suite of guideline-based KPIs for recurrent miscarriage care. Insights into our experiences may help others undertaking similar projects, particularly those undertaken in the absence of a clinical guideline and/or involving a range of stakeholders.

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Keywords: Early pregnancy loss, Care quality, Quality indicators, Quality improvement, Delphi technique, Patient and public involvement

Plain English summary

Women/couples who have recurrent/repeated miscarriages should receive care that meets their needs, through agreed care pathways. This is often not the case. Key performance indicators (KPIs) are measures of specific elements of care (structures, processes and/or outcomes), which can help us to judge the quality of care given. In this paper, we describe how we worked with women and men with lived experience, doctors, nurses, managers, and others, to develop and agree on a list KPIs for recurrent miscarriage care in Ireland. We will use these to check what services are doing across the country and what could be done better. Participants filled out surveys and took part in meetings to vote on and agree on what KPIs were important to include. They also shared their views and experiences of taking part in this work. Together, we developed 110 KPIs for recurrent miscarriage care. These include measures of how care is structured, counselling and supports, investigations and treatments provided, and health-related outcomes. Participants' valued the different views that people brought to discussions and what they learned. They suggested ways that the process could be made more participant-friendly. For example, being up-front about the time it would take, explaining medical terms more, and cutting down on the number of items to be rated in surveys. It is important and possible to develop KPIs with different groups, particularly those with lived experience. Learning from our study may help others who want to do similar projects, such as develop KPIs or guidelines for care.

Background

The population prevalence of recurrent miscarriage is 1–3%, depending on the definition used, i.e. two miscarriages, or three or more miscarriages [1]. There are uncertainties around how to organise recurrent miscarriage care, including debates on the investigations and treatments that should be provided [2, 3]. While there are recurrent miscarriage guidelines [2, 3], clinical practice is inconsistent and poorly organised [2]. Women/couples often attend many different health care professionals/clinics searching for a cause and treatment [2, 4].

Three broad approaches to recurrent miscarriage care globally have been identified: (i) women receive minimal or no care until they have had three miscarriages when they then get investigated, (ii) graded approach through first and subsequent miscarriages, and (iii) women seen in a medical consultant-led clinic after two consecutive miscarriages and offered a full panel of investigations [2]. Standardised care pathways tailored to the need of women/couples instead of the current fragmented approach are required [2]. Recurrent miscarriage is often managed outside of clinical guidance, with suggested reasons including variances in definitions, poor quality evidence, and the strong desire for active management from women with recurrent miscarriage [5, 6]. While a minimum service for couples with recurrent miscarriage is needed globally, country-specific models of recurrent miscarriage care can vary according to healthcare system structures, opportunities for service development/reorganisation, and available resources [2]. While there are European guidelines [7], and others internationally [3], there is currently no clinical guideline for recurrent miscarriage care in Ireland, nor has the current provision of recurrent miscarriage services within all 19 maternity units/hospitals been examined.

Key performance indicators (KPIs) are specific and measurable elements of health and social care, based on standards determined through evidence-based academic literature and/or through the consensus of experts, which can be used to assess care quality [8, 9]. Categories of indicators include structure (i.e. context in which care occurs, as well as how care is organised), process (i.e. transactions between patients and providers throughout the delivery of healthcare), and outcome (i.e. effects of healthcare on the health status of patients and populations) [10]. KPIs can be developed from clinical practice guidelines [11, 12]; however, there is currently no gold standard approach to guideline-based KPI development [13, 14]. As clinical practice guidelines aim to improve quality-of-care processes, guideline-based KPIs predominantly relate to process quality [13]. Indicators relating to the process and structure of care provide specific areas for improvement, whereas good outcomes do not necessarily equate with good care quality given the multiple influencing factors [15–18].

Researchers in the Netherlands have previously developed guideline-based indicators for recurrent miscarriage care [18], and more recently, for Early Pregnancy Assessment Units [19]. Using the RAND-modified Delphi method, van den Boogard and colleagues developed 23 KPIs for care in couples with recurrent miscarriage from the 39 recommendations in the Dutch recurrent miscarriage guideline: These were all process

indicators; no structural or outcome indicators were identified/included [18]. Furthermore, they included recommendations from only one guideline and did not involve those who experience recurrent miscarriage, only the expert opinions of 11 gynaecologists.

Lack of patient involvement is an identified limitation within the literature on guideline-based KPI development [13, 20] and guideline development more broadly [3, 21, 22]. In the development of guideline-based KPIs for UK primary care, despite some initial concerns, Rushforth and colleagues found that patient representatives were able to rate complex recommendations and gave similar opinions on feasibility, control and cost-saving criteria as health professionals on the panel [17]. Patients bring important lived experience insights; they also have a right, and should be given the opportunity, to contribute their views on outcomes, quality targets, and health care priorities that are important to them and to be actively involved in the development of KPIs [20]. While there is much-published guidance on how to develop clinical guidelines and guideline-based KPIs, few examples describe this process, particularly around how to include the views and priorities of diverse stakeholders, including health professionals, decision-makers and those with lived experience [23].

In this paper, we outline the process of developing KPIs for the investigation, management and follow-up of recurrent miscarriage, with a diverse stakeholder group, based on 32 clinical practice guidelines from high-income countries identified from a recent systematic review [3]. We define a stakeholder as "an individual or group who is responsible for or affected by health- and healthcare-related decisions" [24]. We share insights into our process experiences that may help others undertaking similar projects develop guideline-based KPIs.

Methods

We conducted this work according to a pre-specified protocol (unpublished; deviations from protocol noted before the discussion section), which was developed utilising the Guidelines International Network Performance Measures Working Group reporting standards for guideline-based performance measure development and re-evaluation [14]. Patient and public involvement in this study is reported according to the GRIPP2-SF [25], available in Additional file 1.

Composition of the guideline-based indicator development panel

This work was undertaken as an involvement activity with members of the RE:CURRENT Research Advisory Group (RRAG) to generate indicators to be used within a service evaluation. MH, RD, SM, LL, RR, DD and KOD conducted the systematic review of clinical practice guidelines [3] and led the KPI development process. The RRAG comprises 22 individuals with clinical, methodological and lived experience: healthcare and allied health professionals, representatives from advocacy and support organisations, those involved in the administration, governance and management of maternity services, academics, and women and men who have experienced recurrent miscarriage.

Ethical considerations

Ethical approval was not required for this project as it was an involvement activity with members of the RRAG to generate indicators that would be used within a service evaluation [26, 27]; this was confirmed by the Clinical Research Ethics Committee of the Cork Teaching Hospitals (Personal Communication 29/09/2020). Participation in the consensus activities was voluntary. The RRAG operates under an agreed Terms of Reference, including the following principles: respecting differences; no pressure to speak; listening; confidentiality. Members are also encouraged to contact the facilitators if they have any queries or if any issues arise for them. The research team was conscious that Group members brought different areas of expertise, for example, clinical or lived experience. Prior to the study commencing, in September 2020 at a regular meeting of the RRAG, we provided members with an introduction to KPI development (including what KPIs are, why they are needed, and how you develop them) and presented the draft protocol for discussion. During the two rounds of the e-Delphi, and the KPI appraisal survey, participants were given the option to answer, 'not my area of expertise'. The research team, including the Chair of the consensus meetings (DD), also highlighted during each of the meetings that participants should feel that they had received a sufficient explanation about each KPI to inform their voting decisions, that they should feel free to comment or ask questions, or abstain from voting (the latter further to feedback from members during the second consensus meeting). The research team was also conscious, particularly during consensus meetings, that those with lived experience of recurrent miscarriage were engaging in discussions about the merits of various types of investigations and treatments—some for which there was a lack of evidence of benefit—which they may have undertaken, and approached such discussions with sensitivity (e.g. in how discussion framed and evidence presented). Parent advocates/support group representatives were offered a nominal payment, in the form of vouchers, for their role in the RRAG, recognising their contribution to the overall Project. Members were

asked to complete a conflict of interest declaration in line with the RE:CURRENT Project Conflict of Interest Policy which documents how interests are declared and conflicts managed and recorded. We did not identify any conflicts that precluded a member from participating in any aspect of the KPI development process.

Description of the measure development process

This consensus activity comprised a six-stage process (see overview in Fig. 1), involving members of the RRAG: (i) identification and synthesis of recommendations for recurrent miscarriage care from a systematic review of clinical practice guidelines in high-income countries [3]; relevant clinical outcomes were identified through the literature and expert opinion (research team members); (ii) two-round modified e-Delphi survey with members of the RRAG to develop consensus on the recommendations and outcomes that should be used to develop KPIs; (iii) four virtual consensus meetings with members of the RRAG to review the findings from the Delphi survey, and develop and achieve consensus on the final suite of recommendations and outcomes that should be included in KPI development; (iv) development of a list of candidate KPIs by the research team; (v) survey of members of the RRAG to achieve consensus on the final suite of KPIs, and (vi) virtual meeting with members of the RRAG to review the survey findings and agree the final suite of KPIs. A similar process has been used to identify and prioritise midwifery care process metrics and indicators [28].

Stage 1: Development of a list of recommendations and outcomes from which KPIs could be generated

Selection of clinical guidelines

We identified clinical practice guidelines for the investigation, management, and/or follow-up of recurrent miscarriage within high-income countries, published between January 2000 and March 2020 (and currently endorsed and/or valid, as specified by the guideline authors and/or professional body) through a systematic review of major databases, guideline repositories, and the websites of professional organisations [3]. The quality of each clinical practice guideline was assessed using the Appraisal of Guidelines for Research and Evaluation (AGREE II) Tool, a validated tool [29]. We did not apply the Guidelines International Network criterion for clinical practice guidelines to determine the eligibility of guidelines for inclusion in our KPI development work [14, 30].

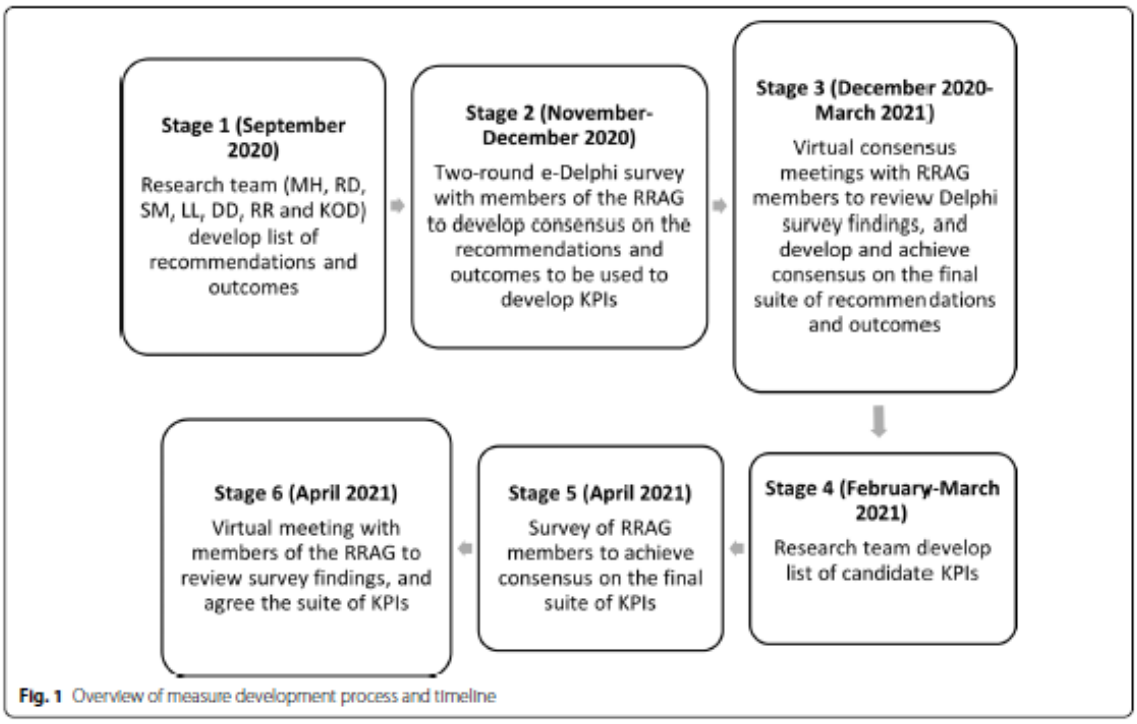


Fig. 1 Overview of measure development process and timeline

Extraction of clinical guideline recommendations

We extracted all recommendations relevant to the investigation, management and follow-up of recurrent miscarriage from included clinical practice guidelines, along with the strength of evidence and/or the grade of recommendation (where available) (data extraction file, available on OSF [31]). We did not place any restriction on including recommendations.

Development of a list of recommendations and outcomes

During a half-day meeting, members of the research team (KOD, LL, SM, MH, RD) reviewed and synthesised recommendations from the clinical practice guidelines identified in the systematic review [3], together with findings from qualitative interviews with service providers and women and men with experience of recurrent miscarriage regarding their views and experiences of current services (Dennehy et al., unpublished). No additional items arose in the qualitative findings (i.e. important aspects of RM care that were not already included); therefore, we did not add any further items. We also identified outcome metrics through the extant literature—e.g. outcomes relating to pregnancy loss, gestation and live births identified by Smith and colleagues in their systematic review of outcomes in trials for the prevention and management of miscarriage [32]—and topic/clinical expertise within the research team. This translation process, including decisions taken, was documented by the lead author.

