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National University of Ireland, Cork



An exploration of miscarriage in the Republic of Ireland: Incidence, management, risk factors, interventions, and populations' knowledge

Thesis presented by **Indra Judit San Lázaro Campillo**

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A Thesis submitted to the National University of Ireland, Cork

for the Degree of Doctor of Philosophy in the Department of Obstetrics & Gynaecology,

College of Medicine and Health, University College Cork

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Table of Contents

List of Tables....12

List of Figures....15

List of Abbreviations....17

Research Outputs and Dissemination....19

Table I. Peer-reviewed publications....20

Table II. PhD Conference presentations....21

Table III. Grants and awards....23

Table IV. Extra credit modules and training completed during PhD....23

Declaration....25

Acknowledgments....25

Thesis Abstract....30

Thesis Outline....34

Overall aim, specific objectives and methods....36

Chapter I. Introduction....39

1.1 Introduction....40

1.2 What is miscarriage?....42

1.2.1 First and second trimester miscarriage....42

1.2.2 Recurrent miscarriage....43

1.2.3 Other pregnancy losses....44

1.3 How common is a miscarriage?....45

1.3.1 Incidence of miscarriage 45

1.3.2 Trends of miscarriage over time 46

1.4 How is miscarriage diagnosed? 47

1.4.1 Clinical findings 48

1.4.2 Type of miscarriages 48

1.4.3 Biochemical markers 49

1.4.4 Ultrasound imaging 50

1.4.5 Surgery and histology examination 52

1.5 What causes miscarriage? 52

1.5.1 Chromosomal abnormalities 52

1.5.2 Metabolic and endocrine disorders 53

1.5.3 Thrombophilia 54

1.5.3.1 Inherited thrombophilias 54

1.5.3.2 Acquired thrombophilia 55

1.5.4 Immunological disorders 55

1.5.5 Structural abnormalities 57

1.5.6 Infective agents 58

1.6 What are the investigations for miscarriage? 58

1.6.1 First-trimester miscarriage 58

1.6.1.1 Histological examination of tissue 58

1.6.2 Investigations for recurrent miscarriage 59

1.7 How is miscarriage managed? 62

1.7.1 Sporadic miscarriages 62

1.7.2 Expectant treatment 64

1.7.3 Medical treatment 64

1.7.3.1 First-trimester miscarriage 65

1.7.3.2 Second-trimester miscarriage.....66

1.7.4 Surgical treatment.....68

1.7.5 Complications depending on the type of treatment.....68

1.7.6 Management in the next pregnancy 69

1.7.6.1 One or two previous miscarriages.....69

1.7.6.2 Recurrent miscarriage 70

1.8 What are the risk factors for miscarriage?.....71

1.8.1 Well-known risk factors for miscarriage.....72

1.8.2 Modifiable risk factors for miscarriage 72

1.8.3 Psychological risk factors.....73

1.9 What are the health and support services available for women who miscarry? 74

1.10 Why is miscarriage important? 76

1.10.1 Public health issues.....76

1.10.2 Psychological morbidity 77

1.10.2.1 Non-pharmacological interventions to reduce levels of stress, anxiety and depression 79

1.10.3 The clinical burden of miscarriage.....80

1.10.3.1 Outcome in future pregnancy.....80

1.10.3.2 Inter-pregnancy interval.....82

1.10.4 Lack of population awareness of miscarriage 82

1.11 Why is data quality important?.....84

1.11.1 Key terms and concepts.....84

1.11.2 Data Quality.....85

1.12 Summary.....86

1.13 Precis.....91

Chapter II. Miscarriage hospitalisations: A national population-based study of incidence and outcomes, 2005-2016.....94

2.1 Abstract.....95

2.2 Plain English Summary.....96

2.3 Introduction.....97

2.4 Methods.....98

2.4.1 Study design and data source.....98

2.4.2 Population.....99

2.4.3 Outcome measures and independent variables.....99

2.4.4 Statistical analysis.....101

2.5 Results.....101

2.6 Discussion.....108

2.7 Implications for practice, policy and research.....111

Chapter III. Assessing the concordance and accuracy between hospital discharge data, electronic health records and register books for diagnosis of inpatient admissions of miscarriage: a retrospective linked data study comparing apples and oranges......113

3.1 Abstract.....114

3.2 Introduction.....115

3.3 Material and methods.....116

3.3.1 Study design and setting 116

3.3.3 Hospital discharge data (HIPE) 116

3.3.2 Electronic health records 117

3.3.4 Register books 118

3.3.5 Data collection form 119

3.3.6 Definitions of miscarriage 119

3.3.7 Exclusion criteria 121

3.3.8 Statistical analysis 121

3.3.7 Ethical approval and consent to participate 122

3.4 Results 122

3.4.1 Comparing EHR and HIPE 125

3.4.2 Comparing EHR and register books 125

3.4.3 Comparing EHR, HIPE and register books 126

3.4.4 Classification of type of miscarriage by three sources 126

3.4.5 Classification of late miscarriage 127

3.4.6 Classification of missing records 128

3.5 Discussion 131

3.5.1 Main findings 131

3.5.2 Comparison with other studies 131

3.5.3 Strengths and limitations 132

3.5.4 Implications for practice and/or policy 133

3.6 Conclusion 135

3.7 Implications for practice, policy and research 136

3.8 Supplementary Tables 137

Chapter IV. Risk factors for miscarriage among women attending an Early Pregnancy Assessment Unit (EPAU): A prospective cohort study.....140

4.1 Abstract.....141

4.2 Introduction.....142

4.3 Methods.....144

4.3.1 Study design.....144

4.3.2 Recruitment and follow-ups.....144

4.3.3 Outcome measures.....145

4.3.4 Risk factors.....145

4.3.5 Statistical analysis.....148

4.3.6 Sample size calculations.....149

4.3.7 Ethical approval.....149

4.4 Results.....150

4.5 Discussion.....158

4.5.1 Main findings.....158

4.5.2 Interpretation.....159

4.5.3 Strengths and Limitations.....162

4.5.4 Implications and conclusions.....163

4.5.5 Conclusion.....164

4.6 Implications for practice, policy and research.....165

4.7 Supplementary Tables.....166

Chapter V University students' awareness of causes and risk factors of miscarriage: a cross-sectional study......174

5.1 Abstract.....175

5.2 Background.....176

5.3 Methods.....177

5.3.1 Study design and data source.....177

5.3.2 Statistical analysis.....179

5.3.3 Ethical approval and consent to participate.....180

5.4 Results 181

5.5 Discussion.....189

5.5.1 Main findings 189

5.5.2 Strengths and limitations 190

5.5.3 Comparison with other studies 191

5.5.4 Implications.....192

5.6 Conclusion.....193

5.7 Implications for practice, policy and research 194

5.8. Supplementary Tables 195

Chapter VI Reproductive health knowledge about miscarriage: a cross-sectional study of university students......203

6.1. Abstract.....204

6.2. Introduction.....205

6.3. Methods.....206

6.3.1 Statistical analysis.....207

6.3.2 Ethical approval and consent to participate.....209

6.4. Results 209

6.5. Discussion.....221

6.6. Conclusion.....223

6.7 Implications for practice, policy and research 224

6.8. Supplementary Tables 225

Chapter VII Psychological distress and general health during pregnancy among women with a history of miscarriage: a pilot prospective study. 229

7.1 Abstract.....230

7.1 Introduction.....230

7.4 Material and Methods 231

7.4.1 Statistical analysis.....233

7.4.2 Ethical approval.....234

7.5 Results 234

7.6 Discussion.....245

7.7 Conclusion.....248

7.8 Implications for practice, policy and research 249

7.9 Supplementary Tables 250

Chapter VIII Psychological and support interventions to reduce levels of stress, anxiety or depression on women's subsequent pregnancy with a history of miscarriage: an empty systematic review. 255

8.1 Abstract.....256

8.2 Article summary.....257

8.3 Introduction.....257

8.4 Methods.....259

8.4.1 Eligibility criteria.....259

8.4.2 Information sources and search.....261

8.4.3 Study selection.....261

8.5 Results 263

8.6 Discussion 266

8.6.1 Comparison with other studies 266

8.6.2 Limitations of the study 267

8.6.3 Implications and conclusion 269

8.7 Implications for practice, policy and research 271

Chapter IX Discussion 272

9.1 Discussion 273

9.2 Incidence of inpatient admissions of miscarriage and data validation (Chapter 2 & Chapter 3) 275

9.2.1 Main findings 275

9.2.1.1 Prospective cohort study 276

9.2.1.2 Concordance study 276

9.2.2 Strengths and Limitations 277

9.2.3 Implications for practice & future research 280

9.2.4 Implications for data quality 286

9.4 Risk factors and interventions (Chapter 4, 7 & 8) 290

9.4.1 Main findings 290

9.4.1.1 Prospective cohort study 290

9.4.1.2 Feasibility 291

9.4.1.3 Systematic review 291

9.4.2 Strengths and Limitations 292

9.4.2.1 Prospective cohort study 292

9.4.2.2 Feasibility 293

9.4.2.3 Systematic review 294

9.4.3 Implications for practice & future research 296

9.4.3.1 Prospective cohort study 296

9.4.3.2 Feasibility.....302

9.4.3.3 Systematic review 303

9.4.4 Summary of implications (Chapter 4, 7 & 8) **Error! Bookmark not defined.**

9.5 Awareness of miscarriage (Chapter 5 & Chapter 6) 305

9.5.1 Main findings 305

9.5.2 Strengths and Limitations 306

9.5.3 Implications for practice & future research 307

9.5.4 Summary of implications (Chapter 5 & Chapter 6)..... **Error! Bookmark not defined.**

9.6 Conclusion.....312

References 314

Appendices.....342

Appendix 1. PRISMA 2009 Checklist. 342

Appendix 2. Search strategy 345

Appendix 3. Eligibility criteria of full-text articles 349

Appendix 4. Main characteristics of excluded RCTs.....358

Appendix 5. Outcome matrix of excluded RCTs 364

Appendix 6. Risk of bias of excluded studies.....366

Appendix 7. Protocol of the systematic review.....369

List of Tables

Table 1.1 Main risk factors for the development of psychological morbidity after and early miscarriage 80

Table 2.1. Incidence rate and incidence rate ratio of hospitalisations for early miscarriage in the Republic of Ireland, 2005-2016..... 103

Table 2.2. Blood transfusion and length of stay over 2 days for hospitalisations of early miscarriage, 2005-2016..... 107

Supplementary Table 2.1. Diagnosis, procedures and complications codes for early miscarriage 112

Table 3.1. Comparison of diagnosis of miscarriage between HIPE and EHR..... 125

Table 3.2. Comparison of diagnosis of miscarriage between EHR and register books 126

Table 3.3. Summary of number and percentages of classification of the type of records by each data source..... 129

Table 3.4. Comparison of excluded records by the three data sources 130

Supplementary Table 3.1. Description of main ICD-10 AM of diagnosis of early pregnancy loss in HIPE..... 137

Supplemental Table 3.2. Data collection form 138

Supplementary Table 3.3 Example of a 2x2 table comparing data sources..... 139

Table 4.1. Odds Ratios for miscarriage (<24 weeks): Socioeconomic characteristics. 151

Table 4.2. Odds Ratios for miscarriage (<24 weeks): past reproductive history. 154

Table 4.3. Odds Ratios for miscarriage (<24 weeks): Perceived stress and psychometric scales. 157
Supplementary Table 4.1. Odds Ratios for miscarriage (<24 weeks): General health and lifestyles behaviours. 166
Supplementary Table 4.2. Odds Ratios for miscarriage (<24 weeks): Partners' characteristics. 171
Supplementary Table 4.3. Odds Ratios for miscarriage (<24 weeks): traumatic and stressful life events. 173
Table 5.1. University students' characteristics by type of relationship with someone who had a miscarriage. 182
Table 5.2. Grade of correct, underestimated and overestimated rate of miscarriage. 183
Table 5.3. University Students' awareness of most common cause of miscarriage 185
Supplementary Table 5.1. Odds Ratios of agreement with strong risk factors for miscarriage. 195
Supplementary Table 5.2. Odds Ratios of disagreement with spurious risk factors for miscarriage. 199
Table 6.1. University students' characteristics by sex and age. 211
Table 6.2. Good and poor knowledge of features of first and second trimester miscarriage among university students. 214
Table 6.3. University students' awareness of treatment available for women who miscarry. 217
Table 6.4. Estimation of the percentage of miscarriages that will have a cause identified for the pregnancy loss (N=745) 219

Supplementary Table 6.1. List of features in first and second trimester of miscarriage 225
Supplementary Table 6.2. University students' knowledge of how a miscarriage can be diagnosed. 226
Supplementary Table 6.3. University students' awareness of investigations available for women who miscarry. 227
Supplementary Table 6.4. Preferences of university students' sources to look for information about miscarriage. 228
Table 7.1. Differences in reproductive maternal characteristics at baseline between women who participate in the study and those who withdrawn. 238
Table 7.2. Socio-demographic and lifestyles characteristics at baseline (N=35) 239
Table 7.3. Stressful life events 240
Table 7.4. Psychological factors and general health 243
Supplementary Table 7.1. Schedule of data collection during pregnancy and after delivery. 250
Supplementary Table 7.2. Questionnaires and psychometric scales 251
Supplementary Table 7.3. Cronbach's alpha and summary of main scores of questionnaires 252
Supplementary Table 7.4. Outcomes at delivery (N=34)* 254
Table 8.1 List of all randomised controlled trials and clinical controlled trials (n=19) and reason for exclusion 265

List of Figures

Figure I. Diagram of the principal methodology of each chapter 38

Figure 1.1 Modified chart of recommendations of investigations and treatment for recurrent miscarriage according to ESHRE, the American Society for Reproductive Medicine (ASRM) and RCOG clinical guidelines. PGT (preimplantation genetic testing). 61

Figure 1.2. Flowchart of pathways of care for first and second-trimester miscarriage 63

Figure 9.2. Definitions of data quality dimensions according to HIQA 86

Figure 1.3. Diagram of principal and secondary objectives of each chapter 93

Figure 2.1. National hospitalisation rates for early miscarriage and type of management 104

Figure 2.2. Average length of stay (days) of hospitalisations for early miscarriage 105

Figure 3.1. Flowchart of included and excluded records from the three data sources 124

Figure 5.1. Percentage of most selected risk factors for miscarriage. 187

Figure 6.1. Identification of main features of first trimester miscarriage. 212

Figure 6.2. Identification of main features of second trimester miscarriage. 212

..... 236

Figure 7.1. Flowchart of screening, recruitment and retention of participants in the feasibility study. 236

Figure 7.2. Number of questionnaires answered by participant. 237

Figure 8.1. Flow diagram of the selection of the studies. 263

Figure 9.1 Limitations of research studies in this chapter and potential solutions for future studies by using the national EHR in Ireland. 285

List of Abbreviations

ACA	Anticardiolipin antibodies
ANA	Antinuclear antibodies
anti-HY	Anti-histocompatibility antigens
aOR	Adjusted odds ratios
aPL	Antiphospholipid antibodies
APS	Antiphospholipid syndrome
AR-DRGs	Australian Refined Diagnosis Related Groups
ASRM	American Society for Reproductive Medicine
BDI	Beck Depression Inventory
BMI	Body mass index
CA 125	Cancer antigen 125
CCTs	Clinical Controlled Trials
CES-D	Centre for Epidemiologic Studies Depression Scale.
CI	Confidence intervals
CIHI's	Canadian Institute for Health Information
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CONSORT	Consolidated Standards of Reporting Trials
CRL	Crown-Rump Length
CUH	Cork University Hospital
CUMH	Cork University Maternity Hospital
CWD	Coping With Depression
D & C	Dilation and Curettage
D&E	Evacuation of Uterus
DAS	Dyadic Adjustment Scale
DNRP	Danish National Registry of Patients
EBSCO	Elton B. Stephens Company
ED	Emergency Department
EHR	Electronic Health Records
EPAU	Early Pregnancy Assessment Units
EPDS	Edinburgh Postnatal Depression Scale
ERPC	Evacuation of Retained Products of Conception
ESHRE	European Society of Human Reproduction and Embryology
ESRI	Economic and Social Research Institute
ESS	European Statistics System
EU-28	European Union of 28 member states
FIGO	International Federation of Obstetrics and Gynecology
GSBPM	Generic Statistical Business Process Model
GTD	Gestational Trophoblastic Disease
HADS	Hospital Anxiety and Depression Scale
HbA1c	Glycated Haemoglobin
hCG or β-hCG	Human Chorionic Gonadotropin
HIPE	Hospital In-Patient Enquiry

HIQA	Health Information and Quality Authority
HLA	Human Leukocyte Antigen
HPA	Hypothalamic-Pituitary-Adrenal
HRSD	The Hamilton Rating Scale for Depression
HSE	Health Service Executive
ICD-10-AM	10th Revision Australian modification of International Statistical Classification of Disease and Related Health Problems
ICS	Irish Coding Standards
IES	The Impact Event Scale
IOG	Irish Institute of Obstetricians and Gynaecologists
IPI	Inter-Pregnancy Interval
IPT	Interpersonal Psychotherapy
IQF	Information Quality Framework
IUI	intrauterine insemination
IVF	In-Vitro Fertilisation
IVIg	Intravenous Immunoglobulin
JSTOR	Journal Storage
LA	Lupus Anticoagulant
LIFE	Longitudinal Interval Follow-up Examination
LMP	Last Menstruation Period
LMWH	Low-Molecular-Weight Heparin
LOT-R	Revised Life Orientation Test
MBR	Medical Birth Register
MDD	Major Depression Disorder
MeSH	Medical Subject Headings
MGSD	Mean Gestational Sac Diameter
MHC	Major Histocompatibility Complex
MN-CMS	Maternal & Newborn Clinical Management System
MOH	Major Obstetric Haemorrhage
MRN	Medical Record Number
MSS	Maternity Social Support Scale
NICE	National Institute for Health and Care Excellence
NK	Natural Killer
NPEC	National Perinatal Epidemiology Centre
NPV	Negative Pedictive Value
NSFG	National Survey of Family Growth
NWIHP	National Women & Infants Health Programme
OR	Unadjusted odds ratios
ORBIT	Outcome Reporting Bias of Trial
PAS	Pregnancy Anxiety Scale
PASS	Power and Sample Size software
PBS	The Perinatal Bereavement Scale
PCOS	Polycystic Ovarian Syndrome
PES	Pregnancy Experience Scale
PLCs	Pregnancy Loss clinics

POC	Products Of Conception
PPH	Postpartum Haemorrhage
PPV	Positive Predictive Value
PRAMS	Pregnancy Risk Assessment Monitoring System
PRISMA	The Preferred Reporting Items for Systematic Review and Meta-Analysis
PROSPERO	International prospective register of systematic reviews
PSS	Perceived Stress Scale
PSQI	Pittsburgh Sleep Quality Index
PTSD	Posttraumatic Stress Disorders
PUL	Pregnancies of Unknown Location
RAND	Research And Development
RCOG	Royal College of Obstetrician and Gynaecologists
RCPath	Royal College of Pathologists, the
RCPI	Royal College of Physicians of Ireland
RCTs	Randomised controlled trials
ROI	Republic of Ireland
RPDQ	Revised Prenatal Distress Questionnaire
RPL	Recurrent Pregnancy Loss
RPOC	Retained Products of Conception
RSE	Relationships and Sexuality Education
SD	Standard deviation
SDT	Second Demographic Transition model
STAI	The State-Trait Anxiety Inventory
STD	Sexual transmitted disease
TAS	Transabdominal Ultrasound
TOP	Termination of pregnancy
TPO	Thyroid Peroxidase
TPO-Ab	Thyroid Peroxidase Antibodies
TSH	Thyroid Stimulating Hormone
TVU	Transvaginal Ultrasound
UCC	University College Cork
UFH	Unfractionated Heparin
UK	United Kingdom
US	United States
USA	United States of America
USS	Ultrasound scans
WHO	World Health Organisation

Research Outputs and Dissemination

Table I. Peer-reviewed publications

Year	Published papers
2019	Indra San Lazaro Campillo, Sarah Meaney, Keelin O'Donoghue, Paul Corcoran. Miscarriage hospitalisations: A national population-based study of incidence and outcomes, 2005-2016. BMC Reproductive health. 2019 Dec;16(1):51.
2019	I San Lazaro Campillo, S Meaney, P Corcoran, N Spillane, K O' Donoghue. Risk factors for miscarriage among women attending an Early Pregnancy Assessment Unit (EPAU): A prospective cohort study. The Irish Journal of Medical Science 2019 Jan.
2018	I San Lazaro Campillo, S Meaney, J Sheehan, R Rice, K O'Donoghue. University students' awareness of causes and risk factors of miscarriage: a cross-sectional study. BMC Women's Health 2018 18:188
2017	I San Lazaro Campillo, S Meaney, K McNamara, K O'Donoghue. Psychological and support interventions to reduce levels of stress, anxiety or depression on women's subsequent pregnancy with a history of miscarriage: an empty systematic review. BMJ Open 2017;7:e017802.
	Papers under review
2019	I San Lazaro Campillo, S Meaney, M Harrignton, K McNamara, AM Verling, P Corcoran, K O'Donoghue. Comparing apples and oranges: a retrospective linked data study assessing the concordance between hospital discharge data, electronic health records and register books for diagnosis of inpatient admissions of miscarriage. Health Information Management Journal (Under review since 16 June 2019)
2019	I San Lazaro Campillo, S Meaney, J Sheehan, R Rice, K O'Donoghue. Reproductive health knowledge about miscarriage: a cross-sectional study of university students. Maternal and Child Health Journal (Submitted on the 16 July 2019)
2019	I San Lazaro Campillo, K O'Donoghue, P Corcoran, AM Verling, S Meaney. Psychological distress and general health during pregnancy among women with a history of miscarriage: a feasibility prospective study. Acta Obstetricia et Gynecologica Scandinavica (Submitted on the 13th August 2019)
	Published related papers
2018	Campillo IS, Meaney S, O'Donoghue K, Corcoran P. Ectopic pregnancy hospitalisations: A national population-based study of rates, management and outcomes. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2018 Dec 1;231:174-9.
	Published abstracts
2019	I San Lazaro Campillo, S Meaney, M Hanif Ariffin MB, O O'Connell, K O'Donoghue. An evaluation of first subsequent pregnancy outcomes among women with recurrent miscarriage: a retrospective cohort study.