Stage 2: Development of consensus on the recommendations and outcomes to be included in the development of a final suite of KPIs for recurrent miscarriage care—e-Delphi surveys

The RRAG participated in a multi-phase process involving a two-round e-Delphi survey and a series of consensus meetings to agree on a final list of recommendations and outcomes to be included in developing a final suite of KPIs for recurrent miscarriage care. Delphi survey design facilitates consensus-building on a topic under investigation [33]. An e-Delphi survey involves a series of questionnaires administered electronically in 'rounds' to a group of stakeholders to gather their opinions, with results from each round presented to participants in subsequent rounds [28].

We invited members (n = 21) of the RRAG, via email, to participate in Round 1 of the e-Delphi survey (administered via QuestionPro) from 02 to 13 November 2020. The survey contained a brief questionnaire seeking participant data (including name and number of years' experience relating to recurrent miscarriage) and a list of recommendations and outcomes, divided into five categories: structure of care, counselling/supportive care, investigations, treatment, and outcomes. Each recommendation and outcome was accompanied by the quality of evidence, where available, and the number of clinical practice guidelines which contained the particular recommendation. Participants were also invited to add any further recommendations and/or outcomes they considered important or relevant for inclusion. We asked participants to rate the extent to which the realisation of a recommendation or outcome was important for measuring quality care for recurrent miscarriage, using a nine-point Likert scale (1–3 = not important, 4–6 = unsure of importance and 7–9 = important); similar wording was used by van den Berg and colleagues when developing guideline-based KPIs for early pregnancy assessment units [19]. Participants were also invited to list their top five recommendations or outcomes for each category, in order of importance from 1 to 5 (see Additional file 2 for a sample survey item). We provided participants with a PDF copy of the survey, which contained a glossary of key terms (e.g. Delphi study, KPI, and outcome), advising that it might be helpful to read in advance of completing the online survey. Consensus on the inclusion of a recommendation or outcome was determined where 70% or more participants rated the recommendation or outcome as 7–9 and less than 15% of participants rated the recommendation or outcome as 1–3; this criteria is used for developing core outcome sets in healthcare (http://www.comet-initiative.org/). Results from Round 1 were collated and used to inform the development of the second round of the e-Delphi survey.

In the second round, administered via QuestionPro from 23 November to 04 December 2020, we presented all participants with the same recommendations and outcomes as those presented in Round 1. In this round, however, we included how the Group rated each recommendation and outcome during Round 1, presenting the overall rating results (percentages) for each; see Additional file 3 for a sample survey item. In the invitation email to each participant, we also provided a separate file containing confidential details of their own ratings for each item. We asked them to consider these ratings and then to rate the importance of each recommendation and outcome again, revising their rating based on how others had rated them, if they wished. As in Round 1, consensus on inclusion of a recommendation or outcome was determined where 70% or more participants rated the recommendation or outcome as 7–9 and less than 15% of participants rated the recommendation or outcome as 1–3. Participants were advised that each survey would take approximately 45–60 min to complete.

Stage 3: Development of consensus on the recommendations/outcomes to be included in the development of a final suite of KPIs for recurrent miscarriage care—consensus meetings

A series of four, three-hour, virtual consensus meetings (09 December 2020; 12 January, 03 February, 03 March 2021) were held with members of the RRAG to discuss the e-Delphi survey findings and develop and achieve consensus on the final suite of recommendations and outcomes that should be included in KPI development. Meetings were chaired by DD, an experienced facilitator of such meetings. We presented participants with the percentage rating for each recommendation and outcome, overall and by stakeholder group from both rounds of the e-Delphi survey via PowerPoint presentation (see Additional file 4 for an example). We did not exclude any recommendations or outcomes based on the ratings received during the e-Delphi survey as we wanted to give participants the opportunity to review and discuss each of them as a group (including the overall ratings, and ratings by stakeholder group), and to ask any questions and re-evaluate any items, prior to excluding any from further consideration. Further to discussion and agreement within the Group, KOD provided a lay explanation for each recommendation and outcome where members felt that greater explanations were needed prior to them making an informed vote. Participants then discussed their views, before voting on whether they felt that each should be included in the final suite of recommendations and outcomes. To be retained, a recommendation or outcome required a yes vote by $\geq$ 70% of participants. Detailed notes of each meeting, including decisions taken and voting results, were taken by MH and verified by the team.

Stage 4: Translation of recommendations into candidate KPIs

Members of the research team (MH, LL and KOD) reviewed the reports from the consensus meetings before translating the agreed key recommendations and outcomes into candidate KPIs; these were then reviewed by remaining members of the research team (RD, DD, RR and SM). For each KPI, we generated the following details: title; number; description; rationale; calculation, comprising a numerator divided by a denominator expressed as a percentage. We detailed the numerator and denominator for each KPI, outlining any exceptions (e.g., age, contraindications) where applicable. Outcome-related KPIs were framed as outcomes which a recurrent miscarriage clinic/service should report/audit. Outcomes related to complications in future pregnancies (e.g. preterm birth, fetal growth restriction, and stillbirth) were included, given that recurrent miscarriage is an important indicator for such complications [1], not that they indicate quality of recurrent miscarriage care per se. We considered the potential for KPIs to be integrated into existing coding and data systems; however, participants highlighted that the data collection systems within the Irish health system were not sufficiently developed in this regard. This translation process, including steps and decisions taken, were documented by MH.

The KPIs will be used to evaluate recurrent miscarriage services in all 19 maternity units/hospitals across the Republic of Ireland as part of the RE:CURRENT study, and were formulated as such. While they are being developed for research purposes to understand what care is currently provided to those who experience recurrent miscarriage, the KPIs may also be used to inform quality improvement efforts at local, regional and national levels; they will not be used for accountability purposes (e.g. pay-for-performance).

Stage 5: Achieving consensus on the final suite of KPIs—survey

We invited 20 members of the RRAG, via email, to participate in a final survey from 14 to 26 April 2021, to appraise each indicator and reach a consensus on the final suite of KPIs. The email included a link to a 10-min video outlining the purpose of the survey and what they were being asked to do, along with a Word version of the survey—given its length, the lack of a 'save and continue later' facility within the free version of QuestionPro, and feedback from participants from the previous e-Delphi rounds—to be completed and returned via email.

The survey contained details of the KPIs developed in Stage 4, by category. At the end of each category/section, we noted details of recommendations or outcomes that were rated as important to include in KPI development by the RRAG in Stage 3, but which were not translated into a KPI, with reasons noted. For example, if there was another similar recommendation, or the recommendation did not translate well into a KPI, i.e. it could not tangibly be measured by a KPI.

Measure appraisal

We asked participants to review each KPI using a framework to help them judge if a KPI was appropriate for inclusion in the final suite of KPIs (see Table 1). We asked them to select YES, NO, or DON'T KNOW, for each of four criteria on which the KPI was being assessed: process-based, important, operational, feasible. Based on their assessments, we then asked them to vote on whether they felt that the KPI should be included in the final suite. As with preceding stages, participants were given the option to exempt themselves from rating a particular KPI/criterion if they felt it was outside of their

Table 1 QCM judgement framework tool[a]

Domain	Description
Process-focused	The metrics/indicator contributes clearly to the measurement of recurrent miscarriage care processes
Important	The data generated by the metric/indicator will likely make an important contribution to improving recurrent miscarriage care processes
Operational	The indicator is quantifiable (i.e. can be measured); definitions are precise, and reference standards are developed and tested or it is feasible to do so
Feasible	It is feasible to collect and report data for the metric/indicator in the relevant setting

[a] Adapted from Flenady and colleagues [34] and Devane and colleagues [28]

area of expertise. (See Additional file 5 for a sample survey item). Consensus on the inclusion of a KPI was determined where 70% or more participants rated the KPI for inclusion in the final suite.

Stage 6: Virtual meeting to review the survey findings and agree the final suite of KPIs

At a further virtual meeting, the KPI appraisal survey results were presented to and discussed with RRAG members, and the final suite of KPIs agreed. As with other meetings, all RRAG members received emails with supporting documentation before and after this final meeting, and had the opportunity to review the final list and contribute to discussions. At this meeting, feedback was also sought on the KPI development process. Members present were invited to think of three words that came to mind when they thought about the process and to enter these into Mentimeter (interactive virtual presentation app; https://mentimeter.com); a word cloud was generated and discussed. Participants were then asked to consider what worked well and what could be done better, and to write their thoughts (anonymously) on two virtual bulletin boards on Padlet (https://padlet.com). SM summarised key themes arising and invited discussion. RRAG members were invited to add any further thoughts to the Padlet walls for a week after the meeting to enable those unable to attend the meetings to contribute their feedback.

Finally, quantitative and qualitative data generated during each stage were entered into Microsoft Excel and verified. Quantitative data were summarised descriptively, while qualitative data was analysed thematically [35].

Results

Participation during various stages of KPI development

Twenty-one members of the RRAG took part, to varying extents, in Stages 2 and 3 of the consensus-building activities. Ninety-five percent of members (20/21) took part in Round 1 of the e-Delphi survey, while 90% (19/21) took part in Round 2 (Stage 2). The bold designates the total numbers for each row above—emboldened to make it stand out. Round 1 had 273 years' experience (clinical/lived) related to recurrent miscarriage (Mean = 13.7 years; Range = 5–25 years), compared with 265 years' experience (Mean = 13.9 years; Range = 5–25 years) in Round 2. All available members were invited to take part (i.e. had voting rights) in the consensus meetings (Stage 3), along with two members of the research team (KOD and LL). Participation in these meetings varied, with 48%, 78%, 70% and 70% participating in meetings 1 to 4, respectively (Table 2). Participation by stakeholder group varied across the four meetings, as follows: health professionals (38–85%); management/governance role (33–50%); parent advocate/support group representatives (75–100%). Fourteen out of 20 RRAG members (70%) completed the final KPI

Table 2 Overview of participants in the KPI development process

Participant group	Total	Delphi round 1		Delphi round 2		Total	Consensus meeting 1		Consensus meeting 2		Consensus meeting 3		Consensus meeting 4		Total	Final survey		Final review meeting	
		n	%	n	%		n	%	n	%	n	%	n	%		n	%	n	%
Health professional	11	10	91	9	82	13[a]	5	38	11	85	11	85	10	77	10	7	70	5	50
Management/governance role	6	6	100	6	100	6	3	50	3	50	2	33	3	50	6	4	67	2	33
Parent advocate/support group representative	4	4	100	4	100	4	3	75	4	100	3	75	3	75	4	3	75	3	75
Total	**21**	**20**	**95**	**19**	**90**	**23**	**11**	**48**	**18**	**78**	**16**	**70**	**16**	**70**	**20**	**14**	**70**	**10**	**50**

The bold designates the total numbers for each row above

[a] Two of the study investigators (KOD and LL) participated in voting during the consensus meetings, given their clinical and research expertise in recurrent miscarriage

appraisal survey (Stage 5). In contrast, ten (50%) participated in the final meeting to review the survey findings and agree on the final suite of KPIs (Stage 6).

KPI development

Each stage of the consensus process, including numbers of removed/reduced included/excluded during each, is outlined in Fig. 2.

Stage 1: Development of a list of recommendations and outcomes from which KPIs could be generated

We identified 373 recommendations from the 32 clinical practice guidelines included in our systematic review and 14 potentially relevant outcomes from the extant literature and expertise within the study team, giving a total of 387 (Fig. 2). Members of the study team agreed a final list of 201 recommendations and outcomes.

Stage 2: Development of consensus on the recommendations and outcomes to be included in the development of a final suite of KPIs for recurrent miscarriage care—e-Delphi surveys

Twenty members of the RRAG rated the importance of the 201 recommendations and outcomes in Round 1 of the e-Delphi survey, while 19 of them re-rated these again in Round 2 (Table 2). While participants were advised that surveys would take 45–60 min to complete, some reported that it took much longer. Levels of consensus on the importance of recommendations and outcomes for inclusion increased across both rounds, except for 'structure of care' as all items there were rated as important in both rounds (Table 3).

In general, participants voted on most, if not all, recommendations within 'structure of care', 'counselling/supportive care' and 'outcomes. For 'investigations' and 'treatment', health professionals voted on more items (Additional file 6). For example, the mean number of recommendations voted on by health professionals in the 'treatment' category (n = 80) in Round 2 was 67.1 (range = 11–80), compared with 20.3 for those in management/governance (range = 0–64), and 28 for parent advocates/support group representatives (range = 0–60).

Participants suggested additional recommendations and/or outcomes for inclusion during each round (R), relating to structure of care (R1: 11; R2:7), counselling/supportive care (R1: 4; R2: 1), treatment (R1: 1), and outcomes (R1: 1; R2: 2). We did not add any additional recommendations or outcomes as the suggestions were either already covered within other items, or they were more suited to being included in a clinical practice guideline.

We did not analyse the ranking data (i.e. top five recommendations and outcomes for each category) provided by participants, primarily because many participants did not complete this activity, stating that it was outside their expertise.

Stage 3: Development of consensus on the recommendations and outcomes to be included in the development of a final suite of KPIs for recurrent miscarriage care—consensus meetings

All 201 recommendations and outcomes presented in the two rounds of the e-Delphi survey were brought forward to the consensus meetings. Throughout these four meetings, through discussion and voting, this number was reduced to 113, across the five categories: structure of care [17]; counselling/supportive care [10]; investigations [35]; treatment [34]; outcomes [17], and 4 additional outcomes/KPIs were suggested (Fig. 2).

Stage 4: Translation of recommendations into candidate KPIs

The research team generated 117 KPIs from the 113 recommendations and outcomes agreed during Stage 3 and the four additional outcomes/KPIs suggested (Fig. 2). Some of the recommendations and outcomes were not translated into KPIs as they were duplicates or covered by another KPI or did not translate well into a KPI.

Stage 5: Achieving consensus on the final suite of KPIs—survey

Fourteen out of twenty RRAG members completed the final survey (Table 2), which resulted in 110 of the 117 KPIs being retained (Fig. 2; details of KPIs retained and excluded in Table 4 and Additional file 7, respectively). Additional comments noted by participants included

(See figure on next page.)

Fig. 2 Stages in the development of guideline-based KPIs for recurrent miscarriage care. *Notes*: [a]Moved to Investigations category, [b]Moved from Structure of care category, [c]Removed during consensus meeting 2 due to overlap with one or more other recommendations, [d]Removed by research team members (KOD + MH) before consensus meeting 3 due to overlap with one or more other recommendations, [e]Removed by research team members (KOD + MH) before consensus meeting 3 due to overlap with one or more other recommendations, [f]Removed during consensus meeting 3 due to overlap with one or more other recommendations, [g]Removed during consensus meeting 4 due to overlap with one or more other recommendations, [h]One outcome was divided into four outcomes during consensus meeting 4, [i]More than one KPI generated for some recommendations, [j]KPIs developed for items suggested by RRAG moved from Outcomes into this section, [k]Recommendation/outcome not translated into a KPI (duplicate/covered somewhat by another KPI; did not translate well into a KPI), [l]KPI generated for additional items suggested by RRAG

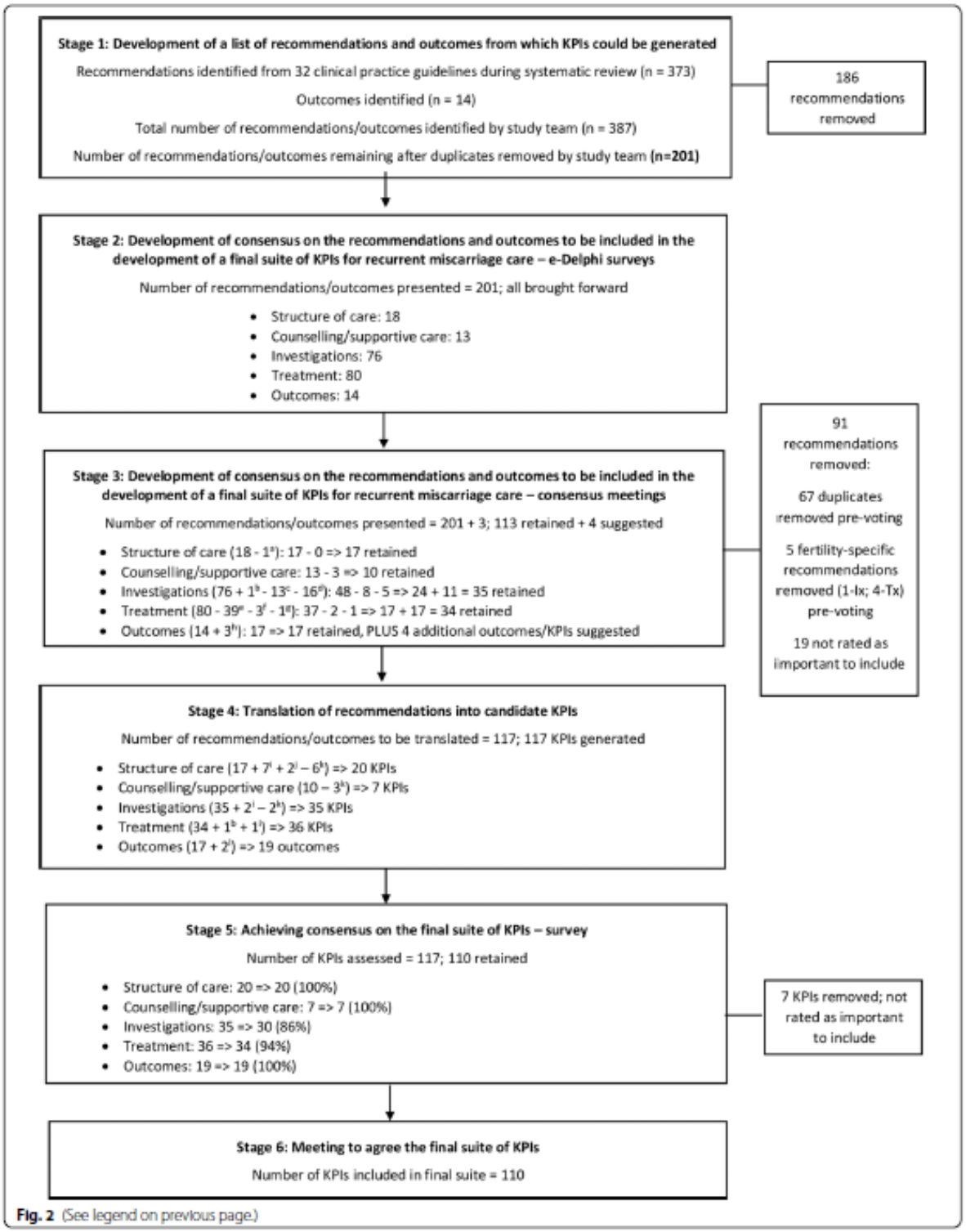


Fig. 2 (See legend on previous page.)

Table 3 Number of recommendations/outcomes voted as important to include (i.e. ≥ 70% voted yes to inclusion) after each round of the e-Delphi survey

Category	Round 1		Round 2	
	No. voted as important/Total no.	%	No. voted as important/Total no.	%
Structure of care	18/18	100	18/18	100
Counselling/supportive care	8/13	62	9/13	69
Investigations	26/76	34	33/76	43
Treatment	17/80	21	37/80	46
Outcomes	7/14	50	10/14	71

concerns about putting some recommendations into practice, i.e. feasibility of recommendations rather than measuring a particular care process (e.g. clinic location, format/language of information; standardised templates); the feasibility of measuring certain KPIs, especially those with multiple components; the framing of some 'negative' KPIs, i.e. instances where a particular investigation or treatment should not be undertaken; the ability of clinics to conduct follow-ups to collect outcome data. There were also suggestions for merging KPIs, e.g. referral criteria & specification, investigation & management plans. These were discussed in Stage 6; no amendments were made, and some suggestions were noted for incorporation into later guideline development.

As with the recommendations and outcomes, participants generally voted on most, if not all, recommendations within 'structure of care', 'counselling/supportive care' and 'outcomes' (except those in management/governance roles for the latter). Similarly, for 'investigations' and 'treatment', health professionals voted on a greater number of items but were followed closely by parent advocates/support group representatives on this occasion (Additional file 8).

Stage 6: Virtual meeting to review the survey findings and agree on the final suite of KPIs

Ten RRAG members attended the final meeting and approved the final list of 110 KPIs, agreed during Stage 5 (Table 4).

Feedback from participants on the KPI development process

The word cloud generated from participants' feedback on the KPI development process is presented in Fig. 3. Words that predominated related to the long, complicated, time-consuming process; despite this, positives were noted relating to comprehensiveness, good facilitation, learning, and engagement/participation.

These findings were further elaborated on in participants' responses to the questions posed around what worked well and what could be done differently; participant quotes are designated by identifiers W(ell) and B(etter), relating to the latter. We generated three themes: accessibility, richness in diversity, streamlining the development process.

Richness in diversity describes the benefits stated by some participants, including multiple/diverse perspectives, the rich discussions, learning (which they may have missed out on if they knew the time commitment involved initially; they would have 'baulked at the outset'), and how it 'gives the project a lot of weight'.

> *"The discussions which flowed during the meetings were brilliant, and the knowledge and passion of the people on the group is inspirational. I am delighted to be part of the group" (W3)*

Within this theme, some areas for improvement were noted, such as the benefit of having more representation from doctors/midwives in training and more

> *"alternative voices to the medical expertise that was on the group but were equally informed in terms of fertility, miscarriage"*(B7).

Accessibility represents the majority of comments received and describes what facilitated participants to access/engage with the process, or not. Sub-themes encompassed: skilled facilitation, communication with/from the research team, virtual access/timing of meetings, and making the process more user-friendly. Participants valued the skilled facilitation during the consensus meetings, lay explanations provided, and adequate time for discussion.

> *"Some of the consensus meetings were.....heavy and I sometimes felt I was overwhelmed with all the medical jargon, but Keelin's [KOD's] explanations were super as well as Declan's [DD's] and other members in the group" (W5)*

Some thought that providing a reference guide with an explanation of medical terms at the outset would have been very beneficial. One parent advocate felt that

> *"the responsibility felt heavy at times, to raise questions from a parent perspective without the medical expertise"*

and suggested that it would have been helpful for the parent representatives to have met together with the team, prior to starting the process to consider their role in it

Table 4 Agreed list of KPIs for recurrent miscarriage care

KPI No.	KPI title	KPI sub-category
KPI category: Structure of care (n = 20)		
1.4(a)	Dedicated recurrent miscarriage clinic on-site	Dedicated clinic
1.4(b)	Access to dedicated recurrent miscarriage clinic	Dedicated clinic
1.6(a)	Core recurrent miscarriage team	Staffing/expertise
1.6(b)	Access to psychological supports	Staffing/expertise
1.12(b)	Staff education and training	Staffing/expertise
1.12(a)	Care experience	Staffing/expertise
1.5	Location of dedicated recurrent miscarriage/pregnancy loss/gynaecology clinic	Location/equipment/facilities
1.10	Laboratory services	Location/equipment/facilities
1.3	Formal referral process	Referral structures
1.2(a)	Referral criteria	Referral structures
1.2(b)	Specification of referral criteria	Referral structures
1.18	Education/information for health professionals about referral processes	Referral structures
1.001	Referral sources	Referral structures
1.002	Referral times	Referral structures
1.1	Timing of investigations	Referral structures
1.14(a)	First visit—written information about what to expect	Information provision and plans
1.14(b)	Written information about sources of support	Information provision and plans
1.14(c)	Written information about recurrent miscarriage	Information provision and plans
1.17(a)	Tailored investigation plan	Information provision and plans
1.17(b)	Tailored management plan	Information provision and plans
KPI category: Counselling/supportive care (n = 7)		
2.9	Information provision—risk factors: advancing age	Information provision
2.10	Information provision—modifiable risk factors	Information provision
2.5	Unexplained recurrent miscarriage—information about prognosis	Information provision
2.11	Information provision—unorthodox investigations/treatments	Information provision
2.7	Information provision—treatment uncertainty	Information provision
2.13	Clinical trials	Information provision
2.12	Genetic counselling	Genetic counselling
KPI category: Investigations (n = 30)		
3.1	Medical, obstetric and family history	Standard investigations
3.2	Information about behavioural and weight-related risk factors	Standard investigations
3.15	Full blood count	Standard investigations
3.16	Electrolytes and liver function tests	Standard investigations
3.4	Assessment of uterine anatomy	Anatomical investigations
3.7	Assessment of uterine anatomy using transvaginal ultrasound	Anatomical investigations
1.9	Access to 3D ultrasound	Anatomical investigations
3.12	Imaging/imaging with hysteroscopy to diagnose uterine septa	Anatomical investigations
3.14	Complete investigation following Müllerian uterine malformation diagnosis	Anatomical investigations
3.20	Measurement of antinuclear antibodies testing	Immunological screening
3.21	Natural killer cell testing	Immunological screening
3.27(a)	Routine screening for hereditary thrombophilia	Haematology

Table 4 (continued)

KPI No.	KPI title	KPI sub-category
3.27(b)	Screening for hereditary thrombophilia, with risk factors	Haematology
3.34(a)	Screening for antiphospholipid syndrome—routine	Haematology
3.34(b)	Screening for antiphospholipid syndrome—non-routine	Haematology
3.36	Monitoring of plasma coagulation markers	Haematology
3.25	Thyroid stimulating hormone, thyroid peroxidase-antibodies, and thyroxine (T4) testing	Metabolic & endocrinologic factors
3.38	Screening for diabetes	Metabolic & endocrinologic factors
3.45	Ovarian reserve testing	Metabolic & endocrinologic factors
3.48	'Day 2–5' hormone profile	Metabolic & endocrinologic factors
3.46	Luteal phase insufficiency testing	Metabolic & endocrinologic factors
3.47	Androgen testing	Metabolic & endocrinologic factors
3.55	Vitamin D measurement	Metabolic & endocrinologic factors
3.51	Infectious screening	Infectious screening
3.60	Cytogenetic analysis of pregnancy tissue at the third miscarriage	Screening for genetic factors
3.58	Array-based comparative genomic hybridisation (Array-CGH)	Screening for genetic factors
3.57	Genetic polymorphism study	Screening for genetic factors
3.64	Peripheral karyotyping	Screening for genetic factors
3.65	Cytogenetic testing of both parents	Screening for genetic factors
3.71	Testing for spermploidy/DNA fragmentation	Screening for male factors
KPI category: Treatment (n = 34)		
4.2a	Treatment of antiphospholipid syndrome—referral to local haematology service	Antiphospholipid syndrome
4.2b	Treatment of antiphospholipid syndrome—low dose aspirin and heparin in next pregnancy	Antiphospholipid syndrome
4.4	Treatment of antiphospholipid syndrome—intravenous immunoglobulin therapy	Antiphospholipid syndrome
4.25	Treatment of subclinical hypothyroidism with levothyroxine	Recurrent miscarriage with metabolic and endocrinologic factors
4.28	Treatment of overt hypothyroidism with levothyroxine	Recurrent miscarriage with metabolic and endocrinologic factors
4.30	Treatment of women with subclinical hypothyroidism in next pregnancy	Recurrent miscarriage with metabolic and endocrinologic factors
4.31	Treatment of women with thyroid autoimmunity and hypothyroidism in next pregnancy	Recurrent miscarriage with metabolic and endocrinologicfactors
4.40	Human chorionic gonadotrophin supplementation in pregnancy	Recurrent miscarriage with metabolic and endocrinologic factors
4.36	Bromocriptine treatment in women with recurrent miscarriage and hyperprolactinemia	Recurrent miscarriage with metabolic and endocrinologic factors
4.42	Metformin supplementation	Recurrent miscarriage with metabolic and endocrinologic factors
4.14	Preimplantation genetic testing	Recurrent miscarriage with genetic background
4.12	Unexplained recurrent miscarriage: Preimplantation genetic screening with in vitro fertilisation treatment	Recurrent miscarriage with genetic background
4.8	Oocyte donation	Recurrent miscarriage with poor ovarian reserve
4.23	Sperm selection	Recurrent miscarriage with male factor
4.67	Myomectomy (laparoscopic or open)	Uterine factors in recurrent miscarriage
4.68	Hysteroscopic septum resection	Uterine factors in recurrent miscarriage