	European Society of Human Reproduction and Embryology (ESHRE), Vienna, Austria, 23-26 June 2019.
2019	I San Lazaro Campillo, S Meaney, M Hanif Ariffin MB, O O'Connell, K O'Donoghue. An evaluation of first subsequent pregnancy outcomes among women with recurrent miscarriage: A retrospective cohort study. The British Maternal and Fetal Medicine Society Annual Conference (BMFMS), Edinburgh, UK, 28-29 March, 2019.
2017	AM Verling, I San Lazaro Campillo, S Meaney, K O'Donoghue. The challenge of classifying the unexplained. The International Stillbirth Alliance Conference, Cork, 22-24 September 2017. BMC Pregnancy and Childbirth 2017, 17(Suppl 1): 299; 39
2017	San Lazaro Campillo I, Meaney S, McNamara K, K O'Donoghue. Non-medical interventions to reduce levels of stress in pregnant women with a history of miscarriage: A systematic review. British Maternal and Fetal Medicine Society (BMFMS) 19th Annual Conference. Amsterdam, The Netherlands, 30 –31 March 2017. British Journal of Obstetrics and Gynaecology 2017; 24 (Suppl S2): 122
2017	McNamara, K; Meaney, S; San Lazaro Campillo, I; Greene, RA; O'Donoghue, K. An evaluation of the effectiveness of available support systems for obstetricians and midwives when dealing with workplace adversity; a systematic review. British Maternal and Fetal Medicine Society (BMFMS) 19th Annual Conference. Amsterdam, The Netherlands, 30 –31 March 2017. British Journal of Obstetrics and Gynaecology 2017; 24 (Suppl S2): 134

Table II. PhD Conference presentations

Year	Oral presentations
2019	The Society for Social Medicine & Population Health and International Epidemiology Association European Congress Joint Annual Scientific Meeting 2019, Cork, Ireland, 4th to 6th October 2019. I San Lazaro Campillo, S Meaney; M Harrington; P Corcoran; A Verling; K O'Donoghue. Concordance between hospital discharge data, electronic health records and register books for diagnosis of miscarriage in a tertiary maternity hospital: a retrospective linked data study.
2018	Improving Maternal Health – From Evidence into Action – (MAMMI Conference), Dublin, Ireland, 23 October 2018. I San Lazaro Campillo, S Meaney, K O'Donoghue, P Corcoran. Ectopic pregnancy and miscarriage hospital admission in Ireland: incidence, type of management and morbidity indicators.
2017	INFANT Centre Research Day 2017, Clayton Hotel Cork, Ireland, 26 October 2017. I San Lazaro Campillo, S Meaney, K O'Donoghue, P Corcoran. Ectopic pregnancy and miscarriage hospital admission in

Ireland: incidence, type of management and morbidity indicators. Awarded prize for best oral presentation. Awarded prize for best oral presentation.

Poster presentations

2019 The International Stillbirth Alliance's 11th annual conference (ISA), Madrid, Spain, 3-6 October 2019. I San Lazaro Campillo, S Meaney; M Harrington; P Corcoran; A Verling; K O'Donoghue. Concordance between hospital discharge data, electronic health records and register books for diagnosis of miscarriage in a tertiary maternity hospital: a retrospective linked data study.

2019 The International Stillbirth Alliance's 11th annual conference (ISA), Madrid, Spain, 3-6 October 2019. AM. Verling, R. Rice, C. Byrne, I San Lazaro Campillo, S Meaney; A Verling; K O'Donoghue. Development of a website for first trimester miscarriage.

2019 European Society of Human Reproduction and Embryology (ESHRE), Vienna, Austria, 23-26 June 2019. I San Lazaro Campillo, S Meaney, M Hanif Ariffin MB, O O'Connell, K O'Donoghue. An evaluation of first subsequent pregnancy outcomes among women with recurrent miscarriage: a retrospective cohort study.

2019 The British Maternal and Fetal Medicine Society Annual Conference (BMFMS), Edinburgh, UK, 28-29 March, 2019. I San Lazaro Campillo, S Meaney, M Hanif Ariffin MB, O O'Connell, K O'Donoghue. An evaluation of first subsequent pregnancy outcomes among women with recurrent miscarriage: A retrospective cohort study.

2019 National Perinatal Epidemiology Centre (NPEC) Study Day, Dublin Ireland, 18 January 2019. I San Lazaro Campillo, S Meaney, K O'Donoghue, P Corcoran. Ectopic pregnancy and miscarriage hospital admission in Ireland: incidence, type of management and morbidity indicators.

2018 Improving Maternal Health – From Evidence into Action – (MAMMI Conference), Dublin, Ireland, 23 October 2018. I San Lazaro Campillo, S Meaney, J Sheehan, R Rice, K O'Donoghue. University students' awareness of signs, symptoms and management of miscarriage: a cross-sectional study.

2017 The British Maternal and Fetal Medicine Society Annual Conference (BMFMS), Amsterdam, Netherlands, 30-31 March 2017. I San Lazaro Campillo, S Meaney, K McNamara, K O' Donoghue. Non-medical interventions to reduce levels of stress in pregnant women with a history of miscarriage: a systematic review.

2017 Annual Conference of the Association of Early Pregnancy Units (AEPU), Warwick, UK, 9-10 November 2017. I San Lazaro Campillo, S Meaney, K O'Donoghue, P Corcoran. Ectopic pregnancy and

	miscarriage hospital admission in Ireland: incidence, type of management and morbidity indicators.
2016	Better Outcomes for Maternal, Fetal and Infant Health. INFANT Centre Research Day, Western Gateway Building, University College Cork, 9 September 2016. I San Lazaro Campillo, S Meaney, K McNamara, K O' Donoghue. Non-medical interventions to reduce levels of stress in pregnant women with a history of miscarriage: a systematic review.
2016	Annual Conference of the Association of Early Pregnancy Units (AEPU), Cardiff, Wales, 7-8 November 2016. I San Lazaro Campillo, S Meaney, K McNamara, K O' Donoghue. Non-medical interventions to reduce levels of stress in pregnant women with a history of miscarriage: a systematic review.

Table III. Grants and awards

2019	Awarded registration and travel bursary for an oral presentation (€90). The Improving Maternal Health - From Evidence into Action' Conference – The MAMMI study, Dublin, 2019 Ireland
2017	Awarded prize for best oral presentation (€250). INFANT research day, Cork, Ireland, 26 October 2017, Cork, Ireland
2017	Doctoral Travel Bursaries, 2017/2018 (€1,000). The College of Medicine and Health, University College Cork. Conference attended: The association of Early Pregnancy Units (AEPU) Annual Scientific Meeting 2017. Location: Warwick, United Kingdom. 9-10th Nov 2017

Table IV. Extra credit modules and training completed during PhD

Year	Extra-credit modules, University College Cork
2018	ST6013 Statistics and Data Analysis for Postgraduate module (10 credits)
2017	PG7016 Systematic reviews for the health sciences
2017	PG6001 STEPS Scientific writing
2017	PG7021 Ethics for healthcare research module (5 credits)
	Other workshops
2016	Statistical Consideration in Clinical Trial Design: 1 Day HRB – TMRN Workshop, UCC
2016	Secrets of Highly Successful Research Students, UCC (Hugh Kearnes) PhD Workshop: Turbocharge your writing, UCC (Hugh Kearnes)
2016	PhD Workshop: Time for research, UCC (Hugh Kearnes)
2016	How to plan your PhD, UCC (Hugh Kearnes)

2016 One day workshop: Designing Effective Interventions for Health behaviour Change, University of Galway, Ireland.
2016 The Stata Workshop, UCC
2016 Project Management in the Real World, UCC (Team Working and Leadership)
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Declaration

I declare that this thesis has not been submitted as an exercise for a degree at this or any other university. The work, upon which this thesis is based, was carried out in collaboration with a team of researchers and supervisors who are duly acknowledged in the text of the thesis. The library may lend or copy this thesis upon request.

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Go raibh maith agat

Thesis Abstract

Background

Miscarriage is one of the most common complications in early pregnancy. It is estimated that approximately one out of five women will have a miscarriage throughout their reproductive lives. Despite the high prevalence of miscarriage and the biopsychological burden associated with experiencing miscarriage, there are several gaps in the literature. For example, there is a lack of standardisation of definitions and types of miscarriage worldwide. This high heterogeneity in cut-offs for defining miscarriage is limiting international comparisons of the evidence available. This is distorting the recording of data related to miscarriage in national and international health databases. Furthermore, little is known about the trends of hospital admissions for miscarriage and the non-fatal complications associated with it. In fact, there is no sufficient evidence of the validity of diagnosis of miscarriage in routinely collected health databases.

In addition, although approximately 50% of miscarriages are linked to chromosomal abnormalities, the underlying causes of miscarriage are still unclear for the remainer. Therefore, it is imperative to understand and identify causes and risk factors of unexplained miscarriage in order to develop effective treatments and promote healthy behaviours among the population. The most well-established risk factors for miscarriage are advanced maternal age, previous pregnancy loss and parity. However,

there is a need to identify risk factors in order to be able to prevent the likelihood of experiencing miscarriage. It is accepted that women who experience miscarriage suffer from psychological morbidity after the loss and in subsequent pregnancies. Nevertheless, further research is needed in order to obtain robust evidence on what specific group of women are more susceptible to develop psychological morbidity after miscarriage, what are the psychological and emotional changes during pregnancy after a miscarriage, and what are the effective non-pharmacological interventions to improve psychological wellbeing as well as future pregnancy outcome.

Outline and aims

In this thesis, I explored several dimensions surrounding the event of miscarriage. To do that, I firstly reviewed the published evidence to date about miscarriage in order to find gaps in the literature. This thesis encompassed a total of six research studies to contribute to the existing body of knowledge about miscarriage. The main objective of the first study was to determine national trends in incidence and management of inpatient admissions for early miscarriage in the Republic of Ireland. After this study, it was essential to validate the diagnosis of miscarriage in the national health system used to obtain these trends. Consequently, the aim of the second study was to compare agreement for the diagnosis of miscarriage between three types of routinely collected hospital-based health records. This thesis includes three research studies that explored several gaps in the literature about pregnant women with a history of miscarriage. The first study explored the risk factors associated with miscarriage among women attending an early pregnancy assessment unit (EPAU). The second study aimed to determine barriers and facilitators when designing large-scale longitudinal studies;

and the third study was a systematic review, which aimed to identify randomised controlled trials that assessed the effect of interventions to reduce stress, anxiety and depression in pregnant women with a history of miscarriage. Finally, this thesis includes a cross-sectional study that was designed to assess university student's knowledge of basic reproductive health information about miscarriage.

Findings and clinical implications

This thesis provides additional evidence to the growing body of work focusing on miscarriage. This thesis highlights the need for unifying inpatient and outpatient data in order to estimate the total burden of miscarriage at a national level. Furthermore, it is crucial to standardise the diagnosis of the type of miscarriage at a national level. The results presented in this thesis also emphasise the misunderstanding of causes, signs and symptoms of miscarriage, which shows it is essential to inform the public about miscarriage in general, as well as its treatments and the scientific evidence available to date. In addition, reproductive health information about miscarriage should be disseminated to a younger stratum of the population, who are at early stages in their reproductive life. Indeed, this would enable better informed decision-making about their reproductive behaviour and lifestyle by helping them to be aware of risk factors for miscarriage, identifying signs and symptoms of miscarriage and learning what to expect when experiencing a miscarriage. Moreover, providing reproductive health information about miscarriage will help the population to be aware of when and where seek for help. In this thesis, I suggest University settings as the ideal scenario to reach and promote reproductive health information about miscarriage in this targeted group.

Efforts to satisfy the population's needs on reproductive health and pregnancy loss should be made by healthcare professionals and researchers, and should also include public health advocates and policymakers. As a result of the findings from this thesis, I suggest further research in the area of miscarriage, and I outline a number of recommendations in relation to clinical practice and public policy. It is essential to obtain robust evidence on the association of poor mental health and adverse pregnancy outcomes that may lead to targeted interventions for women who are at higher risk of developing stress or mental disorder before, during and after pregnancy. The need for targeted interventions to reduce stress and increase mental wellbeing among pregnant women with a history of miscarriage is also warranted. An effort should be made to design and implement high quality, appropriately powered, RCTs that can provide reliable and non-biased evidence on preventable risk factors and effective psychological and behavioural interventions that may improve outcomes in future pregnancies. To achieve this goal, research funders need to acknowledge the burden of miscarriage at national and international level and support well-designed and large-scale RCTs. Funding RCTs in this area will lead to increase the understanding of potential interventions that might improve women´s psychological wellbeing after pregnancy loss.

Thesis Outline

This thesis is comprised of a number of papers exploring several dimensions of miscarriage. It investigates the experience of miscarriage in a biopsychological perspective from an estimation in incidence rates of hospital admissions of miscarriage to an evaluation of the type of management and morbidity associated to hospitalisation and the potential risk factors and population's awareness of miscarriage.

This thesis includes the following chapters:

Chapter 1: Introduction and objectives

Chapter 2: Miscarriage hospitalisations: A national population-based study of incidence and outcomes, 2005-2016 (Paper 1)

Chapter 3: Assessing the concordance and accuracy between hospital discharge data, electronic health records and register books for diagnosis of inpatient admissions of miscarriage: a retrospective linked data study comparing apples and oranges (Paper 2)

Chapter 4: Risk factors for miscarriage among women attending an Early Pregnancy Assessment Unit (EPAU): A prospective cohort study (Paper 3)

Chapter 5: University students' awareness of causes and risk factors of miscarriage: a cross-sectional study (Paper 4)

Chapter 6: Reproductive health knowledge about miscarriage: a cross-sectional study of university students (Paper 5)

Chapter 7: Psychological distress and general health during pregnancy among women with a history of miscarriage: a pilot prospective study (Paper 6)

Chapter 8: Psychological and support interventions to reduce levels of stress, anxiety or depression on women's subsequent pregnancy with a history of miscarriage: an empty systematic review (Paper 7)

Chapter 9: Discussion

Overall aim, specific objectives and methods

The overall aim of this thesis was to explore several dimensions of the miscarriage event. The following specific objectives for each chapter are outlined below:

1. To explore national trends in incidence rates of hospitalisations for miscarriage using the Hospital In-Patient Enquiry (HIPE) in the ROI from 2005 to 2016 (Chapter 2, paper 1)
2. To assess the reliability and validity of routine hospital discharge data of diagnosis of miscarriage in the ROI by determining the level of agreement between three data sources: electronic health records, hospital discharge data using HIPE, and register books in a tertiary maternity hospital in the ROI from January to June 2017 (Chapter 3, paper 2)
3. To determine the relationships between risk factors that might be associated with miscarriage among women attending an EPAU in May 2012 (Chapter 4, paper 3)
4. To explore university students' knowledge and common misconceptions of miscarriage in a single university centre in the ROI between April and May 2016 (Chapters 5 and 6; Papers 4 and 5)
5. To examine the feasibility of a prospective study to assess mental health and general health during pregnancy and subsequent pregnancy outcomes among women who have a history of miscarriage from August 2017 to May 2018 (Chapter 7, paper 6)
6. To examine the literature to explore the effect of psychological and support interventions to reduce levels of stress among pregnant women who have a history of miscarriage (Chapter 8, paper 7)

This thesis applies different methodologies according to the specific objectives of each study. The methodology for each study is described in full in each respective chapter. A summary of the main study designs and statistical tests carried out for each chapter can be seen in Figure I. The introduction of this thesis involved a non-systematic search of the literature in order to cover the broad topics included in this thesis. However, I followed a structured approach for the search of the literature. For the introduction, I used Google Scholar to identify national and international clinical guidelines. I hand searched the reference lists of national and international clinic guidelines for any relevant literature to be included. The main electronic bibliographic databases used to search of the systematic reviews were PubMed, Cochrane Library and Web of Science (Web of Knowledge). Medical subject headings (MeSH) or major topics were used in the search when using the electronic bibliographic databases. I also completed hand searches of systematic reviews reference lists for each of the topics included on the introduction of this thesis.

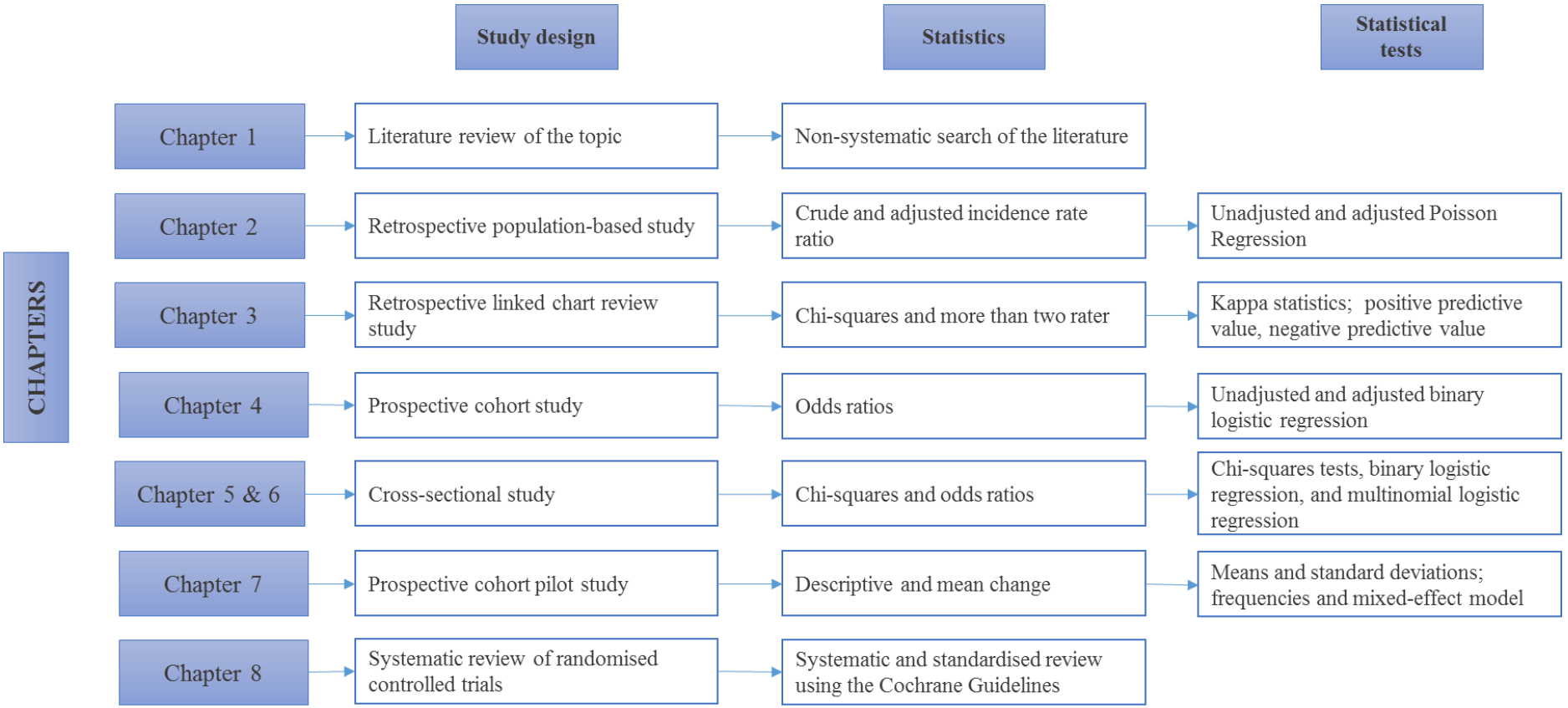


Figure I. Diagram of the principal methodology of each chapter

Chapter I.

Introduction

1.1 Introduction

Pregnancy is usually perceived as a positive and natural stage of a woman's life. Generally, a new pregnancy involves planning and adapting the woman and partners' life for the welcoming of an additional member of the family. In fact, it is well-established that parents start building their bonds of attachment with the future baby at a very early stage during pregnancy [1,2]. Historically, being a woman has been closely linked to the possibility of conception, and therefore, the continuity of a family's lineage. The loss of a pregnancy is commonly experienced as an unexpected and sudden event, and can be considered an unnatural process in a woman's reproductive life by most of society[3].