Table 4 (continued)

KPI No.	KPI title	KPI sub-category
4.71	Metroplasty in women with bicorporeal uterus and double cervix	Uterine factors in recurrent miscarriage
4.70	Uterine reconstruction for hemi-uterus	Uterine factors in recurrent miscarriage
1.7	MDT for hysteroscopic metroplasty of a uterine septum	Uterine factors in recurrent miscarriage
4.74	Surgical removal of intrauterine adhesions	Uterine factors in recurrent miscarriage
4.43	Use of antibiotics	Antibiotics
4.61	Unexplained recurrent miscarriage: Supportive care	Unexplained recurrent miscarriage
4.54	Unexplained recurrent miscarriage: Use of low molecular weight heparin or low dose aspirin	Unexplained recurrent miscarriage
4.1	Corticosteroids (e.g. prednisolone)	Unexplained recurrent miscarriage
4.19	Glucocorticoids (clinical studies)	Unexplained recurrent miscarriage
4.52	Intravenous immunoglobulin	Unexplained recurrent miscarriage
4.27	Empiric progestogen	Unexplained recurrent miscarriage
4.57	Unexplained recurrent miscarriage: Intralipid therapy	Unexplained recurrent miscarriage
4.51	Unexplained recurrent miscarriage: Lymphocyte immunisation therapy	Unexplained recurrent miscarriage
4.58	Unexplained recurrent miscarriage: Granulocyte colony-stimulating factor	Unexplained recurrent miscarriage
4.17	Unexplained recurrent miscarriage: Immuno-therapy	Unexplained recurrent miscarriage
4.22	Unexplained recurrent miscarriage: Therapy with tumour necrosis factor-α receptor blockers	Unexplained recurrent miscarriage
4.59	Unexplained recurrent miscarriage: Endometrial scratching	Unexplained recurrent miscarriage
4.55	Unexplained recurrent miscarriage: Folic acid	Unexplained recurrent miscarriage
KPI category: Outcomes (n = 19)		
5.1	New pregnancy	New pregnancy
5.2a	New pregnancy: Spontaneous conception	New pregnancy
5.2bI	New pregnancy: Ovulation induction and intrauterine insemination	New pregnancy
5.2bII	New pregnancy: IVF and IntraCytoplasmic Sperm Injection	New pregnancy
5.2bIII	New pregnancy: IVF and IntraCytoplasmic Sperm Injection with donor gametes	New pregnancy
5.2bIv	New pregnancy: Any use of Preimplantation Genetic Testing	New pregnancy
5.3	New pregnancy reaches 2nd trimester	New pregnancy
5.4	New pregnancy reaches 3rd trimester	New pregnancy
5.5	New pregnancy: Avoidance of fetal growth restriction	New pregnancy
5.6	New pregnancy: Avoidance of placental abruption	New pregnancy
5.7	New pregnancy: Avoidance of pre-eclampsia	New pregnancy
5.8	New pregnancy: Avoidance of preterm birth	New pregnancy
5.9	New pregnancy: Avoidance of stillbirth	New pregnancy
5.10	New pregnancy: Avoidance of neonatal death	New pregnancy
5.11	New pregnancy: Treated as high risk, with consultant-led care	New pregnancy
5.12	Interval to next pregnancy: < 6 months	New pregnancy
5.13a	Interval to next pregnancy: ≥ 6 months and < 12 months	New pregnancy

Table 4 (continued)

KPI No.	KPI title	KPI sub-category
5.13b	Interval to next pregnancy: < 12 months	New pregnancy
5.16	New pregnancy: Attend early pregnancy clinic/ have an early pregnancy scan	New pregnancy

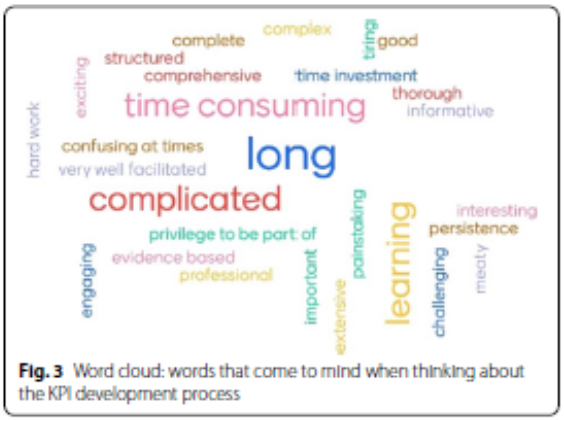


Fig. 3 Word cloud: words that come to mind when thinking about the KPI development process

and to strengthen their voice perhaps (B13). A few participants stated that the time commitment involved should have been made clearer at the outset.

Participants highlighted positives regarding the responsiveness/accessibility of research team members (email/phone communication) when information/clarification was needed, updates regarding progress and information in advance, and honesty around the challenges experienced during the development process. Many felt that the virtual format, and evening meetings, facilitated access; the shorter (3-h) meetings, rather than one long day, were generally preferred. The sub-theme 'making the process more user-friendly' related to comments from a few participants about the difficultly experienced with the Delphi survey, including the inability to 'save and continue later' on the online platform, as well as one noting that the ability to abstain from voting during consensus meeting should have been clearer at the outset.

Streamlining the development process captures comments made by a few participants about how the number of recommendations/KPIs could have been narrowed down—by those with the relevant expertise—before asking all participants to vote on them.

> *"Perhaps the KPIs could have been narrowed down by those who really had the expertise to do that prior to the big group coming together to vote on them - or else, depending on people's backgrounds, being invited to come for voting on sections that were only within people's expertise/experience." (B16)*

Discussion

Standardised care pathways tailored to women/couples who experience recurrent miscarriage are needed to improve care; however, clinical practice is inconsistent and poorly organised. In this paper, we outline how we developed guideline-based KPIs for recurrent miscarriage care, following established guidance [14], to be used to evaluate recurrent miscarriage services in Ireland. Through a six-phase consensus-building process, we developed 110 KPIs, which are well distributed across the five categories, including structures and outcomes, in addition to investigations and treatments. Indicators were developed with the RRAG, a multi-stakeholder group comprising health professionals, those involved in the administration, governance and management of maternity services, and parent advocates/support group representatives. To date, such exercises have generally only involved clinicians, with the need for greater stakeholder involvement highlighted [13, 20]. We sought to establish the feasibility of developing guideline-based indicators with a diverse stakeholder group, including those with lived experience of recurrent miscarriage, and share insights into our collective experiences. We will now explore these further, guided by themes generated from participants' insights.

Richness in diversity

Guideline-based KPI development is often only conducted with clinicians [18, 19], with lack of patient involvement a noted limitation [13, 20], even within guideline development itself [3]. We found that it is possible to involve a range of stakeholders in developing such indicators, including women and men with lived experience of recurrent miscarriage. Participants in our study valued the opportunity to be involved and to discuss and learn from each other, being afforded the 'space to talk' [36], though perhaps some contributors did not feel that they brought equally important knowledge as others. As noted by Rushforth and colleagues [17], we found that, following lay explanations and rich discussions during the consensus meetings, parent advocates/support group representatives could rate complex recommendations/KPIs and often gave similar opinions as health professionals.

Accessibility

The above considered, participant feedback nonetheless suggested that the clinical voice was perhaps strongest throughout; whether this influenced voting during the consensus meetings is unknown. Indeed, Williams and colleagues argue that 'professional advantage' will always be held in patient and public involvement despite efforts to counter such impacts and a willingness to share power [37]. The latter is often incompatible with the traditional research structures in which involvement takes place [22, 38, 39], as well as what knowledge is deemed as legitimate [22, 38]. It should also be noted that there were variations within professional groupings also; with non-clinicians (whether part of the 'health professional' or 'management/governance' groups) abstaining from voting to similar extents to parent advocates/support group representatives during both rounds of the Delphi survey.

Given the initial volume of recommendations and outcomes, we held discussions with the collective group of stakeholders, and there was benefit in having diverse perspectives shared. Smaller group discussions, by stakeholder group—particularly those with lived experience—would have been useful in advance of larger group discussions, as noted by participants. This would have increased the time commitment and should be factored into planning, and resourcing, similar projects. The need to be realistic and upfront about the time commitment for such activities at the outset, was highlighted by participants during feedback. This was an ongoing challenge for the research team throughout, balancing the (sometimes unanticipated) volume of work, the need and desire for meaningful involvement, and participants' time. This was particularly evident when synthesising the recommendations during Stage 1; many were retained as the team did not wish to influence how participants perceived/voted on them—these were further synthesised during Stage 3. It would perhaps be useful to have a meeting at the outset with participants to discuss how such issues would be handled, particularly regarding areas such as recurrent miscarriage where there is a lack of consensus [3, 40]. This could include how participants could be most meaningfully involved [22], how recommendations would be selected, and providing lay explanations—or how such explanations could be facilitated (including perhaps an independent provider of same). This may also enable participants to engage more actively and/or meaningfully in voting during Delphi survey rounds.

Despite the challenging, lengthy process, conducted during the COVID-19 pandemic, there was a relatively high participation rate amongst the diverse stakeholder group throughout (approximately 70% for many of the stages), despite a decline during the latter stages, particularly amongst those in management and governance roles. The high level of commitment and involvement of participants was facilitated, certainly in part, by the skilled facilitation including lay explanations and time for discussion, open communication with/from research team, and the virtual access and timing of meetings. Virtual meetings may also have reduced power differentials between the research team and participants as we shared insights into our personal spaces/lives during calls [41]. However, it is also possible that virtual meetings limited engagement with some contributors [42].

Streamlining the development process

As noted by other researchers, developing KPIs can be time consuming and resource-intensive [16, 17, 43], as was the case here. We started the process with many recommendations (n = 373) and outcomes (n = 14), in the absence of a national guideline for recurrent miscarriage. Participants had to agree recommendations for recurrent miscarriage care, before consensus on which recommendations should be prioritised for KPI development.

Furthermore, the research team did not exclude any guidelines/recommendations based on quality assessment/AGREE II scores. Ideally, indicator development should be conducted as part of the guideline development process and originate from evidence-based guideline recommendations [44]. One hundred and ten KPIs was a large number of indicators to include in the final suite, though similar numbers have been generated for midwifery care processes [28]. Similar to Fiset and colleagues [43], some of the included guidelines focused on specific aspects of recurrent miscarriage care; others were broader in focus, which may be more helpful in guiding practice and identifying KPIs. In developing KPIs for recurrent miscarriage care, van den Boogaard and colleagues noted that degree of acceptance of an indicator diminished with a decrease in evidence level; however some 'authority-based statements' were selected as indicators, potentially because they are part of everyday clinical practice [18]. In our systematic review, we identified much variation in grading systems used to rate the quality of evidence within each of the included guidelines and how the levels of evidence were presented in each, with inconsistency in levels of evidence and strength of recommendations across similar recommendations [3], also noted by Fiset and colleagues [43]. The KPIs generated in our study, were developed from recommendations with varying levels of evidence. Those which recommended against particular practices were particularly challenging for participants to engage with; however the importance of including these was agreed during consensus meetings, given that women/couples with recurrent miscarriage can undergo unnecessary investigations and/or treatments [2].

Strengths and limitations

We used a systematic, pre-determined, approach to generate KPIs for recurrent miscarriage care. While these were developed for the Irish context, our findings have broader relevance internationally. The inclusion of a diverse stakeholder group, particularly parent advocates/support group representatives, and the focus on processes are key strengths of this study. Such diversity in development panels is advocated; it includes those with an interest in the results of the study, in addition to the potential for diverse perspectives about quality of care which can enrich the results [45]. We had a relatively high participation rate amongst the diverse stakeholder group throughout which is also a strength of this study, as discussed in more detail above.

Several potential limitations should be noted. We did not apply any criteria to select recommendations from the guidelines (e.g. level of evidence or strength of the recommendation). Not all quality indicator development criteria may be addressed in guideline development [44]. Nothacker and colleagues recommend consideration of relevance (as a minimum: potential for improvement/clinical relevance), scientific soundness (as a minimum: the evidence supporting the measure), and feasibility (as a minimum: clarity of definition and measurability) when deciding on the most appropriate quality indicators [14]. In this case, relevance and feasibility played a central role, more so than scientific soundness, given the low evidence supporting many of the included guideline recommendations [43]; however, levels of evidence were considered by participants during all stages of development. While we had a high level of participation, and good representation, during each stage, all members of the RRAG could not attend all meetings and therefore were unable to participate in some discussions which may have influenced their interpretation and rating of some of the recommendations, outcomes and/or KPIs. All members did receive emails and supporting documentation before and after meetings however, and had opportunity to contribute to discussions. Finally, our KPIs were developed based on a systematic review of clinical guidelines for recurrent miscarriage within high income countries, given the large discrepancies in pregnancy outcomes and care structures between high, low and middle-income countries [46, 47] and variation in country-specific models of recurrent miscarriage according to healthcare system structures and resources [2]. Further work would be needed to assess the suitability of the KPIs for such contexts, including any potential adaptations, and subsequent measure appraisal. Insights into our processes and experiences of developing guideline-based KPIs for recurrent miscarriage care with a diverse stakeholder group certainly have global relevance and could be use within low and middle income countries to guide similar efforts.