Miscarriage is the most common type of pregnancy loss, and it is one of the most common complications in early pregnancy worldwide [4-6]. This is estimated to occur in one out of four clinically recognised pregnancies [4]. In spite of its incidence, the research area of miscarriage was one of the most understudied fields in obstetric medicine until the late 1960s. Moreover, efforts to investigate and understand the underlying causes of miscarriage and couples' experiences of miscarriage have varied across countries depending on historical, economic, social contexts and culture[7]. For example, Cecil et al. (1996) described differences in the perception of pregnancy loss between populations with high or low infant mortality rates and between diverse cultures[7]. According to the author's findings, high infant mortality rates may contribute to decreasing the social significance of pregnancy loss. Cecil et al (1996) posit that this may be because a fetus or newborn infant are not considered fully social (i.e. they are not considered members of the society) and consequently they are not perceived as "human beings". In contrast, the improvement and accessibility to

ultrasound scans and hormonal assays have helped to identify pregnancy, and consequently to diagnose pregnancy loss, at very early stages in medium and high-income countries with low infant mortality rates. Therefore, the perception of miscarriage as the loss of one or more members of a family has gained greater importance in these communities[7].

The advances in in-vitro fertilisation (IVF) in low infant mortality rate countries have helped to achieve a greater understanding of the process of conception in humans, and some authors have begun to affirm that fertilisation in humans is deemed remarkably inefficient[8]. In spite of all the advances, 50% of cases of miscarriage remain unexplained, and the other half is attributable to chromosomal abnormalities[9]. Other causes of miscarriage are investigated but contradictory evidence is found in the literature. In addition, the psychological and social impact on women and their partners have only started to be extensively explored in the recent decades; hence professionals in the field are demanding appropriate research and support for women's psychological morbidity following miscarriages and in their subsequent pregnancy [10,11]. Despite the achievements accomplished in the field of pregnancy loss, more research is needed to convey a full picture of the causes and risk factors associated with miscarriage, its physical and socio-psychological impact regarding subsequent pregnancies and the development of effective supports for women and their partners.

This chapter covers the most important evidence regarding definition, incidence and etiology of miscarriage, followed by a description of the diagnosis, investigations, management, and health and support services available at the moment for women who

miscarry. Finally, a summary of the research studies, which have been undertaken to add evidence to the field, is outlined along with the main objectives of this thesis.

1.2 What is miscarriage?

1.2.1 First and second trimester miscarriage

Despite the incidence of miscarriage, the definition of miscarriage differs among countries and organisations depending on the gestational week or clinical criteria[12]. The most common definition of miscarriage is "*the spontaneous demise of a pregnancy before the fetus reaches viability*"[13]. In the Republic of Ireland (ROI) and the United Kingdom (UK), clinical guidelines define miscarriage as the loss of a pregnancy within 24 completed weeks of gestation[14,15]. When the loss occurs within 13 weeks of gestation, it can be classified as early or first-trimester miscarriage. The loss is considered late or second-trimester miscarriage when it occurs between 13 and 24 completed weeks of gestation[15,16]. However, other definitions for miscarriage can be found in the literature depending on the cut-offs established for other types of perinatal death such as stillbirth. For example, the American College of Obstetricians and Gynaecologists defines early miscarriage as the loss of a pregnancy before 20 weeks of gestation[17]; whereas the World Health Organisation (WHO) defines miscarriage as the premature loss of a fetus up to 23 weeks of pregnancy and weighing up to 500g[18]; and the Queensland Clinical Guideline in Australia defines miscarriage as the pregnancy loss occurring before 20 completed weeks of gestation or less than 400g birth weight[19].

Therefore, international comparison of the evidence in the field of pregnancy loss is very limited due to the lack of a standardised definition of miscarriage[12]. That means that the cut-offs for defining early or late miscarriage and other types of pregnancy loss, such as stillbirth, vary between countries. For instance, according to the WHO, a stillbirth is defined as a fetal death, occurring in the third trimester of pregnancy, which is after 28 weeks of gestation, or with a birthweight of ≥1000grammes. However, according to the Irish Law, a stillbirth is defined as a baby who is born dead after 24 completed weeks of gestation or if the baby weigh at least 500 grammes or more at birth. Similarly, the UK Clinical Guideline defines, stillbirth as a baby who is born dead after 24 completed weeks of gestation. As a consequence, the discrepancies in weeks of gestation prevents generalisability of the evidence relating to miscarriage when comparing studies which, depending on the definition used, include women with stillbirth or second-trimester miscarriage versus other studies including first-trimester miscarriage only. This also hinders the documentation of miscarriages in the registration systems, the community and/or hospital surveys. Therefore, it creates a large variability in the accuracy of incidence rates or prevalence of miscarriage between different records and countries.

1.2.2 Recurrent miscarriage

The medical term Recurrent Miscarriage or Recurrent Pregnancy Loss (RPL) is used when a woman experiences several miscarriages at different times of her life. However, the same challenges are outlined when defining recurrent miscarriage, and several definitions can be found in the literature. RPL can be defined as a) two or more failed clinical pregnancies as documented by ultrasonography or histopathologic examination[20] or b) three consecutive pregnancy losses, which is not required to be

intrauterine[21]. A standardised definition of RPL is essential primarily because it determines which couples will be investigated for further complications, provided support, counselling and other treatments. Therefore, the agreed definition of miscarriage makes studying the miscarriage phenomenon in-depth possible by offering clinical, genetic and metabolic tests and a thorough investigation of possible risk factors and past reproductive history[22].

The European Society of Human Reproduction and Embryology (ESHRE) attempted to standardize the terminology for the classification of the different types of pregnancy loss for research purposes in 2015[23]. According to the ESHRE, early miscarriage should be defined as spontaneous pregnancy demise before 10 weeks of gestational age, or before the 8th developmental week; whereas missed miscarriage should be defined as an intrauterine pregnancy loss before 10 weeks' size on ultrasound[23]. Similar to miscarriage, in 2017, the ESHRE considered that RPL could be defined as the loss of two or more pregnancies regardless of whether they were consecutive or not[24]. Nevertheless, the ESHRE group members were not in full agreement as to which definition of RPL to use in clinical practice. Consequently, the ESHRE group stated that either definition of RPL could be used in clinical practice depending on the preference of the clinicians and/or individual hospitals[23]. In addition, ESHRE believes that these modifications in the definition will facilitate research and increase the investigations of RPL, as well as the promotion of psychological support for couples who experiencing RPL[23].

1.2.3 Other pregnancy losses

Other pregnancy losses which occur at similar weeks of gestation to miscarriages, and might be misdiagnosed because of similar clinical presentations include: a)

pregnancies of unknown location (PUL), defined as pregnancy demise not visualised on transvaginal ultrasound (TVU) with resolution of serum human chorionic gonadotropin (hCG or β-hCG)[23], b) hydatidiform mole pregnancies (i.e. complete and partial molar pregnancies), which belong to a group of conditions referred as gestational trophoblastic disease (GTD)[25], and c) ectopic pregnancies, defined as the ultrasonographic or surgical visualisation of a pregnancy outside of the endometrial cavity[26].

1.3 How common is a miscarriage?

1.3.1 Incidence of miscarriage

There is a large amount of evidence regarding miscarriage rates in the literature. It is estimated that most miscarriages happen between the 6th and the 12th week of gestation after the last menstruation period (LMP)[27]. In the literature, clinically recognised miscarriages have been estimated to account for approximately 10-20% of all pregnancies[28-31]. The most accurate estimations of biochemical and clinically recognised miscarriages were assessed by two studies in the late 1990s, one in the United Kingdom (UK) and the other in the United States (US). The Wilcox et al (1988) and the Zinman et al, (1996) studies observed an overall pregnancy loss rate of approximately 30%[4,5]; however, the percentages differed between both studies. Indeed, Wilcox et al., (1988) found 22% of biochemical miscarriages among 198 pregnancies detected by assay, and Zinaman et al., (1996) 13% (15/116 pregnancies detected by assay). Similarly, the percentage of clinically recognised miscarriages varies between 12% (18 of 155 clinical pregnancies) and 18% (28 of 158 clinical pregnancies) according to Wilcox and Zinaman respectively. Some estimations have

shown that the total reproductive losses might be even closer to 40% and 50% for women who underwent intrauterine insemination (IUI) or for women over 45 years old[32,33].

For RPL, the estimation of its occurrence varies according to the definition. It is estimated that RPL occurs in 1% of all clinically recognised pregnancies when it is defined as three or more consecutive miscarriages[8,34,35]; whereas the prevalence increases up to 5% when it is defined as two or more consecutive miscarriages[36].

1.3.2 Trends of miscarriage over time

Although several longitudinal studies have reported the incidence of miscarriage, and the potential factors influencing the occurrence of clinical miscarriage (i.e. maternal age, smoking status, number of previous miscarriages or live births, etc.)[29,37,38], the reporting of trends of incidence rates of miscarriage over time is relatively scant in the literature. For example, a retrospective study explored the incidence of self-reported miscarriages among all Swedish women who delivered a child using the Swedish Medical Birth Register (MBR) from 1983 to 2003[30]. This study found an increase of self-reported miscarriages from 7.9% to nearly 13.7% over the 21-year study period[30]. More recently, two studies examined trends in self-reported pregnancy loss (i.e. defined as a composite variable including miscarriages, stillbirths, and ectopic pregnancies) and early pregnancy loss (i.e. before 12 weeks of gestation) using the National Survey of Family Growth (NSFG) in the United States[39,40]. The first study reported an increased rate of reported early pregnancy loss occurring before 8 weeks gestation by 1-2% per year, a weaker increasing trend of less than 1% in losses occurring at 8-12 weeks of gestation, and no changes in the risk of losses occurring

beyond 12 weeks between 1970 to 2000 among women between the ages 13-25[39]. A similar increase in rate was found in the second study including data from 1995 - 2015[40], with an overall risk of pregnancy loss of 19.7% and early pregnancy loss (<12 weeks) of 13.5% respectively[40]. One of the original hypothesis for the increase reported in both studies was the improvements in pregnancy tests and a higher awareness of early pregnancy; however, a recent analysis using NSFG data did not find differences in the mean gestational age at the time of pregnancy awareness[41].

1.4 How is miscarriage diagnosed?

Traditionally, miscarriages were mainly diagnosed by women's clinical signs and symptoms or by a surgical procedure. Some miscarriages might occur without any apparent signs or symptoms. The introduction and improvement in sensitivity of ultrasound scans and assays for human chorionic gonadotropin (hCG or β-hCG) have helped to diagnose and treat miscarriage early in pregnancy[6]. Miscarriages that can only be diagnosed by a decrease in levels of hCG are termed biochemical pregnancy losses. In those cases, women might not even be aware that they were pregnant at the time. This type of pregnancy loss has been called "occult" pregnancy, unrecognised pregnancy loss or preclinical pregnancy loss by several authors[6,4,5]. Since 1959, several studies have explored the reasons behind these types of miscarriages[6]. The advancement in hCG testing and in-vitro fertilization (IVF) techniques have provided an invaluable understanding of the process from ovulation to on-going pregnancy. This has helped to forge a better idea of the reasons behind preclinical pregnancy losses[6].

1.4.1 Clinical findings

The most common clinical findings that affect pregnant women who experience a miscarriage are vaginal bleeding and pain, which are estimated to occur in 20 to 40% of cases[42,43]. Some women might experience light spotting, heavy vaginal bleeding with or without abdominal pain, and vice versa. In other scenarios, women might have a later and heavier than usual period and might not even suspect they had a miscarriage. Women might also report symptoms of fatigue, tiredness and exhaustion during and after a miscarriage. Nevertheless, clinical findings of miscarriage can be inaccurate in more than 50% of cases, as they might suggest the existence of another type of pregnancy loss (i.e. ectopic pregnancies, PUL or molar pregnancies), or the presence of coexisting disorders (e.g. placental dysfunction, a pregnancy complication in which the placenta, which delivers oxygen and nutrients into the fetal bloodstream, fails to properly support a developing fetus, or premature onset of maternal-fetal circulation, which refers to changes in the oxygen tension within the human placenta associated with onset of the maternal arterial circulation at the end of the first trimester of pregnancy, and the impact on placental tissues)[44].

1.4.2 Type of miscarriages

Depending on the type of signs and symptoms, a miscarriage can be clinically classified as threatened, inevitable, incomplete, complete or a missed miscarriage[45]. A threatened miscarriage is a clinical term to describe women who present with vaginal bleeding and spotting or abdominal pain with a closed cervical os with a positive pregnancy test or evidence of a pregnancy on ultrasound scans (USS). Approximately 50% of threatened miscarriages can result in women continuing to have a normal pregnancy[45]. Incomplete miscarriage refers to cases in which symptoms of vaginal

bleeding and/or pain are present, the cervix is dilated, and retained products of conception (RPOC) can be visualised at clinical examination or on ultrasound scan in the uterine cavity. When all the RPOC have been naturally expelled or extracted through a medical procedure from the uterine cavity, the term complete miscarriage is then applied. Finally, missed miscarriage occurs when no symptoms (i.e. pain or bleeding) have been experienced by the woman; she will only become aware of the miscarriage when a non viable pregnancy is identified on routine ultrasound scan[45].

1.4.3 Biochemical markers

The most common biochemical markers to assess the viability of a pregnancy when ultrasound findings are inconclusive or among women with threatened miscarriage are human chorionic gonadotropin (hCG or β-hCG) and progesterone[46]. HCG is a hormone produced by the trophoblast, an external capsule of tissue of the blastocyst that contributes to the development of the placenta and fetal membranes[47]. The blastocyst or blastula is a medical term used to describe the hollow cellular mass at the early stage of development[47]. HCG is the earliest detectable marker, as early as 8-11 days after implantation[48]. Measurement of serum hCG is the mainstay to make a diagnosis of early pregnancy outcomes (i.e. miscarriage, ectopic pregnancy); however more than one measurement is frequently needed[49].

In recent years, various studies have assessed the usefulness of serum progesterone to distinguish a viable pregnancy from a miscarriage or ectopic pregnancy[49]. According to the literature, serum progesterone values higher than 20ng/ml are more likely to be associated to a viable pregnancy and lower than 15ng/ml with adverse pregnancy outcomes such as miscarriage and ectopic pregnancies[50]. Two systematic reviews have

assessed the predictability of the most common biochemical markers on different pregnancy outcomes among women with threatened miscarriage[48,49]. The first one concluded that a single measurement of progesterone at 3.2-6ng/ml can differentiate between viable and non-viable pregnancies[49]. The second meta-analysis included progesterone, hCG and oestradiol as biomarkers. This meta-analysis argued that progesterone and hCG are not useful in predicting the outcome of a pregnancy with a viable fetus; whereas oestradiol and cancer antigen 125 (CA 125) had high predictive value to identify pregnancies that will more likely continue[48].

1.4.4 Ultrasound imaging

The introduction of new techniques, such as ultrasound imaging, has helped to diagnose asymptomatic women who have had a missed miscarriage and to confirm a complete miscarriage early in pregnancy[51,52]. Nonviable pregnancies are diagnosed by transvaginal (TVS) or transabdominal ultrasound (TAS). The main sonographic measurements used to diagnose miscarriage are mean gestational sac diameter (MGSD) and crown-rump length (CRL). The gestational sac, which should be visible at 4.5 to 5 weeks of gestation, is one of the first sonographic signs of an intrauterine pregnancy[53]. The MGSD is a standardised formula to calculate the three perpendicular sac diameter measurements[53]. The CRL is defined as "*the longest straight-line measurement of the embryo measured from the outer margin of the cephalic pole to the rump*" [53]. Visualisations of the embryo are possible with a CRL of at least 5mm.

The criteria to diagnose miscarriage using ultrasound were not internationally standardised among countries until very recently[54]. The Royal College of Obstetrician and Gynaecologists (RCOG) used an MGSD of ≥ 20mm or with a fetal pole with a

CRL of ≥6mm and no heartbeat to diagnose miscarriage. In contrast, the American College of Radiology defined miscarriage as MGSD of ≥ 16mm for an empty gestational sac or visualisation of a fetal pole with a CRL of ≥5mm and no heartbeat. In October 2011, a series of publications demonstrated that these guidelines were inaccurate and that the current cut-off was likely to have an unacceptably high false positive rate for miscarriage[55,56,54]. The RCOG modified its guidelines to one based on an empty gestational sac of MGSD ≥25mm, or with a fetal pole with a CRL ≥7mm and no heartbeat[57]. This modification was followed in 2012 and 2013 by the UK National Institute for Health and Care Excellence[26] and the American College of Radiology[58] respectively. As in other countries, the Irish Institute of Obstetricians and Gynaecologists (IOG) and the Health Service Executive (HSE) also modified their guidelines in 2011[45,59]. According to the Royal College of Physicians of Ireland (RCPI), a miscarriage can be diagnosed when there is a fetus, but there is no cardiac activity (i.e. fetus with CRL length of more than 7mm using TVS or 8mm using TAS), or when a gestational sac can be visualised, but there is no existence of a fetus or a yolk (i.e. MGSD more than 20mm using TVS or 25mm using TAS)[15].

It is also important to consider the possible impact that the miscarriage misdiagnosis report, published in 2010 in Ireland, had in regards to identifying and diagnosing miscarriages in the ROI[59]. As a consequence, new policies, procedures and National Clinical Guidelines were developed by the IOG and the HSE, the national health system in the ROI [45,59]. One of the main recommendations was to perform a second ultrasound scan to confirm the diagnosis of miscarriage when pregnancies are under 8 weeks of gestation[45]. No cases of miscarriage misdiagnosis were identified in three annual audits following the implementation of these new guidelines [60].

1.4.5 Surgery and histology examination

Before the introduction of routine ultrasound scans in early stages of pregnancy, the differential diagnoses between early miscarriage and another type of pregnancy loss (i.e. ectopic or molar pregnancy) was sometimes decided after surgery was performed. Some exceptional cases are still diagnosed after surgery. Similarly histological examination can allow the confirmation of chorionic villi supporting an intrauterine pregnancy or not in the case of an ectopic pregnancy and the exclusion of trophoblastic disease (i.e. hydatidiform mole), although this condition is quite rare"[61].

1.5 What causes miscarriage?

Chromosomal abnormalities are the most important causes of early miscarriage, with cytogenetic abnormalities accounting for at least 50-60% of all miscarriages[62]. Nevertheless, an extremely high number of causes of miscarriage are still classified as unexplained or unknown. In addition, only couples who suffer recurrent miscarriage are usually investigated and treated. Therefore, the vast majority of the evidence which has been published relating to the etiology of miscarriage is based on recurrent miscarriage[9]. Recognised causes of recurrent miscarriage include genetic disorders, metabolic and endocrine disorders, prothrombotic conditions such as anti-phospholipid syndrome, immunological disorders and structural uterine anomalies[62]. However, contradictory evidence is published in the literature.

1.5.1 Chromosomal abnormalities

The most frequent cytogenetic abnormalities in all miscarriages are trisomy, polyploidy and monosomy X (i.e. approximately 60%, 15% and 15% respectively)[13]. Sperm chromosome abnormalities have also been reported among couples with

recurrent miscarriage, yet this only accounts for 7% of trisomies[63]. Approximately 5% of couples with recurrent miscarriage have been shown to carry a balanced reciprocal translocation[64]. Although carriers of a balanced reciprocal translocation have a normal phenotype, approximately 50 to 70% of their gametes will be unbalanced[65]. Nevertheless, the live birth rate for couples who conceive spontaneously and who have a balanced reciprocal translocation is still higher than the fertilisation rate achieved by in-vitro fertilisation (IVF) (i.e. overall pregnancy rate of 29% per oocyte retrieval, increasing to38% when calculated per embryo transfer)[66].

1.5.2 Metabolic and endocrine disorders

The essential function of thyroid hormones for the development of the fetus has been studied for decades[67]. Although a recent review has shown a clear link between thyroid disorders and increased thyroid peroxidase (TPO) antibodies (TPO-Ab) and disrupted development of follicles and sperm development (i.e. folliculogenesis, spermatogenesis), the underlying pathophysiology between thyroid disorder and pregnancy loss is unclear[67]. According to the European Society of Human Reproduction and Embryology (ESHRE), hypothyroidism has been associated with only sporadic pregnancy loss, and subclinical hypothyroidism and TPO-Ab with recurrent miscarriage[13]. However, contradictory evidence can be found in the literature. Two small randomised controlled trials found a reduction in the number of miscarriages among women with TPO-Ab who took levothyroxine compared to women with normal thyroid function[68,69]. Nevertheless, two larger trials did not find differences in the incidence of miscarriage or preterm birth among women who used levothyroxine. The first trial involved 600 women undergoing in vitro fertilization[70],

and the second included 19,585 women with one or more previous miscarriages and women who were receiving treatment for infertility[71]

Uncontrolled diabetes and hyperprolactinaemia are endocrine disorders that have been associated with recurrent miscarriage[72,73]. However, treatment for hyperprolactinaemia using bromocriptine has not been reported to alter the risk of miscarriage or even reduce the rate of subsequent miscarriages[72,74]. Polycystic ovarian syndrome (PCOS) is another endocrine factor that has been extensively studied due to its possible association with an increased risk of recurrent miscarriage; however, the underlying link is not certain[75]. Prevalence of PCOS has been found to be higher among women with recurrent miscarriage compared to parous women or women with uncomplicated reproductive history[76,77]. Nevertheless, some studies reported no differences and were not able to predict live birth rate for women with RPL depending on the presence or absence of PCOS [75,78]. Therefore, in the last decade, more attention has been given to the possible relationship between PCOS, insulin resistance and pregnancy loss[13,79].