Deviations from protocol

The main deviations from the original protocol included: (i) additional consensus meetings, given the volume of recommendations extracted and the extra time required for discussion and voting for consensus-building, and (ii) an extra stage, encompassing a final survey to before—instead of during—the final meeting to review, develop and achieve consensus on the final suite of KPIs given the volume of indicators to be assessed.

Conclusions

From an initial list of 373 recommendations and 14 outcomes, 110 KPIs across the following five categories, were prioritised for inclusion in a suite of guideline-based KPIs for recurrent miscarriage care: (i) structure of care (n = 20); (ii) counselling and supportive care (n = 7); (iii) investigations (n = 30); treatment (n = 34); outcomes (n = 19). The identified KPIs will now be used to assess the quality of recurrent miscarriage care provided in all 19 maternity hospitals/units in the Republic of Ireland; they will be pilot tested at one site prior to administration across all sites. Data and KPIs generated through the various stages will also contribute to the development of a national clinical practice guideline for recurrent miscarriage care. It is important, and feasible, to develop guideline-based KPIs with a diverse stakeholder group, including those with lived experience of recurrent miscarriage. Insights into our process experiences may also help others undertaking similar projects to develop guideline-based KPIs, particularly those undertaken in the absence of a clinical guideline, and/or which involve a range of stakeholders.

Abbreviations

AGREE II: Appraisal of Guidelines for Research and Evaluation; KPI: Key performance Indicator; RRAG: RE:CURRENT Research Advisory Group.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40900-022-00355-9.

Additional file 1. GRIPP2-SF Reporting Checklist.

Additional file 2. Sample Item, Delphi survey—Round 1.

Additional file 3. Sample Item, Delphi survey—Round 2.

Additional file 4. Sample Item, Consensus meetings.

Additional file 5. Sample Item, Final survey.

Additional file 6. Overview of Item rating during e-Delphi survey, by stakeholder category, recommendation/outcome category and round.

Additional file 7. List of KPIs not retained.

Additional file 8. Overview of Item rating during final survey, by stakeholder category, KPI category.

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Author contributions
MH, SM, DD, KOD: study conception and design. SM, DD, KOD: funding acquisition. MH: conduct of searches and data extraction. RD: data checks. MH, SM, LL: AGREE II assessments. MH, LL, RD, DD, RR, SM, KOD: data analysis and interpretation. KOD, SM: supervision. MH: drafting the manuscript. MH, LL, RD, DD, RR, SM, KOD: revising the manuscript critically for intellectual content and approval of the final version. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Ethical approval was not required for this project as it was an involvement activity with members of the RRAG to generate indicators that would be used within a service evaluation [26, 27]; this was confirmed by the Clinical Research Ethics Committee of the Cork Teaching Hospitals (Personal Communication 29/09/2020).

Consent for publication
Participants provided written, informed consent regarding publishing their data, including their names, within this manuscript.

Competing interests
KOD was involved in the development of, and is National Lead within Ireland for implementing the National Standards for Bereavement Care following Pregnancy Loss and Perinatal Death (Health Service Executive, 2016) from which KPIs were developed. None of the other authors has any competing interests to declare.

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Supplementary File 4.1 – Unadjusted Multinomial Regression Analysis Maternal Characteristics vs Reproductive Outcome

Variable	Reproductive Outcome			
	Live birth [a] (n =359)		Pregnancy Loss[a] (n=208)	
Age Category	RRR (95% CI)	p-value	RRR (95% CI)	p-value
<29	2.213 (1.19-4.103)	0.012	0.955 (0.48-1.9)	0.895
30-34	4.598 (2.614-8.088)	<0.01	2.25 (1.248-4057)	0.007
35-39	2.593 (1.644-4.09)	<0.01	1.063 (0.655-1.726)	0.803
>40	1[b]			
Previous Livebirth				
Yes	1		1	
No	1.012 (0.703-1.458)	0.947	1.138(0.76-1.706)	0.53
Medical history				
Yes	0.654 (0.441-0.97)	0.035	0.743 (0.48-1.15)	0.182
No	1		1	
Gynaecological condition				
Yes	0.517 (0.257-1.041)	0.065	0.712 (0.337-1.505)	0.374
No	1		1	
Gynaecological Procedure				
Yes	1		1	
No	0.714 (0.457-1.115)	0.139	0.594(0.418-1.151)	0.157
BMI				
<25	(0.549-2.205)	0.787	1.038 (0.479-2.25)	0.924
>25	1			

Smoker	0.461 (0.265-0.803)	0.006	0.469(0.249-0.887)	0.02
Yes	1		1	
No				
Fertility History				
Yes	0.61 (0.39-0.954)	0.03	0.754 (0.462-123)	0.258
No	1		1	
ART History				
Yes	(0.6-2.312)	0.634	(0.719-3.02)	0.289
No	1		1	
Factor V Leiden				
Mutation Present	(0.482-2.427)	0.85	0.546 (0.19-1.566)	0.26
Mutation Absent	1		1	
Anti-Cardiolipin Antibodies				
Present	(0.351-24.614)	0.32	(0.381-31.070)	0.271
Absent	1		1	
All autoantibodies				
1 or more present	(0.621-1.831)	0.816	0.9 (0.486-1.669)	0.738
No antibodies	1		1	
HbA1c				
Elevated	0.319 (0.053-1.928)	0.213	0.553 (0.091-3.347)	0.519
Not elevated	1		1	
Thyroid function tests				
Abnormal	0.685 (0.371-1.265)	0.227	0.452 (0.209-0.978)	0.044
Normal	1		1	

Previous Fetal karyotype				
Aneuploid	(0.957-7.344)	0.061	(0.403-3.002)	0.852
Euploid	1		1	
Parental Karyotype				
Balanced translocation present	0.479 (0.213-1.074)	0.074	0.187 (0.052-0.673)	0.01
Normal karyotype	1		1	
Pelvic US				
Finding on US	(0.514-2.557)	0.739	(0.611-3.361)	0.407
No finding	1		1	
Any positive investigation finding	0.945 (0.657-1.36)	0.76	0.859 (0.572-1.29)	0.465
Yes	1		1	
No				
Prescribed Aspirin	(0.421-2.686)			
Yes	1	0.897	0.965 (0.352-2.648)	0.945
No			1	
Prescribed Folic Acid 5mg				
Yes	0.866 (0.565-1.327)	0.508	(0.719-1.907)	0.526
No	1		1	
Prescribed Progesterone				
Yes	(0.699-1.468)	0.945	(1.132-2.603)	0.011
No	1		1	
Prescribed LMWH				
Yes	0.775 (0.504-1.192)	0.246	(0.654-1.671)	0.852

No	1		1	
Prescribed Prednisolone				
Yes	(0.45-4.459)	0.552	(0.709-7.259)	0.168
No	1		1	
Prescribed Metformin				
Yes	0.576 (0.153-2.175)	0.416	0.594 (0.131-2.693)	0.499
No	1		1	
[a]Reference category: no pregnancy; [b]1 denotes reference category				

Supplementary File 4.2 – Maternal Characteristics versus Pregnancy Outcome

Maternal Characteristic (n, %)	Livebirth n (%) (N=359)	Pregnancy Loss (N=208)	p-value
Maternal age			
≤29	45 (68.2)	21 (31.8)	
30-34	102 (65.4)	54 (34.6)	
35-39	151 (69.3)	67 (30.7)	
≥40	61 (48.0)	66 (52.0)	<0.001
Previous Livebirth			
Yes	202 (64.5)	111 (35.5)	
No	157 (61.8)	97 (38.2)	0.953
Medical history			
Yes	95 (61.3)	60 (38.7)	
No	259 (64.3)	144 (35.7)	0.513
Smoker			
Yes	35 (63.6)	20 (36.4)	
No	212 (64)	119 (36)	0.953
Fertility History			
Yes	58 (59.2)	40 (40.8)	
No	301 (64.2)	168 (35.8)	0.351
Thyroid function tests			
Normal	329 (62.7)	196 (37.3)	
Abnormal	28 (71.8)	11 (28.2)	0.254
Parental Karyotype			
Balanced translocation present	13 (81.2)	3 (18.8)	
Normal karyotype	326 (62.8)	193 (37.2)	0.132

Supplementary File 4.3 - Maternal Characteristics vs Smokers and Parental Karyotype

Maternal Characteristic (n, %)	Smoker	Non-smoker	p-value
Maternal age			
≤29	25 (41.7)	35 (58.3)	
30-34	20 (15.9)	106 (84.1)	
35-39	25 (12.6)	174 (87.4)	
≥40	15 (12.9)	101 (87.1)	<0.001
Previous Livebirth			
Yes	42 (49.4)	247 (59.4)	
No	43 (50.6)	169 (40.6)	0.09
Medical history			
Yes	29 (35.4)	290 (70.6)	
No	53 (64.6)	121 (29.4)	0.177
Gynae history			
Yes	5 (6.1)	34 (8.2)	
No	77 (93.9)	380 (91.8)	0.287
Fertility History			
Yes	12(14.1)	93 (22.4)	
No	73 (85.9)	323 (77.6)	0.089
BMI			
≤25	9 (37.5)	49 (19.8)	
>25	15 (62.5)	199 (80.2)	0.043
Maternal Characteristic (n, %)	Balanced translocation present	Normal karyotype	p-value
Maternal age			
≤29	2 (2.4)	83 (97.6)	
30-34	5 (2.8)	171 (97.2)	
35-39	3 (16)	241 (93.8)	
≥40	5 (2.8)	174 (97.2)	0.159
Previous Livebirth			
Yes	15 (53.6)	308 (46.0)	
No	13 (46.4)	361 (54.0)	0.434
Medical history			
Yes	7 (25.9)	202 (30.9)	
No	20 (74.1)	452 (69.1)	0.584
Gynae history			
Yes	2 (7.1)	44 (6.8)	
No	26 (92.9)	605 (93.2)	0.940
Fertility History			
Yes	7 (25)	126 (18.8)	
No	21 (75)	543 (81.2)	0.416
BMI			
≤25	2 (28.6)	63 (24.4)	
>25	5 (71.4)	195 (75.6)	0.801
Smoker			
Yes	1 (5.6)	81 (17.8)	
No	17 (94.4)	373 (82.8)	0.177

Supplementary File 5.1 – Service Evaluation Survey

Section 9: Women/couples with fertility issues and recurrent miscarriage

In this section, we are interested in the care you provide to women with a history of infertility (>18 months trying to conceive/>12months and aged over 35 years) or women with known fertility issues conceiving with ART **and** experiencing recurrent miscarriage

Structure of Care

1. How many women and men experiencing recurrent miscarriage (RM) after infertility would present to your clinic annually? Insert no.

If you work in the Health Service

2. Is there a fertility consultant available in the RPL clinic to consult on cases where women have experienced RM after infertility? Yes / No / Don't know
3. If the required fertility consultant is not available, to whom are referrals made? _____
4. Has your hospital access to infertility counselling services? Yes / No / Don't know

If you work in the Private Obstetrics and Gynaecology/Fertility Sector

1. Is there an Obstetrician with training in management of RM available in the fertility clinic? Yes, this is me / Yes, a colleague of mine / No / Don't know
2. If the required specialist is not available, to whom are referrals made? _____
3. When would a referral be made to a RM clinic/specialist? Please answer for each option
    a. 2 or more consecutive pregnancy losses: Yes / No / Don't know
    b. 2 or more non-consecutive pregnancy losses: Yes / No / Don't know
    c. 3 or more consecutive pregnancy losses: Yes / No / Don't know
    d. 3 or more non-consecutive pregnancy losses: Yes / No / Don't know
    e. Criteria varies based on female age: Yes / No / Don't know
    f. Criteria varies based on ART employed e.g., 2 consecutive losses with ICSI. Yes / No / Don't know

Please explain any variances here: _____

1. Has your clinic (RM or fertility) access to a counsellor that is trained in pregnancy-related bereavement? Yes / No / Don't know

Counselling and Supportive Care

1. If a woman/couple experiences RM after infertility, do you counsel about the following, where applicable:
   a) Age-related miscarriage risk (Yes / No)
   b) Age-related aneuploidy risk (Yes / No)
   c) Tests of ovarian reserve (Yes / No)
   d) Pre-implantation Genetic Testing for Aneuploidy (PGT-A) (Yes / No)
   e) Intra-Cytoplasmic Sperm Injection (Yes / No)
   f) Egg donation (Yes / No)
   g) Semen analysis (Yes / No)
   h) Sperm DNA Fragmentation (Yes / No)
   i) Sperm donation (Yes / No)
   j) Surrogacy (Yes / No)
   k) Adoption (Yes / No)
   l) Other: Please specify _____
2. Where do you obtain guidance on managing women with RM and infertility? _____
3. What additional resources do you employ to aid counselling this cohort? (E.g., websites, written information, support groups) _____

Investigations

1. Would you undertake the following blood investigations routinely in women with infertility and RM? Please tick one option only per row	**Yes**	**No**	**If indicated by history only**
a. Antiphospholipid antibodies			
b. Thrombophilia screen			
c. Thyroid peroxidase antibodies			
d. Androgen testing (serum testosterone/SHBG level			
e. Auto-immune screen			
f. Anti-nuclear antibodies			
Additional comments			

(assuming standard baseline fertility investigations have been performed – FBC/U+E/LFTS/Prolactin/HbA1c/TSH/T4/day 2 FSH/LH/Day 21 progesterone/pelvic US/AMH/male partner semen analysis/HSG)

2. Would you undertake the following immune tests routinely? in women with infertility and RM? Please tick one option only per row	**Yes**	**No**	**If indicated by history only**
a. HLA antibodies			
b. Cytokines			
c. Anti-HY antibodies			
d. Natural killer cells			
Additional comments			

1. Would you perform any further imaging in addition to the pelvic US mentioned above? Yes / No
   If yes, please specify the type of imaging you might perform:
3. Would you perform a hysteroscopy in a woman with infertility presenting with RM? Yes / No
4. Would you perform a laparoscopy and dye test in a woman with infertility presenting with RM? Yes / No
5. Would you offer myomectomy in a woman with infertility and RM and corresponding fibroids? Yes / No
6. Would you offer metroplasty to a woman with infertility and RM and a uterine malformation? Yes / No
7. Would you offer hysteroscopic adhesiolysis in a woman with infertility and RM and intra-uterine adhesions? Yes / No
8. Would you perform an endometrial scratch in a woman with RM and infertility? Yes / No
9. If yes, would you test for

   a. chronic endometritis Y/N
   b. uterine Natural Killer cells Y/N
   c.

10. Would you treat chronic endometritis with doxycycline? Y/N

11. I)Would you screen for other infections with a high vaginal swab? Y/N
    II)Please name any specific infections for which you would screen.

12. Would you offer antibiotic treatment should a named infection as per 11 II) be found ?

13. If you cannot provide the surgical procedures offered in q7-12, would you refer women elsewhere for such procedures? Y/N

    If yes, to whom would you refer?

14. Would you request the following investigations on male partners?
    a. Spermploidy Yes / No
    b. Sperm DNA fragmentation Yes / No

Treatment

	Yes	**No**	**In specific circumstances (please specify)**
1. Would you recommend any of the following in women with RM and infertility? Please tick one option only per row			
a. ICSI			
b. PGT-A			
c. IVIG			
d. Intralipid therapy			
e. Other immune therapy			
f. Other IVF add on			
2. In a subsequent pregnancy would you give any of the following to a woman presenting with RM and unexplained infertility? Please tick one option only per row	Yes	No	In certain circumstances (please specify)
a. Aspirin			
b. LMWH			
c. Prednisolone			

d.	**Hydroxychloroquine**
e.	**Progesterone**
f.	**Metformin**

3. Do you record or audit pregnancy outcomes in women with RM and infertility?
   Yes / No

Thank you for taking the time to complete this survey

If you have any questions about this study please contact Marita Hennessy (maritahennessy@ucc.ie) or Dr Laura Linehan (laura.linehan@ucc.ie).

Supplementary File 6.1 - Structure of Care Key Performance Indicators

Structure of Care Key Performance Indicators (n=2)	Denominator	Adherent	N	%
Is there a dedicated RM Clinic on-site?*	1	Yes	1	100
Does the dedicated RM clinic team comprise consultant(s) and specialist nurse(s)/midwife (ves) in bereavement and loss?	1	Yes	1	100
Does the RM clinic have access to psychologists/social workers/counsellors/psychotherapists) either onsite or elsewhere, who can offer support tailored to the psychological needs of the couples	1	Yes	1	100
Does the RM clinic have access to staff education and training programmes, addressing how to best care for women/couples who experience RM/bereavement and loss?	1	Yes	1	100
Does the RM clinic conduct an annual care experience survey of their RM service?	1	Yes	1	100
Is the RM clinic separate from the antenatal clinic, antenatal ward or other antenatal areas where pregnant women may be seen/attend?	1	Yes	1	100
Does the RM clinic have access to (onsite/external) the appropriate laboratories for genetics, biochemistry and haematology testing?	1	Yes	1	100
Does the RM clinic have a formal referral process (i.e. proforma) for RM?	1	Yes	1	100
Does the clinic have referral criteria for RM?	1	Yes	1	100
Do the referral criteria for RM include the following 3 criteria: (i) All women with three or more consecutive pregnancy losses; (ii) All women with a history of pregnancy loss and an associated condition such as antiphospholipid syndrome, polycystic ovary syndrome (PCOS), chronic medical disorder; (iii) All women over 35 years old with two or more pregnancy losses	1	Yes	1	100

Does the RM clinic provide education/information for health professionals (within hospital/GPs) about their referral criteria?	1	Yes	1	100
Does the RM clinic record/report their referral sources?	1	Yes	0	0
Does the RM record/report their referral times (i.e., time from referral to clinic to first appointment)?	1	Yes	0	0
Does the RM clinic investigate women/couples after they have experienced two consecutive clinical pregnancy losses?	1	Yes	1	100
Does the RM clinic provide written information for women/couples about what to expect, in advance of the first visit/appointment?	1	Yes	0	0
Does the clinic provide written information for women/couples about sources of support, from reputable sources? This should include (i) bereavement services within the hospital, (ii) hospital and community / voluntary sector resources	1	Yes	1	100
Does the clinic provide written information for women/couples about RM, from reputable sources?	1	Yes	1	100

Supplementary file 6.2 - Adapted Key Performance Indicators

Structure of Care	
Percentage of dedicated RM/pregnancy loss/gynaecology clinics which provide each individual/couple with a tailored investigation plan, including timelines	Did the couple receive a tailored investigation plan for investigations?
Percentage of dedicated RM/pregnancy loss/gynaecology clinics which provide each individual/couple with a tailored management plan for any immediate treatment and future pregnancy	Did the couple receive a tailored management plan for any treatment and future pregnancy?
Counselling and Supportive Care	
Percentage of dedicated RM/pregnancy loss/gynaecology clinics which provide information to women/couples regarding changes to behavioural/weight-related risk factors as relevant, including; smoking cessation, weight management, healthy eating and physical activity (normal exercise pattern; not excessive), reducing alcohol and drug consumption, and folic acid and vitamin D supplementation	I. Did the RM clinic provide information to women/couples regarding changes on any of the following behavioural/weight-related risk factors as relevant; smoking cessation, weight management, healthy eating and physical activity (normal exercise pattern; not excessive), reducing alcohol and drug consumption? II. Did the RM clinic provide information on a) folic acid and b) vitamin D supplementation?
Percentage of dedicated RM/pregnancy loss/gynaecology clinics which provide information to women/couples about investigations and treatments that are not supported by quality medical research. For example, cytokine testing, HLA determination, anti-HY antibody testing, monitoring of plasma coagulation markers, or treatments involving, for example, human chorionic gonadotrophin, granulocyte colony-stimulating factor (G-CSF), intralipid	Did the RM clinic provide information to women/couples about unorthodox investigations and treatments that are not supported by quality medical research?

therapy, lymphocyte immunisation therapy, antioxidants, antibiotics	
Percentage of dedicated RM/pregnancy loss/gynaecology clinics which offer/provide access to genetic counselling to all individuals and couples with an abnormal parental karyotype result, and a proportion of those with an abnormal fetal karyotype	I. Did the RM clinic offer/provide access to genetic counselling to all individuals and couples with an abnormal parental karyotype result? II. Did the RM clinic offer/provide access to genetic counselling to individuals and couples with an abnormal fetal karyotype result?
Investigations	
Percentage of dedicated RM/pregnancy loss/gynaecology clinics which offer and provide/make available assessment of uterine anatomy	Did the woman undergo assessment of uterine anatomy?
Percentage of dedicated RM/pregnancy loss/gynaecology clinics in which uterine anatomy is assessed using transvaginal ultrasound	Was uterine anatomy assessed using transvaginal ultrasound?
Percentage of dedicated RM/pregnancy loss/gynaecology clinics with access to 3D ultrasound	Was a 3D ultrasound performed?
Percentage of dedicated RM/pregnancy loss/gynaecology clinics in which imaging or imaging with hysteroscopy is used to diagnose uterine septa rather than laparoscopy with hysteroscopy	Did women with a uterine septum undergo a hysteroscopy?
Percentage of dedicated RM/pregnancy loss/gynaecology clinics in which routine screening for hereditary thrombophilia is undertaken in women with RM Percentage of dedicated RM/pregnancy loss/gynaecology clinics in which screening for hereditary thrombophilia is only undertaken in the context of research, or in women with additional	Was screening for hereditary thrombophilia undertaken in women with RM?

risk factors for thrombophilia (such as a family history of hereditary thrombophilia or a history of venous thromboembolism)	
Percentage of dedicated RM/pregnancy loss/gynaecology clinics in which routine screening for antiphospholipid syndrome, based on clinical and laboratory parameters, is undertaken in women with RM Percentage of dedicated RM/pregnancy loss/gynaecology clinics in which screening for antiphospholipid syndrome is only undertaken if clinical manifestations are present (e.g. livedo reticularis, ulcerations, renal microangiopathies, neurological disorders and cardiac manifestations)	Was screening for antiphospholipid syndrome undertaken in women with RM?
Treatments	
Percentage of dedicated RM/pregnancy loss/gynaecology clinics which offer low molecular weight heparin (LMWH) or low dose aspirin in women with unexplained RM	Was low dose aspirin prescribed for women with unexplained RM (i.e. without thrombophilia)? Did women with unexplained RM and Infertility (i.e. without thrombophilia) receive prescriptions for LMWH?
Outcomes	
Percentage of dedicated RM/pregnancy loss/gynaecology clinics which record/report the number of women with RM who achieve a new pregnancy with IVF and IntraCytoplasmic Sperm Injection (ICSI) with donor gametes?	Did the woman/couple achieve a new pregnancy with IVF and/or IntraCytoplasmic Sperm Injection (ICSI)? Did the woman/couple require donor gametes to achieve a new pregnancy?
Percentage of dedicated RM/pregnancy loss/gynaecology clinics which record/report the number of women with RM who become pregnant again and do not have a first trimester miscarriage	Did the woman/couple experience a subsequent first trimester miscarriage?

Percentage of dedicated RM/pregnancy loss/gynaecology clinics which record/report the number of women with RM who become pregnant again and do not have a second trimester miscarriage	Did the woman/couple experience a subsequent second trimester miscarriage?
Additional KPI added to record ectopic pregnancy as an outcome	Did the woman experience a subsequent ectopic pregnancy
Percentage of dedicated RM/pregnancy loss/gynaecology clinics which record/report the number of women with RM who become pregnant again and do not experience fetal growth restriction	Did the woman develop fetal growth restriction in a subsequent pregnancy?
Percentage of dedicated RM/pregnancy loss/gynaecology clinics which record/report the number of women with RM who become pregnant again and do not experience placental abruption	Did the woman experience a placental abruption in a subsequent pregnancy?
Percentage of dedicated RM/pregnancy loss/gynaecology clinics which record/report the number of women with RM who become pregnant again and do not experience pre-eclampsia	Did the woman develop pre-eclampsia in a subsequent pregnancy?
Percentage of dedicated RM/pregnancy loss/gynaecology clinics which record/report the number of women with RM who become pregnant again and whose baby is born at ≥37 weeks' gestation	Did the women experience a preterm birth in a subsequent pregnancy?
Percentage of dedicated RM/pregnancy loss/gynaecology clinics which record/report the number of women with RM who become pregnant again and do not experience stillbirth (defined as: child born having a gestational age of 24 weeks or more and/or weighing 500g or more who shows no signs of life)	Did the woman experience a stillbirth in a subsequent pregnancy?
Percentage of dedicated RM/pregnancy loss/gynaecology clinics which	Did the woman/couple experience a neonatal death?

record/report the number of women with RM who become pregnant again and do not experience neonatal death (defined as: death of a live born baby occurring within 28 completed days of birth)	

Supplementary file 7.1 – Topic guides

Service Users Topic Guide

- Make sure that the participant is clear about what to expect and can ask questions
- Remind participant about the purpose of the study, that participation is voluntary and they are free to withdraw at any time from the interview or the study as a whole
- Ensure that written/electronic consent has been given
- Seek oral consent to commence voice recording
- Ensure that Miscrosoft Teams security features are enabled and lobby is enabled before commencing interview
- Ensure that you have a contact number for the participant and advise that you will call to complete interview by phone if connection breaks down
- If the participant becomes upset during the interview offer to pause and/or stop the interview. If necessary, suggest that the participant contact a family member or friend for support. Advise that they can also contact the Bereavement Midwife at their local hospital or the Miscarriage Association of Ireland. Let them know that you will call to check-in in 24 hours.
- Suggested probes are outlined below. These should be utilised where appropriate and only if needed to promote discussion. You do not need to ask all questions, be guided by the participant

Background/Contextual Information (can be collected in course of interview if more appropriate)

- Can you tell me a little bit about yourself-age/relationship status/children/profession
- Can you tell me a about your pregnancies and your experience with fertility/fertility services?
- Can you tell me about the number of losses that you have experienced and when? -number of losses/order of losses/weeks gestation

Expectations and Experience of Pregnancy before infertility and pregnancy loss

- What were your expectations for pregnancy before dealing with infertility?
- How did miscarriage affect these expectations?

- Can you tell me about your experience of pregnancy before miscarriage/before infertility (if secondary)?