1.5.3 Thrombophilia

1.5.3.1 Inherited thrombophilias

The concept of inherited thrombophilia refers to a group of conditions that are characterised for a genetic predisposition to develop blood clothing[80]. This includes Factor V Leiden mutation, prothrombin mutation, Protein C and S, and Antithrombin deficiency. Generally, the coagulation cascade is altered because of a genetic modification in a functional protein[80]. It is well-documented that inherited thrombophilias increase the risk of venous thromboembolism[80]. In addition, a growing

body of literature has linked hereditary thrombophilia and recurrent miscarriage[13]. However, other studies have shown no association or a weak association[81,82].

1.5.3.2 Acquired thrombophilia

Acquired thrombophilia refers to antiphospholipid syndrome (APS). Antiphospholipid antibodies (aPL) are a group of immune proteins (antibodies) that mistakenly attack phospholipids in an autoimmune response, and consequently damage tissues or cells causing blood clots or thrombosis. The medical term to refer to this clotting tendency is thrombophilia. APS, also known as Hughes syndrome, is an autoimmune system disorder[83]. APS is one of the most important autoimmune disorders that has been linked to recurrent miscarriage[83]. Clinical criteria to identify APS include a persistent presence of antiphospholipid antibodies (aPL), vascular thrombosis and/or pregnancy complications[84]. Approximately, 15-20% of women with recurrent miscarriage present with APS, which is also called acquired thrombophilia[85]. Some of the most important and clinically relevant antiphospholipid antibodies which are associated with recurrent miscarriage are lupus anticoagulant (LA) and anticardiolipin antibodies (ACA, IgG and IgM)[13]. APS is one of the most important immunological causes of recurrent miscarriage, but it is also the most treatable[13]. When it is not treated, the rate of miscarriage in subsequent pregnancies can reach up to 90%[72]. The most effective treatment is a combination of heparin and aspirin, which has been proven to significantly increase the live birth rate[21].

1.5.4 Immunological disorders

There is a considerable amount of research investigating immunological disorders as potential cause of recurrent miscarriage in the literature[13]. There are two types of

immune disorders studied in recurrent miscarriage: autoimmune disorders, such as APS, and alloimmune disorders. Alloimmunity, also known as isoimmunity, is an immune response to nonself antigens from members of the same species (i.e. alloantigens or isoantigens). The fetus is semiallogeneic because of the paternal genetic contribution[86]. In a normal pregnancy, mother and fetus are immunologically compatible; however, an immune reaction can be activated by the mother[86].

Although it was believed that human leukocyte antigen (HLA) and anti-histocompatibility antigens (anti-HY) were responsible for recurrent miscarriage, currently, there is contradictory and insufficient evidence linking HLA and anti- HY with recurrent miscarriage. A meta-analysis reporting different alleles of HLA did not find statistical significant differences between couples with recurrent miscarriage and control couples[87]. A Danish cohort study found a strong association between class II HLA with secondary RPL after the birth of a boy, but only shown in women in this population[88]. Nevertheless, more research needs to be done to confirm this association in a generalisable population.

Antinuclear antibodies (ANA) are another type of antibodies, which are generally directed against the cell nuclei. There is contradictory evidence linking ANA and recurrent miscarriage. Some case-control studies reported an association between ANA and recurrent miscarriage[89,90,91], whereas other have found no association[92,93]. In clinical practice, testing for ANA is still clinically recommended because the majority of case-control studies have found an association with recurrent miscarriage.

Natural killer (NK) cells is the last group of immunological disorders that are of interest in relation to recurrent miscarriage. NK cells are lymphocytes of the innate immune system[94]. "Normal" cells release major histocompatibility complex (MHC) I molecules to inhibit the receptors in NK cells by identifying the cell as "self". An increase in the number of NK cells has been observed in women with recurrent miscarriage[95]. However, there is a great heterogeneity among the studies and there is a lack of consistency in the results[95]. For example, a systematic review found a significant correlation between NK cells and women with unexplained recurrent miscarriage, who were not under immunotherapy treatment[96]. In contrast, increased number of NK cells were found in women with recurrent miscarriage in a recent meta-analysis published in 2014[97]. Although intravenous immunoglobulin (IVIg) was administered during pregnancy as an inhibitor of NK cells, high quality studies found no significant effect[98,99]. According to the ESHRE guideline, clinical testing of NK cells is not recommended because of lack of consistency in the evidence. Similarly, a recent systematic review did not find positive effect of immunisation with paternal leukocytes[100].

1.5.5 Structural abnormalities

Women with recurrent miscarriage are at higher risk of presenting with female genital malformations (i.e. uterine septae, bicornuate uterus and hemi-uterus)[101]. It is estimated that 19% of women with recurrent miscarriage will present with uterine anomalies[102]; nevertheless, the exact prevalence is not clear[101]. In addition, two systematic reviews reported a higher risk of miscarriage among women with congenital uterine malformations compared to controls[103,104]. On the other hand, although acquired uterine malformations such as endometrial polyps, uterine

adhesions and submucous myomas have been more frequently reported among women with recurrent miscarriage, the clinical relevance is unclear[105].

1.5.6 Infective agents

It is known that severe infection (e.g. bacteraemia or viraemia) can leads to miscarriage[106]. Some of the best known infections that affect pregnancy are chlamydia, listeria, toxoplasmosis and parvovirus; yet the underlying causes that link infective agents and miscarriage are not well understood[106]. The possible relationship between bacterial vaginosis and miscarriage has been studied since the early 90s[107]. Bacterial vaginosis has been associated to second trimester miscarriage and preterm birth[108,107]. However, the association with first trimester miscarriage is inconsistent [109,110]. An randomised controlled trial (RCT) found consistent evidence on the positive effect of clindamycin to reduce incidence of second trimester and preterm delivery in the general population[111]. Nevertheless, more research needs to be done to understand the mechanism of infections in causing miscarriage.

1.6 What are the investigations for miscarriage?

1.6.1 First-trimester miscarriage

1.6.1.1 Histological examination of tissue

The rationale behind the routine histopathologic examination of products of conception in sporadic miscarriages is to exclude the possible causes of ectopic pregnancy and gestational trophoblastic disease[45]. The proportion of ectopic and molar pregnancies detected only by histologic examination is very low. For example, Chen et al. (2007) reported two cases of ectopic pregnancy over 468 samples from women who underwent an evacuation of retained products of conception (ERPC) for

miscarriage (0.4%)[112]. According to the Irish clinical practice guideline, routine histopathologic examination of products of conception (POC) is recommended because of the maternal risk associated with undetected ectopic and molar pregnancies[45]. However, other studies which found a similar proportion of undetected conditions concluded that the benefit from routine histological examination among women with first-trimester miscarriage was not justified[113,114]. According to the Royal College of Pathologists (RCPath), recommendations for investigation and analysis of the causes should be agreed in the designated service, but benefits from the histologic examination are more evident with pregnancy losses from 12-23 completed weeks of gestation[115].

1.6.2 Investigations for recurrent miscarriage

Investigations for couples with recurrent miscarriage include tests that help identify possible causes of the loss. The ESHRE group summarised the current evidence available in the literature regarding routine diagnostic tests, which are recommended for couples with recurrent miscarriage[13]. Figure 1.1 summarises the recommendations for investigations and treatments for recurrent miscarriage.

Couples who experience recurrent miscarriage, defined as three or more miscarriages, in the Republic of Ireland (ROI) are offered an exhaustive investigation of the possible causes of miscarriage according to medical and clinical conditions. Investigations for recurrent miscarriage include:

- Genetic analysis such as parental karyotyping and cytogenetic analysis
- Endocrine blood test such as glycated haemoglobin (HbA1c)
- Thyroid function tests

- Autoantibodies screening including antinuclear antibodies (ANA)
- Antiphospholipid antibodies such as Lupus anticoagulant (LA) antibodies and anticardiolipin antibodies (ACA)
- Thrombophilia factors such as Factor V Leiden, Protein C and S and Anti-Thrombin III
- Other investigations including pelvic ultrasound scan

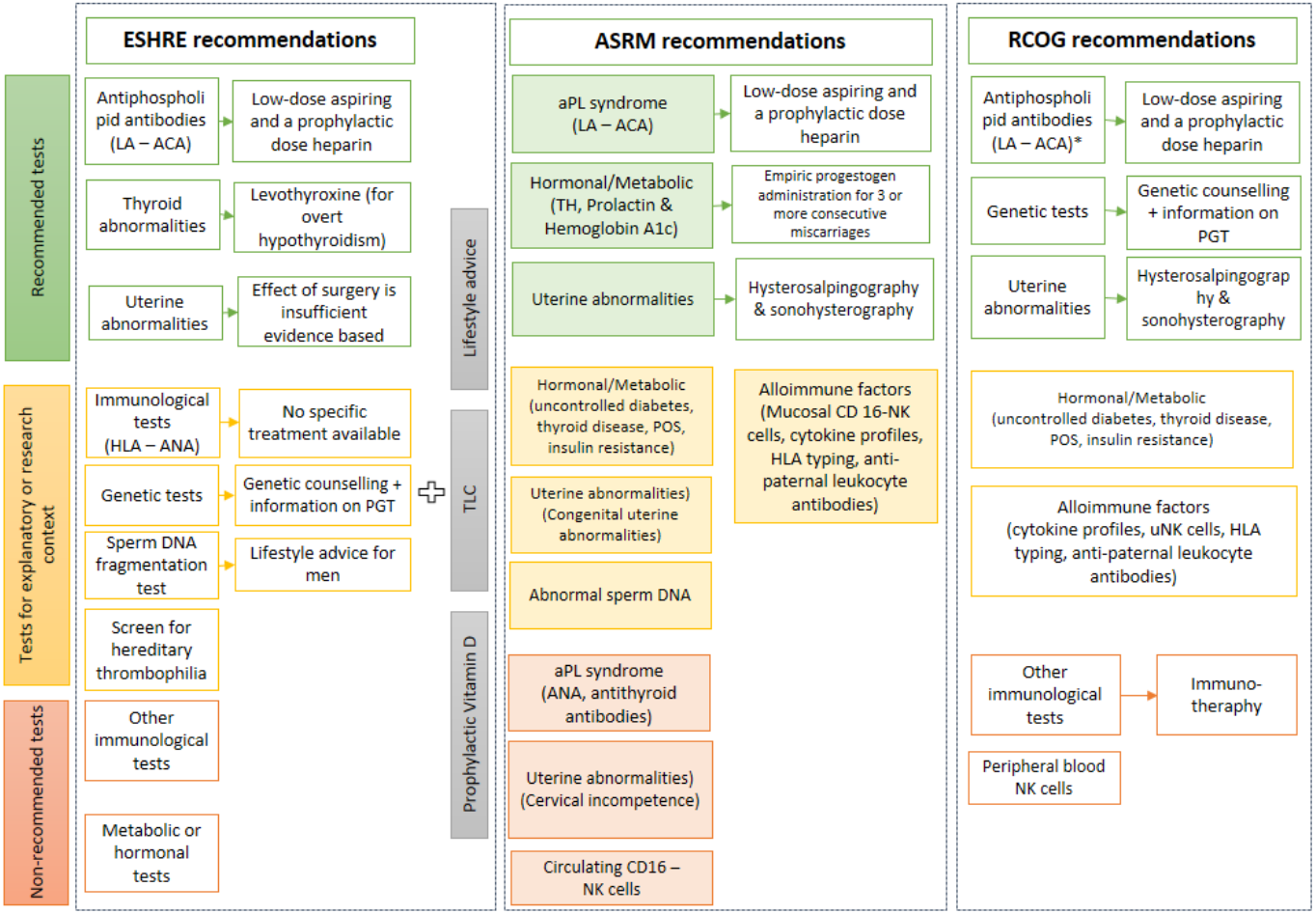


Figure 1.1 Modified chart of recommendations of investigations and treatment for recurrent miscarriage according to ESHRE, the American Society for Reproductive Medicine (ASRM) and RCOG clinical guidelines. PGT (preimplantation genetic testing).

Source: Modified graph from the Guideline of the European Society of Human Reproduction and Embryology (ESHRE). Recurrent Pregnancy loss. ESHRE.

1.7 How is miscarriage managed?

1.7.1 Sporadic miscarriages

Traditionally, the "gold standard treatment" for miscarriage was surgical treatment, which was offered in 88% of the cases up until the past decade[52,116]. This high prevalence was explained by the assumption that retained tissue in the uterus would increase the risk of haemorrhage or infection, and therefore, the best approach was to retrieve the retained products of conception (RPOC) from the uterus[117]. However, it has been proved that there are no statistically significant differences between the incidence of infection and type of treatment for miscarriage[118] and the incidence of infection remains low between 2-3%[118]. In the last decades, the development of new techniques and drug treatments have enabled the introduction of minimally invasive interventions which reduce unnecessary surgical procedures whilst maintaining low rates of morbidity and mortality from miscarriage[61]. The three main types of management for women who miscarry are expectant, medical and/or surgical management[117]. Women's clinical signs and symptoms and women's preferences will define the pathways of care for the management of miscarriage[17]. Pathways of care will differ between first trimester and second-trimester miscarriages, but also between the type of miscarriage (i.e. missed, complete or incomplete miscarriage; Figure 1.2). The success rate of each management will depend on the type of miscarriage, length of follow-up and definition of complete miscarriage[119]. Every management has its own risks and benefits and women should be counselled accordingly to achieve shared decision making[120].

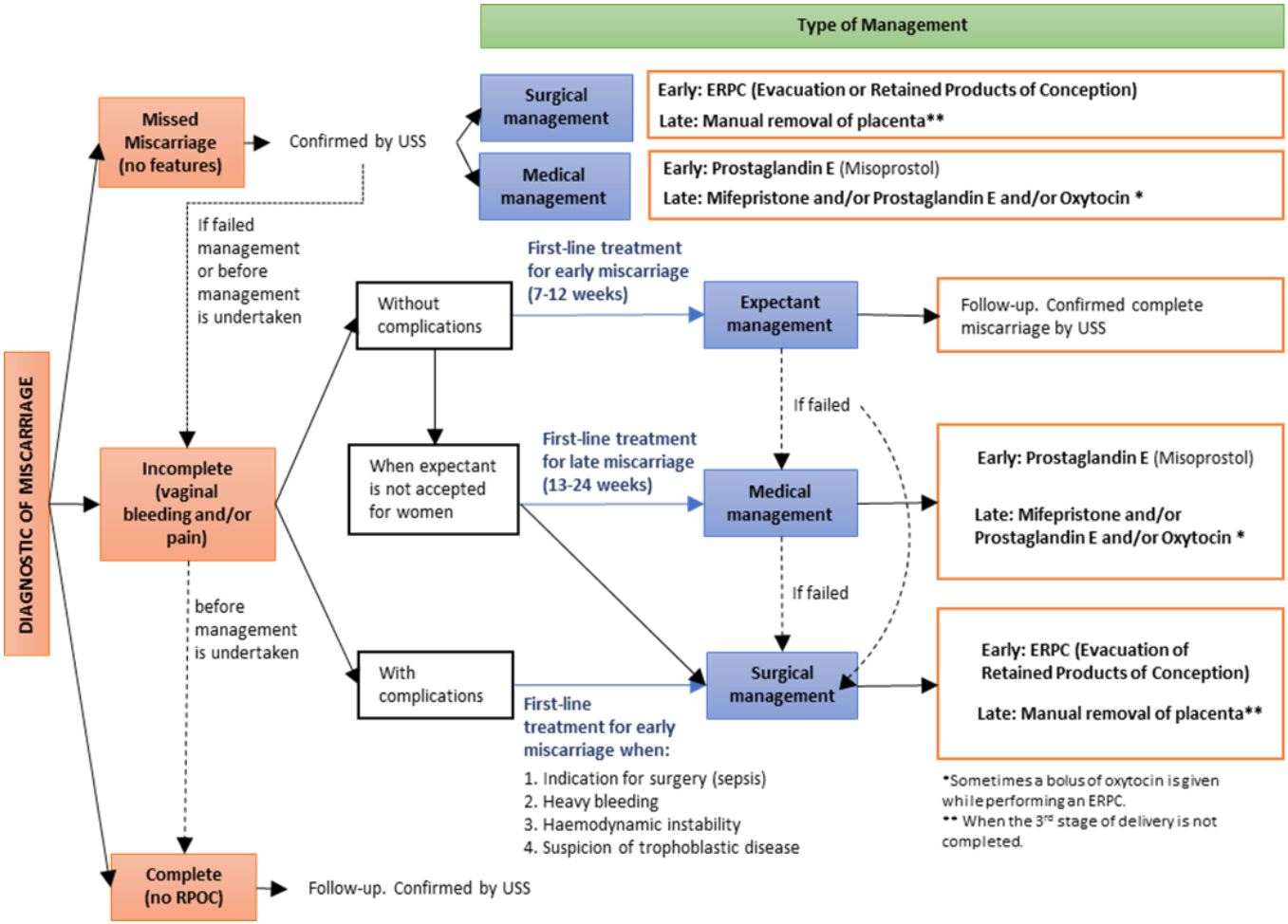


Figure 1.2. Flowchart of pathways of care for first and second-trimester miscarriage

Note: ultrasound scan (USS)

1.7.2 Expectant treatment

Expectant or conservative treatment involves letting the process of miscarriage take its natural course without undertaking any invasive or pharmacological management. It is the first-line management strategy when women have been diagnosed with an early miscarriage (i.e. before 12 completed weeks of gestation) and they are hemodynamically stable[121] (Figure 1.2). It is also the preferred management for women who are less than 6 weeks of gestation and they present with bleeding but without symptoms of pain[121]. Expectant management increases the time to complete expulsion, and therefore, the risk of experiencing moderate to heavy bleeding and cramping is higher[121]. Expectant management should be avoided for women who are at an increased risk of haemorrhage (i.e. late miscarriage, medical history of coagulopathies or impossibility of undertaken blood transfusion); who had previous traumatic or adverse experiences during pregnancy such as miscarriage, stillbirths or antepartum haemorrhage; and/or when there is evidence of an infection[121]. The majority of women will be allowed to go home, and they will be advised about undertaking an ultrasound scan in 10 days to confirm that the miscarriage is complete[45]. It is estimated that 40% of women will have an early miscarriage during this time period[45]. Nevertheless, success rates vary significantly in the literature[122,123].

1.7.3 Medical treatment

Medical management is an acceptable alternative to surgery[124] and it is the first-line treatment for second trimester miscarriage (i.e. between 13 + 0 and before 24 weeks of gestation; Figure 1.2)[61]. Medical management shortens the time of the completion of the expulsion of RPOC compared to expectant treatment[125]. However, it should not be offered to women who have signs of infection, excessive bleeding, pyrexia or

abdominal pain[45]. The main uterotonic drugs used for medical management of miscarriage are prostaglandins, other uterine contraction agents, uterotonic agents/drugs or oxytocic agents[61]. Prostaglandins are lipids derived from arachidonic acid that can be made by nearly all the organs in the body[126]. They mediate in several processes such as inflammation and the formation of blood clots[126]. In addition, they cause the contraction of the muscular wall, which narrows the blood vessel, and therefore, it helps the prevention of blood loss[126].

1.7.3.1 First-trimester miscarriage

The most common prostaglandin used in the treatment of early miscarriage is Misoprostol, a prostaglandin E1 analogue[127]. Although Misoprostol was originally developed for the prevention and treatment of peptic ulcers, it has been found to be effective in contracting the pregnant uterus, which helps the expulsion of the POC[127]. Compared to other prostaglandin or uterotonic drugs, Misoprostol is less costly and widely available worldwide[61]. In addition, it is stable at room temperature and it has few side effects including diarrhoea, nausea, cramping and vomiting[61]. Misoprostol can be administered orally, vaginally, sublingually, buccally or rectally[127]; however, vaginal administration has been found to prolong levels of Misoprostol in serum and to have a more localised effect[127]. According to the Royal College of Physicians of Ireland (RCPI), women who are treated medically for first-trimester miscarriage should be taking two doses of 600 micrograms (µg) of Misoprostol sublingually or vaginally every three hour[45]. In most cases, women will not need to be hospitalised, and they will be advised to have an ultrasound scan a week after to confirm completion of miscarriage[45]. Approximately 80% of women will complete the process of miscarriage during this time[45] but rates vary depending on the time of follow-up care

after administration of the drug[128]. Success rates for medical treatment of early miscarriage vary between 80 to 90% according to the literature[124,129]. The combination of Mifepristone, another progestogen or progesterone and glucocorticoid hormone antagonist, and Misoprostol has been recently reported as being approximately 20% more effective when managing first-trimester miscarriage compared to Misoprostol monotherapy [130].

Nevertheless, clinical protocols for the medical management of first-trimester miscarriage vary broadly among countries and institutions[16]. According to a systematic review and network meta-analysis assessing the effectiveness of Misoprostol for a missed miscarriage, a first dose of 600 µg sublingually or 800 µg vaginally were the most effective doses for completion of miscarriage within 24 hours; nevertheless, the ideal dose or interval is not yet agreed[128]. For example, according to the National Institute for Health and Care Excellence (NICE), a single dose of 600 µg of Misoprostol should be given for women with an incomplete miscarriage and a dose of 800 µg for both missed and incomplete miscarriage to allow alignment of treatment protocols[131]. The International Federation of Obstetrics and Gynecology (FIGO) recommended administration 800 µg of Misoprostol every 3 hours (two doses) vaginally or 600 µg every 3 hours (two doses) sublingually for missed abortion; and 600 µg of Misoprostol orally (one dose) or 400 µg sublingually (one dose) or 400-800 µg vaginally for incomplete miscarriage[132].

1.7.3.2 Second-trimester miscarriage

Mifepristone is an excellent mediator in the induction of labour in second-trimester miscarriages[16]. Consequently, it is broadly accepted that a combination of Misoprostol

and Mifepristone is the best first-line pharmacological intervention for second-trimester miscarriage[16]. The Regulation of Termination of Pregnancy Bill was voted and passed in 2018 for the first time in the ROI[133]. The new law legalised free access to termination of pregnancy up to 12 weeks' gestation in Ireland. Hence, a new clinical guideline has been developed to manage termination of pregnancy (TOP) and fetal anomalies by the Institute of Obstetricans and Gynaecologists (IOG) and the RCPI according to the Health [Regulation of Termination of Pregnancy (TOP)] Act 31 2018[134]. This guideline recommends a combination of Mifepristone (200 mg, orally) and Misoprostol (400 µg, buccally or vaginally) at an interval of not less than 24 hours and not more than 48 hours for induction of labour under 24 weeks of gestation. Misoprostol should be given every 3 hours and it should not be given more than 5 times[134].

As it happens with early miscarriage, several protocols for the administration of a combination of Mifepristone and Misoprostol, or Misoprostol only can be found in the literature for second trimester miscarriage. According to the Royal College of Obstetricians and Gynaecologist (RCOG), a combination of Mifepristone and Misoprostol is recommended for treating second trimester miscarriage. A dose of 200mg of Mifepristone orally, followed 12–48 hours later by Misoprostol 800 µg vaginally, followed by Misoprostol 400 µg orally or vaginally every 3 hours until abortion occurs. If after 24 hours miscarriage does not occur, Mifepristone can be repeated 3 hours after the last dose of Misoprostol, and 12 hours later Misoprostol may be recommenced[135].

1.7.4 Surgical treatment

The evacuation of retained products of conception (ERPC) from the uterine cavity is a surgical intervention widely performed to treat women with incomplete, missed miscarriage, or when a termination of pregnancy is requested[136]. It is the first-line treatment when there is excessive bleeding, when women are hemodynamically unstable, or when there is a presence of RPOC in the uterus (Figure 1)[45]. ERPC is performed using dilation and curettage (D & C)[137], which is a procedure that involves the opening of the cervix (dilatation), followed by the extraction of RPOC using a thin instrument (curettage) from the endometrial cavity[137]. ERPC can be performed using suction or sharp curettage; however, after the publication of a Cochrane review, suction curettage has become widely preferred to sharp curettage because it has been proved to decrease blood loss, pain and/or duration of the procedure[138]. According to Clinical Guidelines in Ireland, surgical management is generally offered in different clinical scenarios[138]:

- to women who specifically request this treatment
- to women whom conservative or medical management have previously failed
- to women who experience heavy bleeding and/or severe pain, when there is suspicion of trophoblastic disease, and/or when women present with signs and symptoms of infection

1.7.5 Complications depending on the type of treatment

Complications among women who have been treated using medical management are uncommon[118,139,140]. In accordance with this, results found in a Cochrane review also reported that complications after surgical treatment for first-trimester miscarriage are rare[141], with an overall complication rate estimated in 6%[142]. In a randomised

controlled trial (miscarriage treatment (MIST) trial) comparing the three types of treatments for miscarriage (expectant, medical or surgical), the expectant care group had more days of bleeding and a greater amount of bleeding compared to surgical curettage[118]. A Cochrane review published in 2001 concluded that vacuum aspiration was associated with less blood loss, less pain and shorter duration of the procedure than sharp curettage[138]. Risks found in the literature after undergoing evacuation of retained products of conception (ERPC) are uterine perforation (1%), cervical tears, intra-abdominal trauma (0.1%), haemorrhage and infection[45]. However, the incidence of infection was low (2-3%) after either expectant, medical or surgical treatment among first-trimester miscarriage and no evidence exists of a difference by the methods of management[118]. In addition, surgical management has been associated with significantly less unplanned admissions and unplanned surgical intervention compared to expectant or medical management[118].

1.7.6 Management in the next pregnancy

1.7.6.1 One or two previous miscarriages

Generally, clinical guidelines in the Republic of Ireland recommend to perform investigations and treatments for women with recurrent miscarriage, defined as three or more miscarriages. Nevertheless, counselling and advice should be provided for women who are planning to get pregnant again following any miscarriage. The main recommendation is to promote healthy behaviours and reduce risk factors to increase the chance of the next subsequent pregnancy being successful[143]. These recommendations include healthy eating behaviours, exercise in moderation, reducing alcohol, smoking or caffeine intake. Weight loss is also advisable among women who are overweight. It is equally important to inform women about the latest evidence in

the field on the risk of another pregnancy loss. Equally important is to inform women that there is not enough evidence to recommend waiting for a specific period of time; however, women and their partners should feel emotionally and psychologically ready to cope with another pregnancy[144]. Counselling, psychological support or psychological therapy (e.g Cognitive Behavioural Therapy) is imperative among women who might be at higher risk of developing stress, anxiety or who are feeling depressed in their next pregnancy[144].

1.7.6.2 Recurrent miscarriage

The management of women with recurrent miscarriage depends on the results from the clinical investigations. The recommended medical management for women in preparation for next pregnancy who have a history of three or more miscarriages and who fulfil the criteria of APS is low-dose aspirin (75 to 100mg/day) starting before conception and prophylactic dose heparin (i.e. unfractionated heparin [UFH] or low-molecular-weight heparin [LMWH])[13]. Women with hypothyroidism before conception or during early gestation should be treated with Levothyroxine[13]. However, evidence for treatment of women with subclinical hypothyroidism is conflicting. Nevertheless, women who get pregnant again and have subclinical hypothyroidism are recommended to check levels of thyroid stimulating hormone (TSH) and they should be treated with Levothyroxine early in pregnancy if the levels remain subclinical or are low[13]. Other medical treatments that have been evaluated to improve pregnancy outcomes in women with recurrent miscarriage are folic acid, progesterone and metformin. It is well-established that a supplement of folic acid before and during the first trimester of pregnancy prevents the development of congenital malformations[145]. Some observational studies have related a reduced level of folate

during pregnancy and adverse pregnancy outcomes[146,147]. Homocysteine is a key amino acid which is involved in several key metabolic processes in the folate pathways[148]. Levels of homocysteine usually drop during normal pregnancy. Disturbances of homocysteine metabolism in the mother of the fetus have been associated with fetal neural tube defects, with recurrent pregnancy loss and with other placental vasculopathy disorders[148]. Daily folate supplementation of 0.5 mg is recommended to reduce the levels of homocysteine, and it has been clearly shown to reduce the risk of fetal neural tube defects. Progesterone has been assessed to improve live birth rate with luteal phase insufficiency[13]. Finally, metformin, a low-risk and effective oral hypoglycemic agent for Type 2 Diabetes Mellitus, is recommended to prevent pregnancy loss among women with glucose metabolism defects[13]. Non-pharmacological managements that are offered to women with recurrent miscarriage are cervical surveillance, weight loss and smoking cessation. Clinical guidelines for the recommendation of investigations and treatment for recurrent miscarriage vary between colleges and countries. A summary of the main recommendations for investigations and treatments according to three main clinical guidelines can be seen in Figure 1.1.

1.8 What are the risk factors for miscarriage?

Identifying risk factors for miscarriage has become a public health priority because of the high number of unexplained cases. For example, as part of a James Lind Alliance Priority Setting Partnership in the UK, Prior et al. (2017), found that five of the top 10 priorities were focused on identifying risk factors for miscarriage (e.g. "*Do lifestyle factors cause miscarriage?, To what extent do pre-existing medical conditions cause miscarriage?*")[149]. These priorities were obtained from a steering group consisting of

women who experienced pregnancy loss, charity representatives, as well as healthcare professionals[149].

1.8.1 Well-known risk factors for miscarriage

One of the most studied and well-known factors associated with an increased risk of miscarriage is advanced maternal and paternal age[13,29,150-155]. As an example, the maternal and fetal loss cohort study in Denmark found that women in their late 30s or older had a higher risk of having a miscarriage, ectopic pregnancy or stillbirth, irrespective of their reproductive history[29]. In addition, several studies have shown an association with advanced maternal age and adverse pregnancy outcomes (i.e. stillbirth, pre-term birth, extremely large for gestational age, ectopic pregnancy, etc.)[156 157]. Furthermore, previous miscarriage[158-162 157], previous infertility and heavy smoking[163-168] have been frequently linked to a higher risk of miscarriage in the literature.

1.8.2 Modifiable risk factors for miscarriage

Miscarriage was considered unpreventable until very recently by medical and obstetrics professionals; therefore, little attention has been given to try to modify lifestyles and psychological factors to prevent unnecessary pregnancy loss[169]. In recent years, a greater amount of studies have explored the association of potentially modifiable or preventable risk factors with the risk of miscarriage[150,152,170,171]. However, study designs and the difficulty of adjusting for several confounders have limited the evidence in this field[172]. Extremes of maternal weight[173-178], caffeine intake and alcohol consumption are good examples of controversial risk factors that have been positively associated with miscarriage in some studies [150,152,171,179-182], although

they have lacked enough significance to be associated to miscarriage in other studies[150,171].

The extent of impact of preventable risk factors is almost innumerable. Physical activity, lifting heavy weight, occupational status and work schedules are some of the modifiable risk factors that have been explored in relation to miscarriage[150,152]. For instance, Nilsson et al. (2014), concluded that more than 25% of the miscarriages that occurred during the study could have been preventable if the identified risk factors included in the study (i.e. exercise, alcohol consumption, smoking, coffee consumption) had been reduced to low risk levels[152]. Also, in a recent and innovate epidemiological study, Bruckner et al. (2016) correlated stressful environmental factors, such as monthly unemployment rates, and the variability of pregnancy loss rates over a period of 15 years in Demark. They found that at least 15% of pregnancy losses were preventable and in a month, this excess in the spontaneous loss was statistically attributable to the unexpected high unemployment rate in the previous month[183].

1.8.3 Psychological risk factors

Depression, anxiety and psychological stressors have been consistently linked to adverse pregnancy outcomes including preterm birth and small for gestational age[184-187]. In particular, stress has gained significant attention in the field because previous studies found a direct relationship between pregnant animals exposured to stressful conditions and adverse pregnancy outcomes[188,189]. However, the literature related to the potential impact of stress on pregnant women is still conflicting. A recent systematic review and meta-analysis published in 2017, found robust evidence that

prior psychological stress before and during pregnancy is associated with miscarriage[190]. Work stressors and stressful life events have been linked to increased risk of miscarriage in several epidemiological studies[150,152]; whereas other studies did not find any association[191,192]. Of the two studies identified which investigated the relationship between biomarkers of stress (i.e. urinary cortisol and salivary alpha-amylase) at preconception, during early pregnancy and pregnancy loss, one of them reported an increase in miscarriage[193], whereas the other did not[194]. One of the main limitations when gathering the evidence on stress and pregnancy loss is the wide variety of type of stress identified in the literature (i.e. perceived stress, physiological stress, stress at work, stressful life factors). The association between pregnancy loss and stress is undoubtedly complex[188,195] and the potential underlying mechanisms in pregnancy disruption are still unclear[195].

1.9 What are the health and support services available for women who miscarry?

Health and emotional support services for women who experience miscarriage differ depending on the type of miscarriage and the women's emotional and clinical conditions at the time of the loss. Services vary around the world with some countries providing more specialised and dedicated management and support services, whereas other countries lack any available services or they are likely to stigmatise the loss of a baby[196]. In Ireland and the UK, women who experience the loss of a baby have a wide range of outpatient and inpatient clinical support services available. Women who experience bleeding and or pain will usually seek help and might even be medically or conservatively managed at the maternity hospital's emergency department (ED). Women who experience a missed miscarriage will more commonly be identified

during a scan examination at Early Pregnancy Assessment Units (EPAU) or general practitioners' assessment. Specialised and critical care as inpatient at the hospital settings needs to be available for women who develop complications during the loss or who prefer to be treated surgically or who need monitoring during the process of delivery in second trimester miscarriages.

Bereavement care following pregnancy loss, end-of-life care or palliative care are provided by clinical midwife specialist in bereavement in some maternity hospitals in the Republic of Ireland[10]. Pastoral and spiritual counselling through the hospital chaplaincy services and social work support/counselling through social work departments are also support services available to women who miscarry in the Republic of Ireland and the UK[10]. In addition, specialised services are available to women who have a history of recurrent miscarriage at various pregnancy loss or miscarriage clinics (PLCs). The main aim of a PLC is to investigate the medical causes of recurrent pregnancy loss and to provide specialised and dedicated medical care, information and support to parents. Charitable organisations and community based psychological support services are available in Ireland and the UK (e.g. *The miscarriage association of Ireland and the UK).*

The quality of care and support provided during miscarriage have improved in the past decades[10]. However, more research is needed to identify effective emotional support interventions to prevent miscarriage and/or treat women and their partners after a miscarriage. In fact, the Prior et al. (2017) study included this need as one of the top 10 research priorities recognised by women with a history of miscarriage[149]. Despite the high incidence and emotional burden of miscarriage, much of the research has

focused on identifying risk factors of miscarriage and only a few studies have explored women's experiences and support needs following this event[150,197-199]. These studies suggest that parents who visit hospital settings because of miscarriage do not receive appropriate clinical and supportive information at the emergency departments[197,198]. Pregnant women and their partners acknowledged the compassion shown by midwives and/or nurses at the ED when providing physical care; nevertheless, they emphasised the unfulfilled need to discuss their emotions at that critical time[198]. More research needs to be done to assess the health and support services availables for women who miscarry in the community and in hospital settings. It is essential to provide adequate training and eduction in relation to miscarriage for health professionals involved in the obstetric care of women who miscarry in order to promote appropriate care to couples who experience pregnancy loss[197,200].

1.10 Why is miscarriage important?

1.10.1 Public health issues

Miscarriage is considered a public health issue worldwide. Firstly, because of the high rate of occurrence but also because of the long-standing psychological and medical morbidity associated with it. Considering that 25% of clinically recognised pregnant women will experience a first-trimester miscarriage, approximately 14,000 miscarriages will occur every year in the ROI alone[201]. Traditionally, miscarriage was only studied from a biomedical point of view (i.e. treating signs and symptoms, surgery the only treatment available…); nevertheless, a more holistic approach including alternatives to surgical treatment and psychological support for women who

experience miscarriage is slowly being introduced into the healthcare pathways for these women[144 61]. The evolution of the management and support available to women who miscarry highlights the response to the known impact of miscarriage which is associated with psychological, medical, economic and social morbidity.

1.10.2 Psychological morbidity

The psychological impact of miscarriage has been extensively studied in the literature[202-215]. Historically, women's grief after an early pregnancy loss was considered to be mild and to recede shortly after the event; however, further research has shown that women's psychological impact after a miscarriage is as significant as losing any loved relative and it can last a prolonged period of time after the loss[212].

A meticulous review published at the beginning of 2018 gathered the main longitudinal studies which assessed the psychological impact of early pregnancy loss on women and their partners[215]. This review was focused on the prevalence, intensity and duration of depression, anxiety and posttraumatic stress disorders (PTSD) symptoms after the adverse pregnancy outcome (i.e. early miscarriage, ectopic pregnancy or late miscarriage only if more than 90% of the sample had experienced a loss within the first 24 weeks of gestation)[215]. A total of 27 articles were included in this review. Depression and anxiety were found to be significantly relevant in the first month after a miscarriage. According to this review, moderate levels of depression appeared to have a prevalence of between 8% and 20%. Women's partners showed lower levels of depression and anxiety in all the studies. Among those studies which assessed anxiety, the reported prevalence was between 18% and 32%. In agreement with previous studies, symptoms of depression were still present up to one year after

the event of miscarriage[212,216-219]. Conversely, Lok et al. (2010) found that levels of depression were not higher in women one year after miscarriage[212]. The highest incidence in the review was reported for PTSD; between 25% and 39% of women reached the threshold for the diagnosis of PTSD three months after a miscarriage[215]; however, only three studies assessed this condition, and some of them did not have a comparison group. Therefore, it was possible to quantify the overall psychological pathology in the population with pregnancy loss, but it was not demonstrated to be statistically significantly associated with the loss itself[215]. In addition, Farren et al. (2018) did not include studies that assess the psychological impact on pregnant women who have a previous history of miscarriage[215].One potential limitation of this review was that only clinical conditions were included in the review (i.e. anxiety, depression and PTSD), excluding other important aspects of women health such as psychological stress and grief. However, women who miscarry have reported higher levels of psychological stress and grief, among others[190,220-223].

It is increasingly accepted that women's psychological wellbeing is influenced not only following the event of a miscarriage but also during women's subsequent pregnancy[203,205,224]. A systematic review and meta-analysis assessed the effect of miscarriage on pregnant women's depression, anxiety and stress with a history of previous pregnancy loss (i.e. pregnancy loss was analysed as a composite variable including miscarriage, stillbirth and neonatal death)[203]. Overall, the authors found higher levels of anxiety and depression during pregnancy (i.e. first, second and third trimester of pregnancy); whereas no significant association was found between previous pregnancy loss and increased stress levels in women during the subsequent pregnancy[203]. Although random effects were analysed using pregnancy loss as a

composite variable, almost 90% (4446/5114) of the sample were women who had a miscarriage[203]. This is important to keep in mind because it is suggested that the type of perinatal loss might affect women's psychological wellbeing differently[203,225]; therefore, more targeted research is needed to examine this variation and to identify potential variations in women's need[203].

Evidence on risk factors for psychological morbidity after miscarriage is another important question in this field, which is limited by poor quality and insufficiently powered studies[215]. Table 1.1 summarises the main risk factors for the development of psychological morbidity after early miscarriage according to the evidence published in the most recent review[215].

1.10.2.1 Non-pharmacological interventions to reduce levels of stress, anxiety and depression

The latest Cochrane systematic review in miscarriage, published in 2012, explored the effectiveness of psychological and counselling interventions to reduce anxiety and depression among women following early miscarriage [226]. A total of 1001 women and six randomised controlled trials were included in the analysis. The authors concluded that there was not enough evidence to state that psychological interventions were effective to reduce levels of anxiety and depression in this target group. Further recommendations are limited by high heterogeneity between types of interventions, status of health professionals who delivered the interventions, timing of counselling or for follow-up methods[226]. In addition, this systematic review did not include women in subsequent pregnancies, and it did not assess the effect of other types of well-accepted distress factors such as perceived stress or grief. To the best of my

knowledge, there are no studies assessing the effectiveness of non-pharmacological interventions to reduce the psychological morbidity of miscarriage among pregnant women. Hence, more research is needed to identify optimal psychological support for women who are at higher risk of developing psychological disorders following a miscarriage, and also in subsequent pregnancies.

Table 1.1 Main risk factors for the development of psychological morbidity after and early miscarriage

	Risk factor	Protective impact
Depression	• Fewer existing children • History of infertility • Had previous miscarriage • Had previously seen a viable foetus on ultrasound • Planned pregnancy (partners) • Lower marital satisfaction or higher marital discord	• Older age of women
Anxiety	• No children or previous miscarriages	
PTSD	• History of abuse • Feeling responsible for the loss • Lack of control over one's life	
Depression, anxiety and PTSD	• A longer gestation • Unplanned pregnancy (women) • Being single • Lower perceived spousal support • Past psychiatric history	

Source: Farren J, Mitchell-Jones N, Verbakel JY, Timmerman D, Jalmbrant M, Bourne T. The psychological impact of early pregnancy loss. Human reproduction update. 2018 Sep 11;24(6):731-49.

1.10.3 The clinical burden of miscarriage

1.10.3.1 Outcome in future pregnancy

Recurrent miscarriage has not only been associated with psychological and emotional impact, but also with maternal and fetal complications during subsequent pregnancies.