Experience of Infertility

- Did you undergo investigations for infertility?
    - Who did you attend to start this process?
    - Can you talk me through the investigations you had? (who/when/what/where/referrals/time taken?)
    - second opinion sought?
- What were your expectations on investigating infertility?
- Did you receive any treatments for infertility? (again who/when/what/where/referrals/time taken?)
- What were your expectations for future pregnancy after undergoing investigations/treatment for infertility?
- Plans for future pregnancy?
- Overall experience of fertility services – service structures/efficiency/attendance with/without partner(inclusivity)

Experience and Management of Recurrent Miscarriage (two or more miscarriages)

- What were your expectations of care after experiencing multiple miscarriages (two or more)?
- Did you enquire about investigating the miscarriages at any point or did anyone talk to you about investigating the miscarriages? (After how many losses was this discussed/what were you advised/management of miscarriage-conservative, medical, surgical)
- *If offered investigations and follow-up*-Can you take me through the care you received and how this came about?
    - Did you opt for public or private care? Why?
    - Was this at the same location where infertility investigations happened?
    - Did you get a referral, from who, to where and for what? How was this communicated?
    - What were you asked to do?
    - What did you hope to get out of the appointment?
    - How long were you waiting for appointments?
    - Where did you have to go? (phlebotomy clinic, gynae ward, etc.)
    - Did anyone go with you?
    - Who did you meet? (consultant, midwife, SPR, nurse)
    - What was discussed? Did you receive results? Was treatment or a plan of care discussed? How did you feel about this?

    - How did you feel about the appointment and any plan that was discussed? (ask about space/environment if not mentioned)
    - Was your fertility history discussed? Was it factored into investigations and treatments for RM?
    - Did anyone speak to you about future pregnancies? (Who/what information/advice was provided/were you satisfied with the information/advice)?
- *If not offered/refused investigations and follow-up*-Can you tell me about the reasoning that was given-if any, how did you feel about this? Were you given any other advice at this point?
- Did you at any point consider or seek a second opinion (or private care)? If so, who and why? Can you tell me about this?

Subsequent Pregnancy

- Can you tell me about your experience of pregnancy after a previous loss and infertility? What were your expectations? How did you feel?
- Can you tell me about the care received in your pregnancies after loss? (GP/hospital/fertility clinic/public or private care/Reassurance scan/clinic)
- If a treatment plan was put in place for this pregnancy, did you know what to do, where to go?
- Were you offered or did you avail of any support in subsequent pregnancy(ies)?

(formal/informal)

If no subsequent pregnancy (and willing to discuss)

- If you feel able, could we discuss where you are now with trying to conceive?
- If seeking to conceive, what will this entail in terms of further ART? Feelings and expectations around this?
- If not TTC, was this a conscious decision? Other fertility factor contributing to this?
- If a decision from the couple, what factors brought you to this decision? Did any factors in your care lead to this choice? Were there any factors in your care that if changed/improved would have led you to consider trying again? (ie cost/availability of certain treatments)?

Knowledge and Understanding

- Before experiencing miscarriage and infertility, did you feel like you knew enough about pregnancy, fertility, pregnancy loss? Where did you get this information? What would you liked to have known? Would you do anything different, given your experience / what do you know now?

- Did you feel like you were informed enough about the care you received for infertility and miscarriage/recurrent miscarriage? (investigations, treatment, subsequent pregnancy plan)
- What kind of information was provided (what format) and was this useful? -were these useful? What would you liked to have known?
- Did you seek information elsewhere? (professional/family/friends/support organisations/internet)? Did you speak to any of your care providers about this?

Impact

- In your experience, what has been the impact of infertility and recurrent miscarriage on you and your family? (self/partner/children/wider family-work, social, mental and physical health/financial)

Support Received or Sought

- Did you feel that you needed support at that time?
- Can you tell me about any support offered to you or your partner?
- Did you avail of any supports? (hospital/GP/private counselling/support organisation/family/friends). How did you hear about these supports and what encouraged you to attend? What happened? Did this meet your needs at the time?

Experience/Recommendations

- Reflecting on the care you have received for recurrent miscarriage after an experience of infertility-what are you overall thoughts about your experience?
- What do you think have been the positives-what worked well?
- What are the negatives, is there anything that did not work so well?
- What would you like to have happened?
- Is there anything that health professionals could/should have done differently?
- Is there anything that you would do differently?
- Do you have any recommendations to improve the care and support for those who experience recurrent miscarriage?

Is there anything that I haven't touched on that you feel is important to mention? Do you have anything else to add or is there anything that you feel hasn't been discussed?

Service Provider Topic Guide

- ❖ Remind participant about the purpose of the study, that participation is voluntary and they are free to withdraw at any time from the interview or from the study as a whole
- ❖ Make sure that the participant is clear about what to expect and has the opportunity to ask questions
- ❖ Ensure that consent has been given (written/electronically)
- ❖ Confirm consent verbally before commencing recording
- ❖ Suggested probes are outlined below, to be utilised where appropriate and only if needed to promote discussion.

Roles and Responsibilities

- Can you tell me about your current role? How long have you been in this position?
- Can you tell me about your role(s)/experience(s) in relation to miscarriage/recurrent miscarriage?
- Can you tell me about your role(s) /experience(s) in relation to infertility care?
- Have you received any specific training to support the provision of care to those who experience recurrent miscarriage/infertility/both?
- If you do not have a direct role in providing care for those with recurrent miscarriage and infertility, do you see a potential role for you/your profession and what might this look like?

Structure of Care

- What informs current practice in relation to recurrent miscarriage and infertility in your area? (evidence, local/national guidelines, professionals)
- Who is involved in the decision-making/organisation/co-ordination of recurrent miscarriage care when women/couples have a history of infertility?
- Where are investigations undertaken for women/couples with RM and infertility?
- Who is responsible for following these investigations and imparting results to women/couples?
- Do women/couples with infertility and RM require referrals for investigations or treatments often? Are these within the hospital/clinic?
- Is there continuity of care in a subsequent pregnancy?

Management of Recurrent Miscarriage and Infertility (diagnosis, investigation, treatment, management)

- Can you tell me about the current management of recurrent miscarriage when the woman/couple have a history of infertility?
- When women/couples experience RM after infertility, are there any differences in how it is diagnosed compared to others without a fertility history? Eg, where, when and by whom?
- What happens following a diagnosis of recurrent miscarriage in women/couples with infertility (procedure/pathway/timelines)? Does this differ to those without infertility? Are there any other factors in these differences? (public vs private/age/number of losses/ART)
- Can you tell me about information/advice provided, if any? Is the information provided appropriate/sufficient?
- Can you tell me about the investigations offered, if any? Who is involved in the decision-making about investigations? Where do these investigations take place? What is the procedure for investigation and follow-up?
- What happens if investigations are inconclusive?
- Can you tell me about the treatment (for fertility issues and RM) options available? Who is involved in the decision-making about treatment? Where is treatment provided and who is responsible for overseeing treatment?
- In your experience, what are the outcomes for couples following investigation and treatment? (Sustained pregnancy/further loss)
- What happens in the case of a further pregnancy loss?
- Do you (or the clinical lead) discuss the likelihood of pregnancy success based on the woman/couple's fertility and miscarriage history? What factors are considered in this assessment? (age/no of losses/specific infertility diagnosis/treatments to date?)
- At what point are treatment options such as PGT-A/donor egg/sperm/surrogacy/adoption discussed?

Impact and Support

- In your opinion, what is the impact of recurrent miscarriage with an infertility history on those affected? (Women, men, children, extended family)?
- In your opinion, how do couples experience pregnancy after loss and infertility?

- In your opinion, how does current care (the diagnosis, investigation and treatment process) impact those who experience recurrent miscarriage and infertility? (the process/the system)
- In your opinion, what are the support needs of women and men experiencing recurrent miscarriage and infertility? Do these differ by case/demographic/care pathway? In your opinion, are these needs being met? If not, what is needed to improve this?
- How does the current system impact you and/or other health professionals? What is it like to provide care in this context?

Knowledge and Understanding

- In your opinion, do couples have adequate understanding of infertility and recurrent miscarriage (the condition, the impact, investigations, treatments, outcomes)? if not, why is this the case and what could be done to improve this?
- What information is provided in the maternity unit regarding diagnosis, investigation, treatment, outcomes, future pregnancies, available supports?
- In your experience, is this information sufficient?
- Do women and men look for information and advice elsewhere about recurrent miscarriage and infertility? Where do they look? Does this differ by demographic? What is the impact?

Recommendations

- What are the factors that make it easier to care for those who experience recurrent miscarriage with a history of infertility? What works well? Can you provide examples of good practice?
- Are there any barriers to providing care for those who experience recurrent miscarriage and infertility?
- Is there anything you would do differently?
- What would ideal care for women/couples with infertility and recurrent miscarriage look like in your opinion?
- What is needed to achieve this?

Supplementary file 7.2 - Standards for Reporting Qualitative Research (SRQR)

Title and abstract	
Title - Concise description of the nature and topic of the study Identifying the study as qualitative or indicating the approach (e.g., ethnography, grounded theory) or data collection methods (e.g., interview, focus group) is recommended	1
Abstract - Summary of key elements of the study using the abstract format of the intended publication; typically includes background, purpose, methods, results, and conclusions	1
Introduction	
Problem formulation - Description and significance of the problem/phenomenon studied; review of relevant theory and empirical work; problem statement	introduction
Purpose or research question - Purpose of the study and specific objectives or questions	End of introduction
Methods	
Qualitative approach and research paradigm - Qualitative approach (e.g., ethnography, grounded theory, case study, phenomenology, narrative research) and guiding theory if appropriate; identifying the research paradigm (e.g., postpositivist, constructivist/ interpretivist) is also recommended; rationale**	Methods , Study design

Researcher characteristics and reflexivity - Researchers' characteristics that may influence the research, including personal attributes, qualifications/experience, relationship with participants, assumptions, and/or presuppositions; potential or actual interaction between researchers' characteristics and the research questions, approach, methods, results, and/or transferability	Methods, reflexive statement
Context - Setting/site and salient contextual factors; rationale**	Methods, setting
Sampling strategy - How and why research participants, documents, or events were selected; criteria for deciding when no further sampling was necessary (e.g., sampling saturation); rationale**	Methods, Sampling
Ethical issues pertaining to human subjects - Documentation of approval by an appropriate ethics review board and participant consent, or explanation for lack thereof; other confidentiality and data security issues	Methods, ethical considerations
Data collection methods - Types of data collected; details of data collection procedures including (as appropriate) start and stop dates of data collection and analysis, iterative process, triangulation of sources/methods, and modification of procedures in response to evolving study findings; rationale**	Methods, data collection
Data collection instruments and technologies - Description of instruments (e.g., interview guides, questionnaires) and devices (e.g., audio recorders) used for data collection; if/how the instrument(s) changed over the course of the study	

Units of study - Number and relevant characteristics of participants, documents, or events included in the study; level of participation (could be reported in results)	Results
Data processing - Methods for processing data prior to and during analysis, including transcription, data entry, data management and security, verification of data integrity, data coding, and anonymization/de-identification of excerpts	Methods, Data collection
Data analysis - Process by which inferences, themes, etc., were identified and developed, including the researchers involved in data analysis; usually references a specific paradigm or approach; rationale**	Methods, data analysis
Techniques to enhance trustworthiness - Techniques to enhance trustworthiness and credibility of data analysis (e.g., member checking, audit trail, triangulation); rationale**	Methods, data collection
Results/findings	
Synthesis and interpretation - Main findings (e.g., interpretations, inferences, and themes); might include development of a theory or model, or integration with prior research or theory	Results
Links to empirical data - Evidence (e.g., quotes, field notes, text excerpts, photographs) to substantiate analytic findings	Results tables
Discussion	

Integration with prior work, implications, transferability, and contribution(s) to the field - Short summary of main findings; explanation of how findings and conclusions connect to, support, elaborate on, or challenge conclusions of earlier scholarship; discussion of scope of application/generalizability; identification of unique contribution(s) to scholarship in a discipline or field	Discussion
Limitations - Trustworthiness and limitations of findings	Strengths and limitations
Other	
Conflicts of interest - Potential sources of influence or perceived influence on study conduct and conclusions; how these were managed	COI statement
Funding - Sources of funding and other support; role of funders in data collection, interpretation, and reporting	Funding statement
*The authors created the SRQR by searching the literature to identify guidelines, reporting standards, and critical appraisal criteria for qualitative research; reviewing the reference lists of retrieved sources; and contacting experts to gain feedback. The SRQR aims to improve the transparency of all aspects of qualitative research by providing clear standards for reporting qualitative research.	

**The rationale should briefly discuss the justification for choosing that theory, approach, method, or technique rather than other options available, the assumptions and limitations implicit in those choices, and how those choices influence study conclusions and transferability. As appropriate, the rationale for several items might be discussed together.

Reference:

O'Brien BC, Harris IB, Beckman TJ, Reed DA, Cook DA. **Standards for reporting qualitative research: a synthesis of recommendations.** *Academic Medicine*, Vol. 89, No. 9 / Sept 2014

DOI: 10.1097/ACM.0000000000000388

Supplementary file 7.3 – Participant information sheets and consent forms

Service Provider Information Sheet

You are being asked to participate in a study called "Exploring stakeholder views and experiences of recurrent miscarriage and infertility services and supports in the Republic of Ireland". In order to decide whether or not you want take part in this research, you should understand enough about its risks and benefits to make an informed judgement. This process is known as informed consent.

Please read this information carefully and discuss it with others if you wish. A researcher will also discuss this information with you. If you decide to take part, you will be asked to give formal consent.

What is the purpose of this study?