Poor reproductive history has been consistently associated with an increased risk of miscarriage. According to several epidemiological studies, the risk of having a miscarriage cumulatively increases as the number of previous miscarriages rises from one to three[9,227]. Women whose only pregnancy has ended in miscarriage have a 20% higher risk of having a subsequent pregnancy loss compared to 5% among women who have always had successful pregnancies[158]. This percentage increases to 28% after two consecutive miscarriages and to 48% for women who had three or more consecutive miscarriages[158]. In contrast, women with one previous birth or primigravid women had a much lower incidence of miscarriage estimated at 5%[158]. These results were corroborated by another Danish population study including more than 300,000 pregnancies. In this study, the risk of pregnancy loss increased from 0 to 4 consecutive miscarriages from 16%, 25%, 45% and 54% respectively[228]. Similar results were found in a Scottish population-based study including over 140,000 pregnancies [227]. According to this study, the risk increased from 0 to 4 consecutive miscarriages from 14%, 23%, 28% and 42% respectively[227]. After adjusting for age and smoking, the risk of having a miscarriage sequentially increased in women with one or two previous miscarriages compared with women whose last pregnancy was not a miscarriage (Odds Ratio, OR=1.60; 95% CI 1.44-1.78 and OR=2.28; 95% CI 1.77-2.94 for one and 2 previous miscarriages)[227]. However, there was no significant association between women who had three or more miscarriages and an increased risk of having a subsequent pregnancy loss[227]. Previous miscarriages have been also associated to a higher risk of preterm delivery and antepartum haemorrahage[229,230,231]. For example, threatened miscarriage has been associated with an increased risk of placental abruption from 1.0% to 1.4%[232,233].

Similarly, second-trimester miscarriage also increases the risk of having a subsequent second-trimester loss or preterm birth[234]. A retrospective cohort study found that women who had a second-trimester miscarriage were 10.8 times more likely to have a recurrent pregnancy loss[235]. Second-trimester miscarriage was also associated with a 33% increased risk of having a preterm birth in subsequent pregnancies[235].

1.10.3.2 Inter-pregnancy interval

Inter-pregnancy interval (IPI) is another factor that has been extensively studied in relation to miscarriage[236]. However, the optimum IPI following a miscarriage has not been identified. For example, a cohort study including 514 women with a previous miscarriage, found that an IPI of less than 3 months was associated with a decreased risk in having a subsequent miscarriage[237]. However, other IPIs have been investigated in the literature. A population-based cohort study including over 30,000 women who experienced a miscarriage found that an IPI of 6 or less months was associated with a decreased risk of having a subsequent miscarriage compared to women who conceived between 6 and 12 months after the miscarriage[236]. Contradictory results were found by a systematic review and meta-analysis published in 2016. A total of 16 studies with a total of 1,043,840 women were included in the analysis[238]. This review concluded that an IPI of less than 6 months was not associated with an increased risk of adverse pregnancy outcomes (e.g. further miscarriage, preterm delivery, stillbirth, low birthweight and pre-eclampsia) following miscarriage[238].

1.10.4 Lack of population awareness of miscarriage

Despite the prevalence of miscarriage, the population's awareness and knowledge of risk factors and reproductive health information about this issue is poor. Two studies

assessed the knowledge and awareness of information related to miscarriage in the general population. The first one was a cross-sectional study assessing the public perceptions of miscarriage using an online survey freely available in 49 states in the United States (US)[239]. Some of the most surprising results were that respondents believed that miscarriage was a rare complication of pregnancy happening in 5% or less of all pregnancies. In addition, widespread misconceptions about miscarriage were common among the respondents such as believing that use of an intra-uterine device (28%), birth control (22%), stressful events (76%) or lifting heavy object (64%) could provoke a miscarriage[239]. Bardos et al. (2015) concluded that the lack of knowledge in risk factors for miscarriage could potentially influence the false sense of responsibility after a miscarriage event. This also meant that women who had a misunderstanding of risk factors could be more likely to feel responsible for the loss because of their lifestyles before or during pregnancy[239]. One of the potential limitations of this study was that 80% of the study population were enrolled in a specific medical degree program (e.g. Medicine). No more specific information about the level of education and/or detail of degree programmes of the remaining 20% of the study population was available; and therefore, differences between different educational backgrounds could not be investigated[239].

The second study was also a cross-sectional study which was conducted in the US but in a single university[240]. This time only undergraduate students who were enrolled in a single Introduction to Psychology course were approached. The main outcome of this study was to investigate preconception health and pregnancy, and therefore, only a few questions about risk factors for miscarriage were assessed. Overall, students had a low to moderate awareness of preconception of health and pregnancy, with less than

65% of correct responses. One of the main limitations of this study is its low external validity because students were selected from a single course and not randomly selected courses[240]. Lack of information on miscarriage might impact on poor reproductive behaviours. Therefore, further research should evaluate the public's knowledge of miscarriage, specifically among young stratums of the population. Promoting reproductive health education among the population, who are at early reproductive ages, will help to increase the likelihood for healthier reproductive behaviours in future generations[197,200]

1.11 Why is data quality important?

Data quality and data management are essential steps of every single study and are very often neglected or overlooked. Regardless of the study design or the clinical area, the quality of the data will affect the reliability of the research findings, the conclusions and further recommendations[241,242]. For that reason, I would like to dedicate this section of this thesis to the importance and significance of data quality.

1.11.1 Key terms and concepts

Abdelhak, 2014 defines data as " *a collection of elements on a given subject; the raw facts and figures expressed in text, numbers, symbols, and various media that can be captured, communicated, and processed either manually or electronically*"[243]. Data that has been processed into meaningful form is called information, and knowledge is understood as "*the information that is further enhanced with meaning*"[243]. In general, data follow a lifecycle in which it can become information. The first stage of the lifecycle is the capture of the data, followed by the submission, processing, analysis

and dissemination of the data, in which data are produced as information to be available for data users[244]. However, information and knowledge are not meaningful if the quality of the data is not preserved in each of these stages.

1.11.2 Data Quality

According to the European Statistics System (ESS), quality of data "*is a multi-dimensional concept and encompasses all aspects of how well statistics are fit for their purpose*"[245]. That means that data quality should be consistent with international standards and best practice in order to meet data users' needs[244]. The Health Information and Quality Authority (HIQA) in Ireland has adopted the most internationally recognised dimensions in the assessment of data and information quality within the health and social sector (Figure 9.2)[244,245]. In their guideline for assessing data quality, HIQA provides a data-quality assessment tool. This tool is based on the Canadian Institute for Health Information (CIHI's), the Information Quality Framework (IQF) and the Generic Statistical Business Process Model (GSBPM)[244].

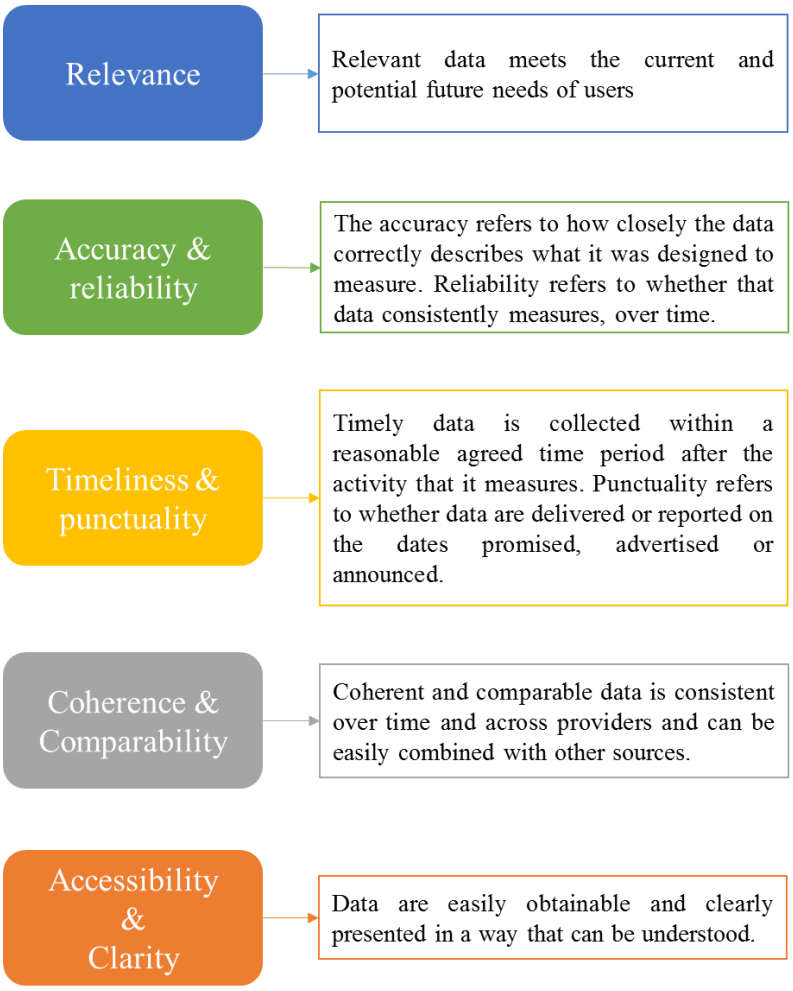


Figure 9.2. Definitions of data quality dimensions according to HIQA

Source: Health Information and Quality Authority (HIQA). Guidance on a data quality framework for health and social care. 2018. HIQA.

1.12 Summary

Worldwide, miscarriage is one of the most common complications in early pregnancy. Miscarriage is clinically classified as missed, incomplete or complete miscarriage, but it can also be defined according to the weeks of gestation at which it occurs (e.g. early or late miscarriage). Nevertheless, there is no consensus on the criteria to define miscarriage among the different countries and guidelines. In Ireland, early miscarriage is defined as the loss within 12 completed weeks of gestation (e.g. first-trimester

miscarriage), and late miscarriage is defined as the loss of a pregnancy before 24 weeks of gestation (second trimester miscarriage).

Approximately 25% of clinically recognised pregnancies will end in a first-trimester miscarriage; yet, in some cases, the use of new hormonal tests to identify biochemical pregnancies have increased this estimated rate up to 50%. Nevertheless, estimating and validating the number of early miscarriages in a population is a challenge. Some miscarriages occur at home, some are managed at outpatient departments, some are admitted as inpatients in the hospital and, in some cases, the information is incomplete in the medical history. For example, most of the studies that report trends of early miscarriage based their numbers on self-reported miscarriages. Consequently, these estimations cannot be validated. In addition, outpatient data is not always available at a national level. On the other hand, the prevalence of recurrent miscarriage varies from 1% to 5% depending on the definition used. Some definitions will only consider recurrent miscarriage when the woman has experienced two or more miscarriages, whereas other definitions require three or more miscarriages. Similarly, definitions also differ when considering whether the miscarriages were consecutive or not. This discrepancy in definitions challenges the comparison of the evidence in the area of pregnancy loss.

It is well-documented that miscarriage has a significantly negative psychological impact on women, their partners and family. Some studies have shown that women who have experienced a miscarriage show higher levels of stress, anxiety and depression in subsequent pregnancies compared to women without a history of

pregnancy loss. Despite the knowledge of the psychological burden of miscarriage, the potential benefit for non-pharmacological interventions in this targeted group is not clear. There is a gap in the knowledge of effective psychological support interventions following a miscarriage. Moreover, to my knowledge, there are no studies assessing the effectiveness of non-pharmacological interventions in pregnant women with a history of prior miscarriage.

Despite the high frequency of miscarriage, chromosomal abnormalities only account for 50-60% of the cases. In other words, more than half of miscarriages are idiopathic or unexplained. Without a clear etiology of miscarriage, efforts in research have focused mainly in two directions: investigating efficient treatments to increase the rate of success in the following pregnancy, and identifying potential risk factors to prevent miscarriage. Although investigation methods on causes of miscarriage have been extensively studied over the years, the optimal management and treatment has not yet been established. Recommendations for investigations and treatments vary between the different clinical guidelines. However, it is generally accepted that a combination of aspirin and heparin will improve the successful rate of livebirth among women with antiphospholipid syndrome. Nevertheless, recommending other types of investigations and treatments is still controversial. More research is needed to understand the potential effect of hormonal or metabolic disorders (e.g. uncontrolled diabetes, PCOS), but also the effect of alloimmune factors (e.g. cytokine profiles, uNK cells) in recurrent miscarriage. As was stated in the previous section, the number of miscarriages that a woman has experienced during her reproductive life will affect her risk for subsequent miscarriage. Therefore, recognising effective treatments that can prevent miscarriage and increase successful pregnancy outcome is key.

Advanced maternal age and poor reproductive history are some of the strongest risk factors associated with miscarriage. Although advanced maternal age can be considereded a preventable risk factor, some authors emphasise the difficulty of forming a family or becoming pregnant at early stages because of a lack of political, social and economic support. In recent years, there has been growing interest in the link between modifiable risk factors (e.g. lifestyles or psychological disorders) and adverse pregnancy outcomes. Smoking and high body mass index (BMI) are two of the most known modifiable risk factors for miscarriage. In view of the high occurrence of psychological disorders after a miscarriage, some authors focused their attention on the potential negative impact of depression, stress or anxiety on pregnant women following miscarriage. Although there is a substantial amount of evidence assessing the potential effect of lifestyles and distress during pregnancy, there is a lack of consistency in the results. There is a need to establish modifiable risk factors that can help prevent the risk of miscarriage. Also, it is equally important to identify subgroups of women who are at higher risk of developing psychological disorders following a miscarriage. An effort should be made to screen and appropriately treat this target group in healthcare settings.

Producing evidence about potential effective treatments and risk factors to prevent miscarriage in the scientific community is of limited use if that same evidence is not translated, communicated and provided to the general population. Promoting healthy behaviours prior to and during pregnancy is a crucial milestone to increase the population's knowledge and awareness of causes and risk factors for miscarriage.

Only a few studies have investigated the level of awareness of miscarriage among the general population. Poor awareness and a lack of knowledge of causes and risk factors for miscarriage have been reported from the scant amount of evidence in this field. There is a need to identify the public's knowledge of miscarriage, and consequently, to design and implement a preconception health education programme according to their needs.

1.13 Precis

This thesis has provided an extensive review of the literature on the biomedical, psychological, behavioural and social context of miscarriage in Ireland. The following chapters in this thesis consist of seven papers, which present insights into these dimensions of miscarriage. The following specific objectives for each chapter are described below and outlined in Figure 1.3:

7. To explore national trends in incidence rates of hospitalisations for miscarriage using the Hospital In-Patient Enquiry (HIPE) in the ROI from 2005 to 2016 (Chapter 2, paper 1)
8. To assess the reliability and validity of routine hospital discharge data of diagnosis of miscarriage in the ROI by determining the level of agreement between three data sources: electronic health records, hospital discharge data using HIPE, and register books in a tertiary maternity hospital in the ROI from January to June 2017 (Chapter 3, paper 2)
9. To determine the relationships between risk factors that might be associated with miscarriage among women attending an EPAU in May 2012 (Chapter 4, paper 3)
10. To explore university students' knowledge and common misconceptions of miscarriage in a single university centre in the ROI between April and May 2016 (Chapter 5 and 6, paper 4 and 5)
11. To examine the feasibility of a prospective study to assess mental health and general health during pregnancy and subsequent pregnancy outcomes among women who have a history of miscarriage from August 2017 to May 2018 (Chapter 7, paper 6)

12. To examine the literature to explore the effect of psychological and support interventions to reduce levels of stress among pregnant women who have a history of miscarriage (Chapter 8, paper 7)

This thesis concludes with a detailed discussion, which is divided in three main themes: the incidence of inpatient admissions of miscarriage and data validation, the risk factors and interventions for miscarriage, and the awareness of miscarriage in the Republic of Ireland. I will discuss the main findings, the strengths, limitations, and the implications for practice, policy and research for each theme.

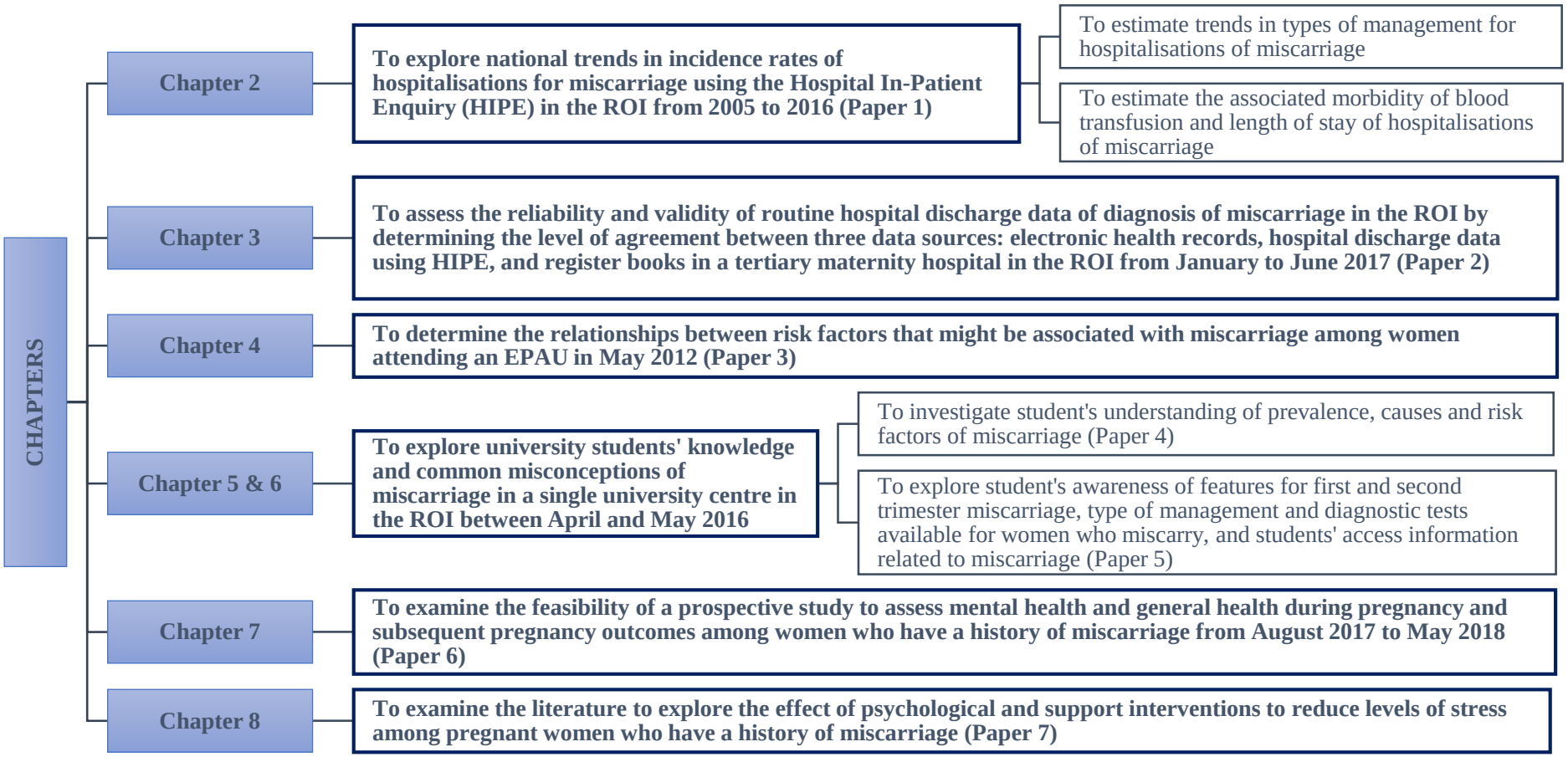


Figure 1.3. Diagram of principal and secondary objectives of each chapter

Chapter II.

Miscarriage hospitalisations: A national population-based study of incidence and outcomes, 2005-2016

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2.1 Abstract

Background: Early miscarriage is one of the most common obstetric causes of maternal morbidity early in pregnancy. However, data concerning non-fatal complications among hospitalisations for early miscarriage are lacking. The aim of this study was to determine whether there were changes in the incidence, management and outcomes of early miscarriage hospitalisations between 2005 and 2016. **Methods:** This is a nationwide population-based study of 50,538 hospitalisations with a diagnosis of early miscarriage of all acute maternity hospitals in Ireland. Electronic health records were retrieved using the Hospital In-Patient Enquiry database. Main outcomes include the incidence rates of hospitalisations and management for early miscarriage, and rates of blood transfusion and length of stay over 2 days. **Results:** Overall, 50,538 hospitalisations for early miscarriage were identified from 2005 to 2016. The risk of hospitalisation decreased from 70.6 per 1000 deliveries (95% CI 68.4 to 72.8) in 2005 to 49.7 per 1000 deliveries (95% CI 49.7 to 53.3) in 2016; however, the risk of blood transfusion increased over time (ratio: 2.0; 95% CI 1.6 to 2.4). Women of advanced maternal age had a higher risk of hospitalisations. There were less blood transfusions among women who undertook medical treatment (ratio: 0.3; 95% CI 0.1 to 0.5), but they had an increased risk of staying over 2 days at the hospital (ratio: 1.5; 95% CI 1.2 to 1.9) compared to evacuation of retained products of conception. **Conclusions:** Hospitalisation rates for early miscarriage decreased over time with an increase in risk of blood transfusion and an extended length of stay at the hospital. Women who underwent medical management did not have as many blood transfusions as those undergoing surgical management. However, they had an increased risk of an extended stay. Research is needed to explore both outpatient and inpatient settings in order to improve the management and care provided.

Keywords: Miscarriage, hospitalisations, rates, morbidity

2.2 Plain English Summary

Approximately, 1 out of 4 women will experience an early miscarriage in their reproductive life. Despite the burden of early miscarriage, there is a lack of information regarding trends in incidence rates of hospitalisations and type of management of early miscarriage, but also about the morbidities associated to hospitalisations of early miscarriage. Therefore, the objectives of this study were to explore national trends in incidence rates of hospital admissions for early miscarriage in the Republic of Ireland from January of 2005 to December of 2016, and to estimate morbidity associated with blood transfusion and length of stay over 2 days.