The aim of this study is to find out about the care provided to those who experience two or more consecutive miscarriages in the first trimester in addition to experiencing infertility. We would like to learn about the investigation, management and follow-up of recurrent miscarriage with infertility as well the supports that are available. The findings from the research will inform efforts to improve the quality of recurrent miscarriage and infertility care.

Who is conducting this research?

This research is being conducted by Dr Laura Linehan at the INFANT Centre, University College Cork (UCC). Dr Linehan is a member of the Pregnancy Loss Research Group based at Cork University Maternity Hospital (CUMH) and the project is supervised by Marita Hennessy PhD, UCC, and Professor Keelin O' Donoghue, UCC and Consultant Obstetrician and Gynaecologist, CUMH.

What does taking part involve?

You will be asked to take part in a once-off interview with a member of the research team. This will involve an informal conversation about your experience of the services and supports available to those who experience recurrent miscarriage and infertility. The interview will take about one hour and will be held in a way that is agreeable with you such as face-to-face or over a telephone or video call via Microsoft Teams. With your consent, the conversation will be digitally recorded so that we have an accurate record of your thoughts and experiences.

Can I change my mind?

You can withdraw from the study at any time without giving a reason by notifying the research team of your decision.

What are the possible risks and benefits of taking part?

Taking part will give you a chance to share your experience and views of the services and supports available to those who experience recurrent miscarriage and infertility. You may not benefit personally, however, the results of the study will be used to help improve the quality of services and supports provided in Ireland. We don't envisage any negative consequences for you. However, we understand that discussing this subject may cause upset. If this occurs, a member of the research team will provide support and will link you with formal supports if you wish.

What will happen to the information I provide?

UCC is the Data Controller for this project and owns the information collected as part of the study. If you take part, information about you (also called "personal data") will be accessed, collected and stored for the purposes of this study. This personal data includes information that directly identifies you (such as your name, email address and/or postal address), your gender, and information about your occupation. Please be assured that

your personal data will be treated with the strictest of confidence, it will be password protected and stored electronically on secure servers at UCC. A study number will be assigned to your interview data and a list linking your study number to your name will be securely stored separately. Your data will be retained for a minimum of ten years after the completion of the project.

Will this be confidential?

Your participation in this study and any personal information provided will be managed with the strictest of confidence. Every person that has access to your uncoded data is subject to professional secrecy and confidentiality.

What will happen to the results of the study?

We may use quotes from your interview in reporting the results but these will be anonymised so that you cannot be identified. The results will be shared with those involved in the provision of pregnancy loss services. They will also be published in international peer-reviewed journals, shared at research meetings, and conferences and may be used for teaching purposes.

Is this study approved by an ethics committee?

Yes, ethical approval for this study was granted to us by the Clinical Research Ethics Committee of the Cork Teaching Hospitals (CREC). If you have any concerns about this study you may contact CREC on 021-4901901 or crec@ucc.ie.

What are my rights?

You have various rights under data protection law, subject to certain exemptions, in connection with our processing of your personal data, including the right:

- to find out if we use your personal data, access your personal data and receive copies of your personal data
- to have inaccurate/incomplete information corrected and updated
- in certain circumstances, to have your details deleted from systems that we use to process your personal data or have the use of your personal data restricted in certain ways
- to object to certain processing of your data by UCC
- to exercise your right to data portability where applicable (i.e. obtain a copy of your personal data in a commonly used electronic form)
- to withdraw your consent to the processing of your data at any time without giving a reason by notifying your decision to the researcher. This will not affect the lawfulness of processing data about you based on your consent before the withdrawal. If you withdraw your consent for data processing, your participation in the study stops and no further data will be collected from you. A researcher will present you the options you have concerning your personal data.
- Along with study withdrawal, you have the right to request the deletion of data about you if your data are no longer necessary for the purposes of processing or there is no other legal ground for their further processing.

How do I give my consent to participate?

If you agree to take part, you will be asked to provide explicit consent in writing or via email. You will also be asked to verbalise your consent before your interview begins. This is to demonstrate that you have understood what is involved and that you have read the Information Sheet. After you give your consent you still have the right to withdraw from the study at any time.

Who can I contact about this study?

If you have any questions about this study please contact Laura Linehan laura.linehan@ucc.ie or Marita Hennessy maritahennessy@ucc.ie.

If you have any complaints in connection with our processing of your personal data, you can contact UCC's Information Compliance Manager: Information Compliance Manager, Office of Corporate & Legal Affairs, UCC, Western Road, Cork E: foi@ucc.ie Tel: +353 21 4903949

Service Provider Consent Form

Please read the following statements carefully and initial the "yes" or "no" box to indicate your response		Yes	No
1.	I confirm that I have read and understood the information sheet for the study "Exploring stakeholder views and experiences of recurrent miscarriage and infertility services and supports in the Republic of Ireland", received a copy and have had the opportunity to ask questions		
2.	I understand that participation in this study is voluntary and that I am free to withdraw without consequence, at any time, without giving a reason		
3.	I agree to participate in an interview to discuss my experience of recurrent miscarriage and infertility services and supports		
4.	I give permission for my interview to be audio recorded		
5.	I agree to the quotation/publication of anonymised extracts from my interview in reports, presentations and other publications		
6.	I understand that I can request a copy of my personal information at any time by contacting Laura Linehan laura.linehan@ucc.ie or Marita Hennessy maritahennessy@ucc.ie or via 021 4920500		
7.	I understand that confidentially of records concerning my involvement in this project will be maintained in an appropriate manner		
8.	I understand that when required by law the records of this research may be reviewed by government agencies and sponsors of the research		
9.	I understand that I can contact Laura Linehan laura.linehan@ucc.ie or Marita Hennessy maritahennessy@ucc.ie or via 021 4920500 for further information about this study		
10.	I agree to be contacted about this research in the future		
11.	I agree to be contacted about projects related to maternal health and/or maternity services in the future		

I, the undersigned, hereby consent to participate in the project. I have received a copy of this consent form and information sheet for my records. I understand that if I have any questions concerning this research, I can contact the research team. If I have further queries concerning my rights in connection with the research, I can contact the Clinical Research Ethics Committee of the Cork Teaching Hospitals, Lancaster Hall, 6 Little Hanover Street, Cork or on 021-4901901/crec@ucc.ie.

Participant Signature	Name in Block Capitals	Date
Researcher Signature	Name in Block Capitals	Date

Participant Information Sheet

Women and men who have experienced infertility and recurrent miscarriage

You are being asked to participate in a study called "Exploring stakeholder views and experiences of recurrent miscarriage and infertility services and supports in the Republic of Ireland". In order to decide whether or not you want take part in this research, you should understand enough about its risks and benefits to make an informed decision. This process is known as informed consent. Please read this information carefully and discuss it with others if you wish. A researcher will also discuss this information with you.

What is the purpose of this study?

The aim of this study is to find out about the care provided to those who experience two or more consecutive first trimester miscarriages and infertility. We would like to learn about the investigation, management, and follow-up of recurrent miscarriage for women/couples with infertility as well the supports that are available. The findings from the research will inform efforts to improve the quality of services and supports for women/couples with recurrent miscarriage and infertility.

Who is conducting this research?

This research is being conducted by Dr Laura Linehan at the INFANT Centre, University College Cork (UCC). Dr Linehan is a member of the Pregnancy Loss Research Group based at Cork University Maternity Hospital (CUMH) and the project is supervised by Marita Hennessy PhD, UCC, and Professor Keelin O' Donoghue, UCC and Consultant Obstetrician and Gynaecologist, CUMH.

What does taking part involve?

You will be asked to take part in a once-off interview with a member of the research team. This will involve an informal conversation about the services and supports you

encountered during and after your experience of recurrent miscarriage following infertility. The interview will take about one hour and will take place in a way that is agreeable with you such as face-to-face or over a telephone or video call via Microsoft Teams. With your consent, the conversation will be digitally recorded so that we have an accurate record of your thoughts and experiences.

Can I change my mind?

You can withdraw from the study at any time without giving a reason by contacting the research team. Please remember that whatever you decide, it will not affect your access to the services normally available to you.

What are the possible risks and benefits of taking part?

Taking part will give you a chance to share your experience and views of the services and supports available to those who experience recurrent miscarriage and infertility. You may not benefit personally, however, the results of the study will be used to help improve the quality of services and supports provided in Ireland. We don't envisage any negative consequences for you. However, we understand that discussing your experience may cause upset.

If this happens, please talk to your care provider, or contact the support services below. These details will be provided again at the end of the interview.

Pregnancy and Infant Loss Website

https://pregnancyandinfantloss.ie/

The Miscarriage Association of Ireland provide peer to peer support to those who have experienced miscarriage

http://www.miscarriage.ie/

Cork Miscarriage Information and Resources

www.corkmiscarriage.com

What will happen to the information I provide?

UCC is the Data Controller for this project and owns the information collected as part of the study. If you take part, information about you (also called "personal data") will be accessed, collected and stored for the purposes of this study. This personal data includes information that directly identifies you (such as your name, email address and/or postal address), your gender, and information on your health, and/or that of your partners, during fertility treatment, pregnancy and following miscarriage. Please be assured that your personal data will be treated with the strictest of confidence, it will be password protected and stored electronically on secure servers at UCC. A study number will be assigned to your interview data and a list linking your study number to your name will be securely stored separately. Your data will be retained for a minimum of ten years after the completion of the project.

Will this be confidential?

Your participation in this study and any personal information provided will be managed with the strictest of confidence. Every person that has access to your uncoded data is subject to professional secrecy and confidentiality.

What will happen to the results of the study?

We may use quotes from your interview in reporting the results, but these will be anonymised so that you cannot be identified. The results will be shared with those involved in the provision of pregnancy loss services. They will also be published in international peer-reviewed journals, shared at research meetings, and conferences and may be used for teaching purposes.

Is this study approved by an ethics committee?

Yes, ethical approval for this study was granted to us by the Clinical Research Ethics Committee of the Cork Teaching Hospitals (CREC). If you have any concerns about this study, you may contact CREC on 021-4901901 or crec@ucc.ie.

What are my rights?

You have various rights under data protection law, subject to certain exemptions, in connection with our processing of your personal data, including the right:

- to find out if we use your personal data, access your personal data and receive copies of your personal data
- to have inaccurate/incomplete information corrected and updated
- in certain circumstances, to have your details deleted from systems that we use to process your personal data or have the use of your personal data restricted in certain ways
- to object to certain processing of your data by UCC
- to exercise your right to data portability where applicable (i.e., obtain a copy of your personal data in a commonly used electronic form
- to withdraw your consent to the processing of your data at any time without giving a reason by notifying your decision to the investigator. This will not affect the lawfulness of processing data about you based on your consent before the withdrawal. If you withdraw your consent for data processing, your participation in the study stops and no further data will be collected from you. The researchers will present you the options you have concerning your personal data.
- Along with study withdrawal, you have the right to request the deletion of data about you if your data are no longer necessary for the purposes of processing or there is no other legal ground for their further processing.

How do I give my consent to participate?

If you agree to take part, you will be asked to provide explicit consent in writing or via email. You will also be asked to verbalise your consent before your interview begins. This is to demonstrate that you have understood what is involved and that you have read the Information Sheet. After you give your consent, you still have the right to withdraw from the study at any time.

Who can I contact about this study?

If you have any questions about this study, please contact Laura Linehan laura.linehan@ucc.ie or Marita Hennessy maritahennessy@ucc.ie or via 021 4920500.

If you have any complaints in connection with our processing of your personal data, you can contact UCC's Information Compliance Manager: Information Compliance Manager, Office of Corporate & Legal Affairs, UCC, Western Road, Cork E: foi@ucc.ie Tel: +353 21 4903949

Consent Form

Women and men who have experienced recurrent miscarriage and infertility

Please read the following statements carefully and initial the "yes" or "no" box to indicate your response		Yes	No
12.	I confirm that I have read and understood the information sheet for the study "Exploring stakeholder views and experiences of recurrent miscarriage and infertility services and supports in the Republic of Ireland", received a copy and have had the opportunity to ask questions		
13.	I understand that participation in this study is voluntary and that I am free to withdraw without consequence, at any time, without giving a reason		
14.	I agree to participate in an interview to discuss my experience of recurrent miscarriage services and supports		
15.	I give permission for my interview to be audio recorded		
16.	I agree to the quotation/publication of anonymised extracts from my interview in reports, presentations and other publications		
17.	I understand that I can request a copy of my personal information at any time by contacting Laura Linehan laura.linehan@ucc.ie or Marita Hennessy maritahennessy@ucc.ie or via 021 04920500		
18.	I understand that confidentially of records concerning my involvement in this project will be maintained in an appropriate manner		
19.	I understand that when required by law the records of this research may be reviewed by government agencies and sponsors of the research		
20.	I understand that I can contact Laura Linehan laura.linehan@ucc.ie or Marita Hennessy maritahennessy@ucc.ie or via 021 04920500 for further information about this study		
21.	I agree to be contacted about this research in the future		
22.	I agree to be contacted about projects related to maternal health and/or maternity services in the future		

I, the undersigned, hereby consent to participate in the project. I have received a copy of this consent form and information sheet for my records. I understand that if I have any questions concerning this research, I can contact the research team. If I have further queries concerning my rights in connection with the research, I can contact the Clinical Research Ethics Committee of the Cork Teaching Hospitals, Lancaster Hall, 6 Little Hanover Street, Cork or on 021-4901901/crec@ucc.ie.

.....	.....	
Participant Signature	Name in Block Capitals	Date
.....	.....	
Researcher Signature	Name in Block Capitals	Date