This is a retrospective population-based study using the Hospital In-Patient Enquiry (HIPE). The HIPE is a computer-based system designed to collect demographic, clinical and administrative data on discharges and deaths in the Republic of Ireland. However, data from the emergency department and outpatient settings are not available.

Over this period of time there were approximately 50,000 hospitalisations for early miscarriage. Early miscarriage hospitalisations became 19% less common during 2005–2016 but the risk of blood transfusion doubled. The risk of an extended length of stay also increased over the same time period. Women who underwent medical management did not have as many blood transfusions compared to those who had surgical management. However, women who underwent medical treatment had a

higher risk of a prolonged stay at the hospital. More research is needed to explore the patterns of care and morbidities associated to hospitalisation in order to improve protocols of management and the care provided for women who miscarry.

2.3 Introduction

Miscarriage is one of the most common complications in early pregnancy[131,201,246]. It is clinically classified as either early miscarriage, within 12 weeks of gestation, or late miscarriage, after 12 and before 24 completed weeks of pregnancy[15,16,45,246]. Early miscarriage occurs in 10 to 30% of all pregnancies [4,5] and in 11 to 16% of all clinically recognised pregnancies[228,247]. Late miscarriage is estimated to occur in less than 1% of pregnancies[34,248]. Despite the burden of miscarriage, to our knowledge, no studies have published national trends in incidence rates of hospitalisations for early miscarriage.

The pathways of care for early miscarriage have evolved[249]. Traditionally, the "gold standard treatment" for early miscarriage was surgical uterine evacuation[45]. The introduction and improvement in sensitivity of transvaginal scans (TVS) has helped to diagnose miscarriage early in pregnancy[45,250]. Furthermore, medical management, using Misoprostol[124], and expectant management are acceptable alternatives to surgery, which are currently offered to haemodynamically stable patients[123,249]. However, the optimal management for miscarriage and their associated adverse effects are still being investigated[61].

Hospitalisations during pregnancy are indicative of severe complications[251]. Early miscarriage is associated with less severe complications than ectopic pregnancy[141];

however, heavy bleeding is one of the clinical complications of miscarriage that requires admissions to hospital[45,252]. Moreover, second-trimester miscarriage, while less common, almost always requires inpatient admission and senior obstetric input[34]. Yet, clear and generalised evidence concerning morbidities among hospitalisations for early miscarriage are lacking[253]. Therefore, this study aimed to explore national trends in incidence rates of hospitalisations for early miscarriage, to explore trends in management, and to estimate the associated morbidity of blood transfusion and length of stay.

2.4 Methods

2.4.1 Study design and data source

A retrospective population-based study was conducted using the Hospital In-Patient Enquiry (HIPE) database. All inpatient admissions for early miscarriage in all public maternity hospital settings in the Republic of Ireland from January 1st 2005 to 31st December 2016 were included. The HIPE is an anonymous national health computer-based system designed to collect demographic, clinical and administrative data on discharges and deaths from all 62 acute hospitals in the Republic of Ireland[254,255]. Therefore, outpatient data, (i.e. emergency department, day patient, early pregnancy assessment units or post-anaesthetic care department) are not available[254,255]. Outpatient and inpatient data are not linked at a national level in the Republic of Ireland, and therefore, this study was unable to report how many hospitalisation of early miscarriage were referred from the emergency department or other outpatient settings. The Economic and Social Research Institute on behalf of the Health Service

Executive is the executive organism which administered and managed the HIPE database[256].

2.4.2 Population

From 2005, the *10th Revision Australian modification of International Statistical Classification of Disease and Related Health Problems* (ICD-10-AM) and t*he Australian Refined Diagnosis Related Groups* are the coding classification systems of diagnosis used in the Hospital In-Patient Enquiry system[254]. All miscarriage hospitalisations within the HIPE dataset were identified using the diagnostic codes for outcome of miscarriage (O03). The unit of analysis was the annual number of delivery discharges within the HIPE dataset using the diagnostic code for outcome of delivery (Z37). According to the ICD-10-AM, miscarriage is defined as the spontaneous expulsion or extraction of the productos of conception by any means, before viability, that being less than 22 weeks of pregnancy. Miscarriage can be classified as complete miscarriage (i.e. when products of conception are not evident on ultrasound) and also incomplete miscarriage (i.e. when patient is admitted because of retained products of conception). However, HIPE data does not specify gestational age in single weeks but uses ranges between < 5, 5 to 13, 14 to 19, 20 to 25, 26 to 33 and 34 to 36 completed weeks of gestation. Therefore, our analysis were restricted to early miscarriage, which was defined as a miscarriage before 14 completed weeks.

2.4.3 Outcome measures and independent variables

This study included blood transfusion as a complication and length of stay as an indicator of efficiency. Diagnostic codes for blood transfusion were identified using codes within the HIPE dataset (920,600 & 9,206,200 &1,370,601–1,370,603). Length

of stay was automatically obtained using the menu of the HIPE database. Hospitalisations with length of stay greater than 2 days were also considered a complication for the purpose of this study. Demographic and pregnancy-related variables within the HIPE dataset included year of discharge, maternal age (in years) and public or private health insurance. All women who are pregnant and ordinarily resident in the Republic of Ireland are entitled to free maternity care, covering antenatal visits, labour and delivery and postnatal care under the Maternity and Infant Care Scheme[257]. Those inpatient admissions who were treated under the Maternity and Infant Care Scheme were classified as public patients. The only alternative option is to be treated using private health insurance were classified as private patients.

Management for early miscarriage was categorised as surgical and medical treatment. Women were classified as being managed expectantly when neither of the previous procedures codes were identified (i.e. other treatments) or when women had no recorded procedures in HIPE. Surgical treatment included evacuation of retained products of conception. Evacuation of retained products of conception applied when a code for one of the following procedures was recorded: curettage of uterus with (D&C) or without dilatation (3,564,300, 35,640–00 & 35,640–01), suction curettage of uterus (3,564,003 & 3,564,301), dilation and evacuation of uterus (D&E) (35643–03). Medical treatment of early miscarriage involving specific types of prostaglandin E1 (i.e. Misoprostol and cervagem) or Mifepristone could not be identified as no procedure codes are recorded in HIPE to indicate administration of these drugs. Instead, medical management using codes for prostaglandin, as a general group, or oxytocin were used as the reference medical treatment for early miscarriage. A more

detailed description of the principal procedures codes is included in Supplementary Table 2.1.

In the Republic of Ireland, women with no signs of infection (i.e. vaginal discharge), excessive bleeding, pyrexia or abdominal pain are offered expectant or medical management from the outpatient departments. Surgical management of early miscarriage should be offered to women who make a specific request, who change their mind during the course of conservative or medical management, who have heavy bleeding and/or severe pain, when gestational trophoblastic disease is suspected or when infected intrauterine tissue is present[45].

2.4.4 Statistical analysis

Hospitalisation incidence rates were estimated using the annual number of inpatient discharges for early miscarriage divided by the annual number of deliveries in the Republic of Ireland over the 12-year period (2005–2016). The crude and adjusted incidence rate ratio of hospitalisation for early miscarriage with 95% confidence intervals (CI) were calculated using univariate and multivariable Poisson regression. All analyses were adjusted by year of discharge, maternal age, public versus private patient and weeks of gestation. The crude and adjusted incidence rate ratio with 95% CI for blood transfusion and length of stay over 2 days were calculated using a multivariable Poisson regression model. Data analysis was performed using Stata software (version 12) and IBM SPSS Statistics for Windows (version 21.0).

2.5 Results

In total, 50,538 hospitalisations for early miscarriage up to 14 completed weeks of gestation and 801,764 deliveries were identified between January 2005 and December 2016. Overall, the rate for hospitalisation of early miscarriage was 63.0/1000 deliveries (95% CI 62.5 to 63.6; Table 2.1). Approximately 59.0% (n=29,835) of early miscarriages were diagnosed as incomplete miscarriage. Almost 99.4% of all women admitted to maternity hospitals were between 5 to 13 weeks of gestation (n=50,252).

The rates for women with early miscarriage decreased from 70.6/1000 deliveries (95% CI 68.4 to 72.8) in 2005 to an incidence rate of 51.5/1000 deliveries (95% CI 49.7 to 53.3) in 2016 (Figure 2.1). The risk of being hospitalised for early miscarriage increased steadily with age, with the exception of women aged between 25 to 29 years old, who had a lower risk (adjusted incidence rate ratio 0.61; 95% CI 0.59 to 0.63). Women of 40 years of age or older had approximately a three-fold increased risk of being hospitalised compared to younger women aged 25 or less (adjusted incidence rate ratio 3.34; 95% CI 3.22 to 3.45). Public patients had almost double the risk of being hospitalised compared to private patients (Table 2.1).

Table 2.1. Incidence rate and incidence rate ratio of hospitalisations for early miscarriage in the Republic of Ireland, 2005-2016.

		Deliveries	No of hospitalisations for miscarriage	Rate* (95% CI)	Crude incidence rate ratio (95% CI)	Adjusted incidence rate ratio † (95% CI)
	All	801764	50538	63.0 (62.5 - 63.6)		
Year	**2005-2008**	257750	17958	69.7 (68.7 - 70.7)	1.0 (ref. group)	1.0 (ref. group)
	2009-2012	285751	17956	62.8 (61.9 - 63.8)	0.93 (0.91 - 0.95)	0.85 (0.84 - 0.88)
	2013-2016	258263	14624	56.6 (55.7 - 57.5)	0.95 (0.93 - 0.97)	0.77 (0.75 - 0.78)
Maternal Age	**<25**	109812	6404	58.3 (56.9 - 59.7)	1.0 (ref. group)	1.0 (ref. group)
	25-29	177647	9071	51.1 (50.0 - 52.1)	0.60 (0.58 - 0.62)	0.61 (0.59 - 0.63)
	30-34	281961	14697	52.1 (51.3 - 53.0)	0.90 (0.87 - 0.92)	1.10 (1.02 - 1.10)
	35-39	191970	14250	74.2 (73.0 - 75.4)	1.27 (1.24 -1.31)	1.60 (1.55 - 1.65)
	40+	40374	6116	151.5 (147.7 - 155.3)	2.60 (2.51 - 2.69)	3.34 (3.22 - 3.45)
Health insurance	**Private**	200014	8951	44.8 (43.8 - 45.7)	1.0 (ref. group)	1.0 (ref. group)
	Public	601750	41587	69.1 (68.4 - 69.8)	1.38 (1.35 - 1.41)	1.87 (1.83 - 1.92)

*Rate per 1000 deliveries; † Adjusted incidence rate ratio from multivariable analysis including all variables in the table.

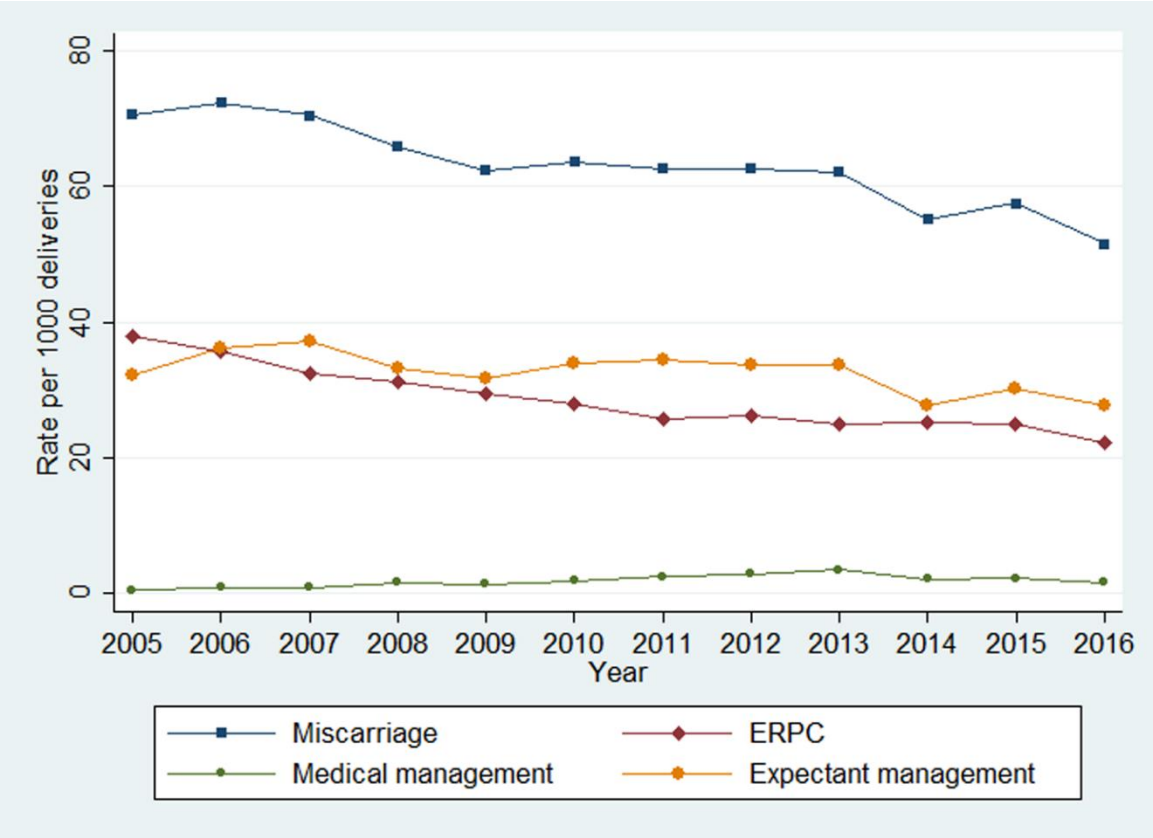


Figure 2.1. National hospitalisation rates for early miscarriage and type of management

Among hospitalisations for early miscarriage over the same time period, evacuation of retained products of conception was undertaken in almost half of the total sample (n=22,897; 45.3%), and only 2.8% were medically managed (n=1404). Half of the women were expectantly managed (n=26,225; 51.9%); among those, only 3.5% had other types of treatment (n=914). Expectant management remained the most frequent type of treatment over the study period (Figure 2.1). Evacuation of retained products of conception gradually decreased from 38.0/1000 deliveries (95% CI 36.4 to 39.6) in 2005 to 22.3/1000 deliveries (95% CI 21.1 to 23.5) in 2016. Medical management steadily increased over time from 0.4/1000 deliveries (95% CI 0.2 to 0.5) in 2005 to 1.6/1000 deliveries (95% CI 1.3 to 1.9) in 2016 (Figure 2.1). The average length of

stay for early miscarriage fluctuated during the 12-year period from 1.3 days (SD 0.8) in 2005 to 1.2 (SD 0.7) days in 2016; with an overall average of 1.2 days (SD 0.7) (Figure 2.2). Approximately 86.4% (n=43,679) of inpatients for early miscarriage stayed in hospital for one day and 10.0% (n=5,049) stayed for two days, with only 3.6% (n=1,810) having a length of stay of more than two days.

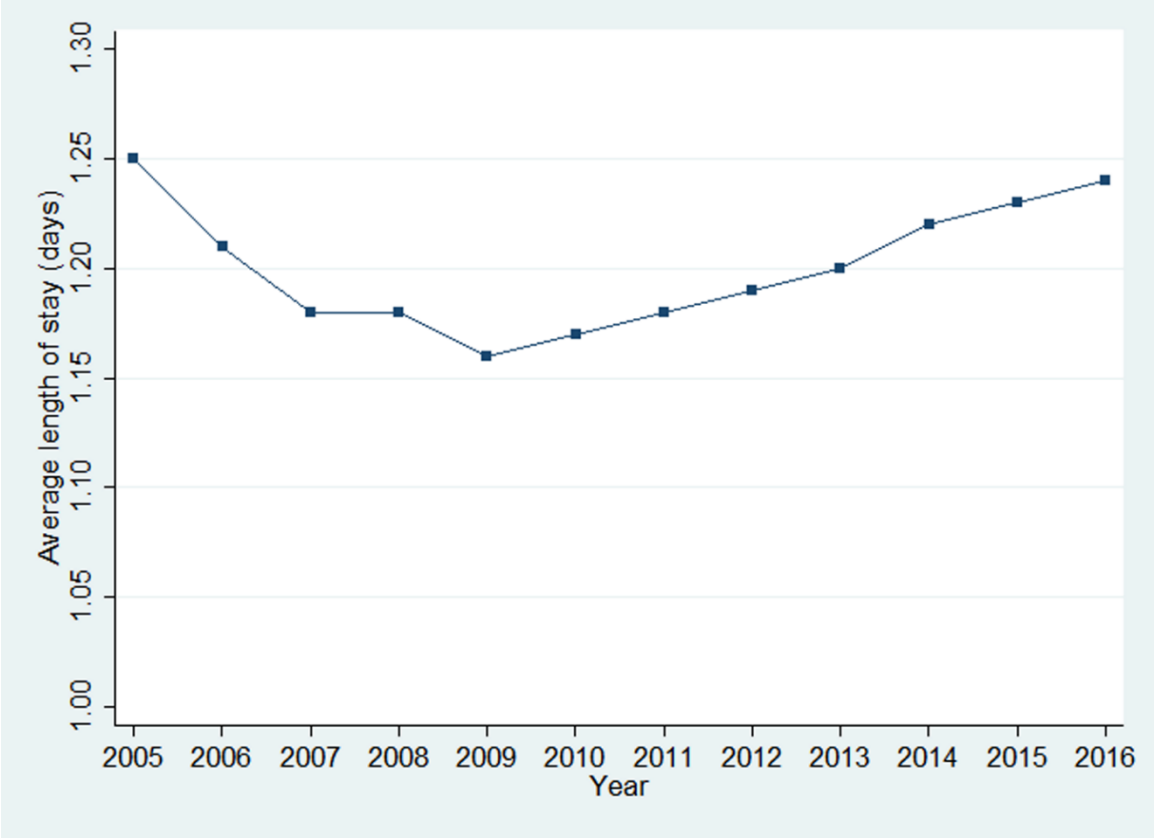


Figure 2.2. Average length of stay (days) of hospitalisations for early miscarriage

Among the 50,538 hospitalisations for miscarriage, 554 (1.1%) had a blood transfusion and 1,810 (3.6%) had a length of stay longer than 2 days (Table 2.2). The risk of blood transfusion among hospitalisations for early miscarriage increased over time. No significant differences were found for maternal age and risk of blood transfusion, except for those women who were 25 to 29 years old compared to those

younger than 25 years old. Public patients had more than double the risk of a blood transfusion than private patients (adjusted incidence rate ratio 2.5; 95% CI 1.9 to 3.3). Women who were medically, expectantly treated or who had another type of treatment had less blood transfusions as those undergoing evacuation of retained products of conception (adjusted incidence rate ratio 0.3; CI 0.1 to 0.5 & adjusted incidence rate ratio 0.3; 95% CI 0.2 to 0.4 respectively). Incomplete miscarriage had almost two times the rate of blood transfusion compared to early miscarriage (adjusted incidence rate ratio 1.5; 95% CI 1.1 to 2.0; Table 2.2).

The incidence rate ratio for length of stay over 2 days among hospitalisations for early miscarriage was reduced from 2009 to 2012 compared to 2005-2008 and was increased from 2013 to 2016 compared to 2005-2008 (Table 2.2). The risk of a prolonged stay at the hospital was reduced with advanced maternal age. Public patients had almost twice the risk of having a length of stay over two days than private patients (adjusted incidence rate ratio 1.7; 95% CI 1.5 to 1.9; Table 2.2). Women who were medically treated had almost twice the risk of having a length of stay over two days compared to those undergoing evacuation of retained products of conception (adjusted incidence rate ratio 1.5; CI 1.2 to 1.9). Women who were expectantly treated or who had another type of treatment were less likely to have a prolonged stay at the hospital compared to those treated with evacuation of retained products of conception (Table 2.2). Finally, no significant differences were found between complete and incomplete miscarriage and the risk of an extended stay at the hospital.

Table 2.2. Blood transfusion and length of stay over 2 days for hospitalisations of early miscarriage, 2005-2016

			Blood Transfusion				Length of stay over 2 days			
		No of hospitalisations for miscarriage	***n***	**%**	**Crude incidence rate ratio (95% CI)**	**Adjusted incidence rate ratio * (95% CI)**	***n***	**%**	**Crude incidence rate ratio (95% CI)**	**Adjusted incidence rate ratio * (95% CI)**
	All	50538	554	1.1			1810	3.6		
Year	**2005-2008**	17958	143	0.8	1.0 (ref. group)	1.0 (ref. group)	645	3.6	1.0 (ref. group)	1.0 (ref. group)
	2009-2012	17956	182	1.0	1.3 (1.0 - 1.6)	1.3 (1.1 - 1.7)	555	3.1	0.9 (0.8 - 1.0)	0.9 (0.8 - 1.0)
	2013-2016	14624	229	1.6	2.0 (1.6 - 2.4)	2.0 (1.6 - 2.4)	610	4.2	1.2 (1.0 - 1.3)	1.2 (1.0 - 1.3)
Maternal age	**<25**	6404	75	1.2	1.0 (ref. group)	1.0 (ref. group)	310	4.8	1.0 (ref. group)	1.0 (ref. group)
	25-29	9071	78	0.9	0.7 (0.5 - 1.0)	0.7 (0.5 - 1.0)	350	3.9	0.8 (0.7 - 0.9)	0.9 (0.7 - 0.9)
	30-34	14697	154	1.0	0.9 (0.7 - 1.2)	0.8 (0.6 - 1.1)	469	3.2	0.7 (0.6 - 0.8)	0.7 (0.6 - 0.8)
	35-39	14250	166	1.2	1.0 (0.8 - 1.3)	0.9 (0.7 - 1.2)	465	3.3	0.7 (0.6 - 0.8)	0.7 (0.6 - 0.8)
	40+	6116	81	1.3	1.1 (0.8 - 1.5)	1.0 (0.7 - 1.4)	216	3.5	0.7 (0.6 - 0.9)	0.8 (0.7 - 0.9)
Health insurance	**Private**	8951	56	0.6	1.0 (ref. group)	1.0 (ref. group)	200	2.2	1.0 (ref. group)	1.0 (ref. group)
	Public	41587	498	1.2	1.9 (1.5 - 2.5)	2.5 (1.9 - 3.3)	1610	3.9	1.7 (1.5 - 2.0)	1.7 (1.5 - 2.0)
Management	**ERPC†**	22897	427	1.9	1.0 (ref. group)	1.0 (ref. group)	870	3.8	1.0 (ref. group)	1.0 (ref. group)
	Medical treatment	1404	8	0.6	0.3 (0.2 - 0.6)	0.3 (0.1 - 0.5)	90	6.4	1.7 (1.4 - 2.1)	1.5 (1.2 - 1.9)
	Expectant/ other treatment	26225	119	0.5	0.2 (0.2 - 0.3)	0.3 (0.2 - 0.4)	850	3.2	0.9 (0.8 - 0.9)	0.7 (0.6 - 0.8)
Type of miscarriage	**Complete**	20700	89	0.4	1.0 (ref. group)	1.0 (ref. group)	718	3.5	1.0 (ref. group)	1.0 (ref. group)
	Incomplete	29835	464	1.6	3.6 (2.9 - 4.5)	1.5 (1.1- 2.0)	1092	3.7	1.1 (1.0 - 1.2)	0.8 (0.7 - 1.0)

*Adjusted incidence rate ratio from multivariable analysis including all variables in the table; †ERPOC, Evacuation of retained products of conception.

2.6 Discussion

This is a population-based study including more than 50 thousand hospitalisations for early miscarriage. The incidence of early miscarriage hospitalisations became 19% less common during 2005-2016, but the risk of blood transfusion doubled. Women aged 40 years or older had a three-fold risk of hospitalisation compared to those aged 25 years or less; and public patients had twice the rate. Women undergoing medical management did not have as many blood transfusions as those undergoing evacuation of retained products of conception; whereas it increased the risk of length of stay over two days. Incomplete miscarriage was associated with an increased risk of blood transfusion.

It is well-documented that older maternal age is a risk factor for adverse pregnancy outcomes[29,150,258] and this is further supported by the results in our study. For example, the maternal and fetal loss cohort study in Denmark also found that women in their late 30s or older had a higher risk of having ectopic pregnancy, miscarriage or stillbirth, irrespective of their reproductive history[29]. We found no other study assessing the possible impact of health insurance coverage on the risk of complications among hospital admissions for miscarriage. In order to promote an equal provision of care to pregnant women who miscarry in hospital settings, this possible association should be investigated.

It is important to highlight the possible impact of the modification of the ultrasound values used to diagnose early miscarriage. This change was made to reduce false positive cases of miscarriage (i.e. a patient who may have an early sonogram with unknown viability and another sonogram where fetal heart activity is found) at an

international level in 2011, 2012 and 2013 by the Royal College of Obstetrician and Gynaecologists[57], the UK National Institute for Health and Care Excellence[26] and the American College of Radiology[58] respectively. As in other countries, the Royal College of Physicians of Ireland (RCPI) also modified their guidelines in 2011[45,59]. One of the recommendations was to perform a second ultrasound scan to confirm the diagnosis of miscarriage when pregnancies are under 8 weeks of gestation[45]. Although the rate of hospitalisations was reducing before the guidelines, it is sometimes the case that guidelines are produced after a period of time when clinical practice has already been changing. For example, the reduction of the incidence of miscarriage during 2005-2011 may suggest an improvement in miscarriage diagnosis in the years leading up to the revised clinical guidance.

In contrast to our results, studies carried out by The National Institute for Health and Care Excellence found that women with a miscarriage who are managed expectantly have a higher risk of blood transfusion and more days of bleeding compared to those who have surgical treatment[131,259]. One possible explanation for these divergent results is that pregnant women with severe haemorrhage or pain were excluded from some randomized controlled trials[118,260-262]. Another explanation could be that we were unable to explore if women who were surgically managed had initially been expectantly or medically treated as an outpatient. For example, it is well-documented that there is a higher risk of bleeding and unplanned intervention after expectant or medical management compared to surgical treatment; with medical management failure varying from 10% to 20%[124,263].

The sample size of our study population is one of the main strengths of this study. In addition, the HIPE data are recorded following standardised methods using the ICD-

10-AM diagnosis code across all the hospitals[254]. Because single weeks of gestation were not available, analysis were restricted to early miscarriage before 14 completed weeks of gestation. Analysing second trimester miscarriage would have included pregnancy loss up to 25 completed weeks of gestation, resulting in the inclusion of a number of stillbirths rather than miscarriages in our analysis. A limitation of the study is that only inpatient data are available from the HIPE database[254]. As a result, this study will under-estimate the overall burden of miscarriage given the lack of outpatient data available nationally. However, this study will probably not under-estimate the morbidity as all were hospital based. In order to estimate the overall burden of miscarriage, both outpatient and inpatient cases should be investigated.

In conclusion, maternal age, type of health insurance, type of treatment and incomplete miscarriage significantly affected the risk of blood transfusion and length of stay over two days at the hospital after being adjusted by confounders. However, a better understanding of the morbidities associated with early miscarriage hospitalisations is needed to improve management and care provided.

2.7 Implications for practice, policy and research

Implications for practice

- Women who underwent ERPC had a higher risk of blood transfusion than those who were managed conservatively
- There is a need for senior clinical involvement in all inpatient surgical procedures for pregnancy loss

Implications for policy

- There is a need to standardise definitions of miscarriage at a national and international level in order to be able to compare the evidence related to pregnancy loss

Implications for research

- There is a need to estimate the overall burden of hospitalisations of miscarriage including outpatient and inpatients data using the EHR
- More research is needed to explore the patterns of care and clinical indications at both outpatient and inpatient settings in order to improve protocols of management and the care provided for women who miscarry
- Future research should investigate the possible association between disparities in care and the risk of complications (e.g. blood transfusion, waiting time, stay at the hospital and other morbidities) among inpatient admissions for miscarriage

2.7 Supplementary Tables

Supplementary Table 2.1. Diagnosis, procedures and complications codes for early miscarriage

Diagnosis codes	**ICD-10-AM**	**Diagnosis/procedure field**
Miscarriage	O03	Principal diagnosis
Procedures codes for miscarriage	**ICD-10-AM**	**Procedure field**
Evacuation of retained products of conception (ERPC)		
Dilation and evacuation of uterus (D&E); Suction curettage of uterus; Dilatation and curettage of uterus (D&C) with and without dilatation; Dilation and curettage; D&C for retained products of conception (RPC) following delivery; excludes that with suction curettage. suction curettage; by suction curettage; for retained products of conception following delivery	3564303;3564003; 3564000/ 3564001; 1656400; 1656401	Principal procedures
Manual removal of placenta	9048200	Principal procedures
Medical management*		
Insertion of prostaglandin suppository for induction of abortion; Medical induction of labour, prostaglandin	9046200; 9046501	Principal procedures
Medical induction of labour, oxytocin; other medical induction of labour; excludes that with surgical induction of labour	9046500; 9046502	Principal procedures
Expectant/Other management		Principal procedures
No procedure		
Other type of management		
Other type of treatment including intravenous administration of pharmacological agents, passive immunisation with Rh(D) immunoglobulin and other allied health interventions.	9619709; 9619902-09;9217300; 9555001-14…	Principal procedures
Outcomes measures	**ICD-10-AM**	**Procedure field**
Blood transfusion	9206000/1370601/ 1370602/1370603/ 9206200	Additional procedures
Length of stay (LOS) over 2 days		

*No specific code of medical management using Misoprostol or Mifepristone for miscarriage were available.

Chapter III.

Assessing the concordance and accuracy between hospital discharge data, electronic health records and register books for diagnosis of inpatient admissions of miscarriage: a retrospective linked data study comparing apples and oranges.

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3.1 Abstract

Background. Despite the high prevalence of miscarriage, there are few studies which assess the concordance of a diagnosis of miscarriage in routinely collected health databases.

Objectives. To determine agreement and accuracy for the diagnosis of miscarriage between electronic health records (EHR), the Hospital Inpatient-Enquiry (HIPE) system, and hospital register books in Ireland. **Methods**. This is a retrospective study comparing agreement of diagnosis of miscarriage between three hospital data sources from January to June 2017. All inpatient admissions for miscarriage were reviewed from a single, tertiary maternity hospital in Ireland. Kappa, sensitivity, specificity, positive and negative predictive value were calculated. **Results**. In this retrospective concordance study, EHR records confirmed 96.2% diagnosis of miscarriage of HIPE records, and 95.1% of register books records. A total of 105 records were not recorded in the register books but were recorded in HIPE and EHR. This study found a considerable variability when comparing definitions of type of miscarriage (i.e. missed miscarriage, incomplete and complete) between the three data sources **Conclusion**. Although this study found a high concordance in inpatient admissions for miscarriage between EHR, HIPE and register books, a considerable discrepancy was found when classifying miscarriage between the three data sources.

Keywords: Electronic Health Records, miscarriage, Data Accuracy, inpatients

3.2 Introduction

Routinely collected health data, also called "big data", are becoming an essential source of information to generate research about population health.[264] Reliability and validity of the information recorded in the databases are key to ensuring consistency and high-quality evidence of the outcome investigated.[265] Miscarriage is one of the most common complications during early pregnancy, with up to one third of clinically recognised pregnancies ending in miscarriage.[28-31] Nevertheless, prevalence and trends in rates of miscarriage vary considerably depending on the type of miscarriage identified (i.e. biochemical versus clinically recognised miscarriage) but also depending on the source of data from where it is measured (i.e. self-reported data [29,37-40] versus routine hospital registered data).[266] For example, a comparison between the prevalence of miscarriage between three Danish studies showed that between 17 to 30% of miscarriage diagnosis were not recognised in registered hospital data compared to self-reported data. [267-269] However, evidence of reliability and accuracy of the diagnosis of miscarriage in routinely collected health sources are surprisingly scant in the literature[266,270,271].

The Hospital In-Patient Enquiry (HIPE) is a computer-based system designed to collect demographic, clinical and administrative data on discharges and deaths in the Republic of Ireland (ROI).[272] HIPE is a national health information system which serves as a reliable source of inpatient data from all 62 acute hospitals in the ROI. [254,255] Although, HIPE is not designed as a research tool, a series of initiatives to improve data accuracy has been implemented in the ROI since 2001 (i.e. computer-based edits/checks, clinical coder training, chart-based audits).[254] However, accuracy and reliability of the diagnosis of miscarriage using hospital charts have not been

published, and consequently, errors in coding or "rule-out" diagnosis might be reported. The lack of evidence raises the following questions in particular in the country where the study was conducted: is routine hospital discharge data of diagnosis of miscarriage comparable between three main clinical data sources in Ireland? and is routine hospital discharge data accurately identifying types of miscarriage in Ireland? Therefore, the first aim of this study was to assess the reliability of routine hospital discharge data of diagnosis of miscarriage at admission in the ROI by determining the level of agreement between three data sources: electronic health records (EHR), hospital discharge data using HIPE, and register books (paper-based hospital records) from 1st January 2017 to 30th June of 2017. The second aim of this study was to evaluate the accuracy of routine hospital discharge data for classifying types of miscarriage on admission in the ROI.

3.3 Material and methods

3.3.1 Study design and setting

This is a concordance study of diagnosis and types of miscarriage using a retrospective chart review methodology of three data sources at a large, tertiary maternity hospital with approximately 7,500 deliveries annually in the ROI. The three data sources reviewed were the HIPE database, the EHR, and register books.

3.3.2 Hospital discharge data (HIPE)

A list containing all hospital discharge data of diagnosis of miscarriage and early pregnancy loss from the 1st of January 2017 to 30th of June 2017 was identified using the HIPE database. This list included the medical record number (MRN) for each inpatient admission of miscarriage, a unique identification number which is given to

each woman who is pregnant and ordinarily resident in Ireland. All inpatient admissions of miscarriage and early pregnancy loss identified by the list were then searched for in the EHR and the register books. Therefore, the data was linked in the three data sources using the MRNs. The HIPE database records each individual hospital admission even if it is related to a single miscarriage event.

Diagnoses and procedures performed as an in-patient are recorded in all of the patient's notes and clinical coders translate the medical terminology into alpha-numeric codes (ESRI). All inpatient admissions for miscarriage and early pregnancy loss coded in the HIPE dataset were identified using the 10th Revision Australian modification of International Statistical Classification of Disease and Related Health Problems (ICD-10-AM) and the Australian Refined Diagnosis Related Groups (AR-DRGs). The ICD-10-AM and AR-DRGs are the coding classification systems of diagnosis used in the HIPE system since 2005. A list of the inclusion criteria based on main ICD-10-AM codes containing the diagnoses of interest are listed in Supplemental Table 1 (ST1). Only inpatient admissions are recorded in the HIPE database, and consequently, data from the emergency department (ED) and outpatient settings were not available.[254,255]

3.3.3 Electronic health records

Inpatient admissions identified by HIPE were manually reviewed using patient notes in the EHR for the same time period at Cork University Maternity Hospital (CUMH). The Maternal & Newborn Clinical Management System (MN-CMS) has been recently implemented in the Irish maternity services.[273] The main aim of the MN-CMS Project was to design and implement an EHR for all women and babies who access the

maternity services to move from paper-based records to electronic records in the 19 maternity hospital in the ROI.[274] CUMH was the first hospital to launch MN-CMS in a nationally in December 2016.[274].

Even though the EHR contains all the clinical information for women admitted to the hospital, it does not provide a definitive diagnosis of miscarriage. That means that the information in the medical notes and clinical reports for each hospitalisation had to be individually reviewed. A specialist registrar in obstetrics and gynaecology and in pregnancy loss (K.M.N) was responsible for identifying the diagnosis and type of miscarriage by assessing the available information gathered in the EHR and classifying the diagnosis and type of miscarriage. The information available included medical notes for both outpatient and inpatient admissions, nursing reports of surgical procedures such as evacuation of retained products of conception (ERPC) and manual removal of placenta (MROP), histological exam results and ultrasound scans. This detailed information was not available in the HIPE dataset nor in the register books; therefore, the diagnosis and type of miscarriage identified by the specialist registrar in the EHR was considered the gold standard.

3.3.4 Register books

For the purpose of this study, charts of consecutive admissions of miscarriage and early pregnancy loss were retrospectively reviewed using register books from a dedicated ward at CUMH. Register books are paper-based records which contain key information related to the diagnosis and procedures of inpatient admissions during the admission process. Information identified from the register books included: MRN, age, gravity and parity, weeks of gestation at admission, nature of loss (i.e. missed

miscarriage, miscarriage, incomplete or complete miscarriage, late (second trimester) miscarriage, ectopic pregnancy, molar pregnancy, etc.), main procedure during admission (i.e. ERPC, medical treatment, manual removal of placenta, etc.). Identification of main examinations and investigations carried out during admission (i.e. post-mortem examination, histology and/or cytogenetic investigations).

3.3.5 Data collection form

A data collection form was designed to collect information about miscarriage from the three sources. This data collection form was designed to provide a standardised collection of the data from the three databases, but also to discern discrepancies or duplications between the three datasets. The main variables included were: MRN, date of admission and discharge, weeks of gestation at admission, diagnosis at admission including missed miscarriage, incomplete or complete miscarriage, late miscarriage, or other early pregnancy loss such as ectopic pregnancy and molar pregnancy. Additional information such as type of treatment undertaken during the hospitalisation and histological reports was also added order to ascertain the diagnosis of miscarriage and the type of classification of miscarriage (e.g. molar or parcial molar pregnancies, ectopic pregnancies). All the variables included in the data collection form can be seen in Supplemental Table 3.2 (ST2).

3.3.6 Definitions of miscarriage

It is known that the definition of miscarriage varies between countries and health organisations[12]. According to the National Clinical Guideline in Obstetrics and Gynaecology in Ireland, miscarriage is defined as the loss of a pregnancy before 24 completed weeks of gestation, excluding perinatal deaths.[15] However, according to the

coding definition standards used by the HIPE database, miscarriage is defined as the expulsion or extraction of the products of conception before 21 completed weeks of gestation.[275].

Similarly, this study followed the Irish clinical guidelines to classify type of miscarriage as early or late miscarriage based on the weeks of gestation in the EHR and the register books. When a miscarriage occurred before 13 weeks of gestation. It was classified as an early (first trimester) miscarriage was identified, and when a miscarriage occurred at 13 or more weeks up to 24 weeks of gestation, and it was classified as a late (second trimester) miscarriage.[16] However, HIPE data does only uses ranges between < 5, 5 to 13, 14 to 19, 20 to 25, 26 to 33 and 34 to 36 completed weeks of gestation. Therefore, our analysis was restricted to early miscarriage, which was defined as a miscarriage before 14 completed weeks of gestation.

Furthermore, this study was interested in assessing the agreement between type of early miscarriages in the routine collected health records in Ireland. Thus, early miscarriages were classified as incomplete, complete and missed miscarriages. Incomplete miscarriage was identified if the women presented with symptoms of vaginal bleeding and/ or pain, and with retained products of conception (RPOC). Complete miscarriage was identified if all the RPOC had been expulsed or extracted from the uterine cavity, and missed miscarriage was defined when no symptoms had been experienced by the women; therefore women will only become aware of the miscarriage following a routine ultrasound.[45]

3.3.7 Exclusion criteria

Women who did not have a miscarriage in this pregnancy, who were pregnant at the time of the discharge were excluded from the analysis. Records were excluded from the analysis when they were not registered in HIPE but were registered in the EHR and the register books. Or vice versa, when the records were registered in the register books but not in HIPE. Records were also excluded from the analysis when miscarriage was not confirmed in the EHR (e.g. threatened miscarriage, still pregnant at the time of the inpatient admission), when an intervention was undertaken in another country (e.g. termination of pregnancy (TOP)), or when the main diagnosis was missing in the register books. In addition, women who had a stillbirth, which is defined as a child born weighing 500 grammes or more or having a gestational age of 24 weeks or more who shows no sign of life according to the stillbirth registration act of 1994 in Ireland, were also excluded.[276]

3.3.8 Statistical analysis

Inpatient admissions for miscarriage and other types of early pregnancy loss were compared using 2x2 tables for each pair of data sources (i.e. HIPE versus EHR, HIPE versus register books, and EHR versus register books). In HIPE, inpatient discharges are counted as unique cases even though several discharges might be related to a unique miscarriage event.[275] When a women, who was previously admitted and managed for miscarriage in the hospital, was readmitted because of a complication without being managed for the miscarriage per se, these cases were included in the analysis as complications after miscarriage.

The crude prevalence of miscarriage was calculated for each data source. Cohen's Kappa was calculated to provide a measure of agreement for the diagnosis of miscarriage between two data sources (raters) using Stata´s "kap" command. Therefore, positive and negative predictive values (PPV and NPV) were calculated to assess the concordance of diagnosis of miscarriage between each pair of register sources. An exploration for more than two raters with binary outcomes was also carried out using Stata's Kappa command. In this case, the nonunique rater case had two possible ratings, which were positive (when a diagnosis of miscarriage was made) and negative (when no diagnosis of miscarriage was made). Negative ratings were calculated by subtracting the total number of positive ratings to the total number of raters for each admission to the maternity hospital. All analysis were undertaken using STATA v.12. A summary of main formulas can be seen in Supplemental Table 3.

3.3.9 Ethical approval and consent to participate

This study received ethical approval from the Clinical Research Ethics Committee of the Cork Teaching Hospital on ECM 4 (I) 17/10/2017. A patient consent form was not required by the Ethics Committee because this was an observational study which did not include any intervention and which examined routinely collected data. All data and information was stored safely and securely.

3.4 Results

Overall, a total number of 405 records were reviewed between the three sources (i.e. HIPE, EHR and register books). Figure 3.1 outlines the record which were included and excluded in this study for each data source. This study included 385 records after excluding duplicates and other types of inpatient admissions which did not meet the

inclusion criteria (i.e. neonatal death, stillbirth, gynaecology hospital admissions). After excluding duplicates, four records were excluded from EHR, 12 records from HIPE and 123 records from the register books. These records were excluded if not register in HIPE but register in the EHR and the register books, or vice versa, or excluded when the diagnosis of miscarriage was not identified.

Following exclusions, 304 inpatient admissions of miscarriage out of a total of 370 records of early pregnancy loss in EHR (82.2%), 291 out of 360 records in HIPE (80.8%), and 219 out of 255 records in register books (85.9%).

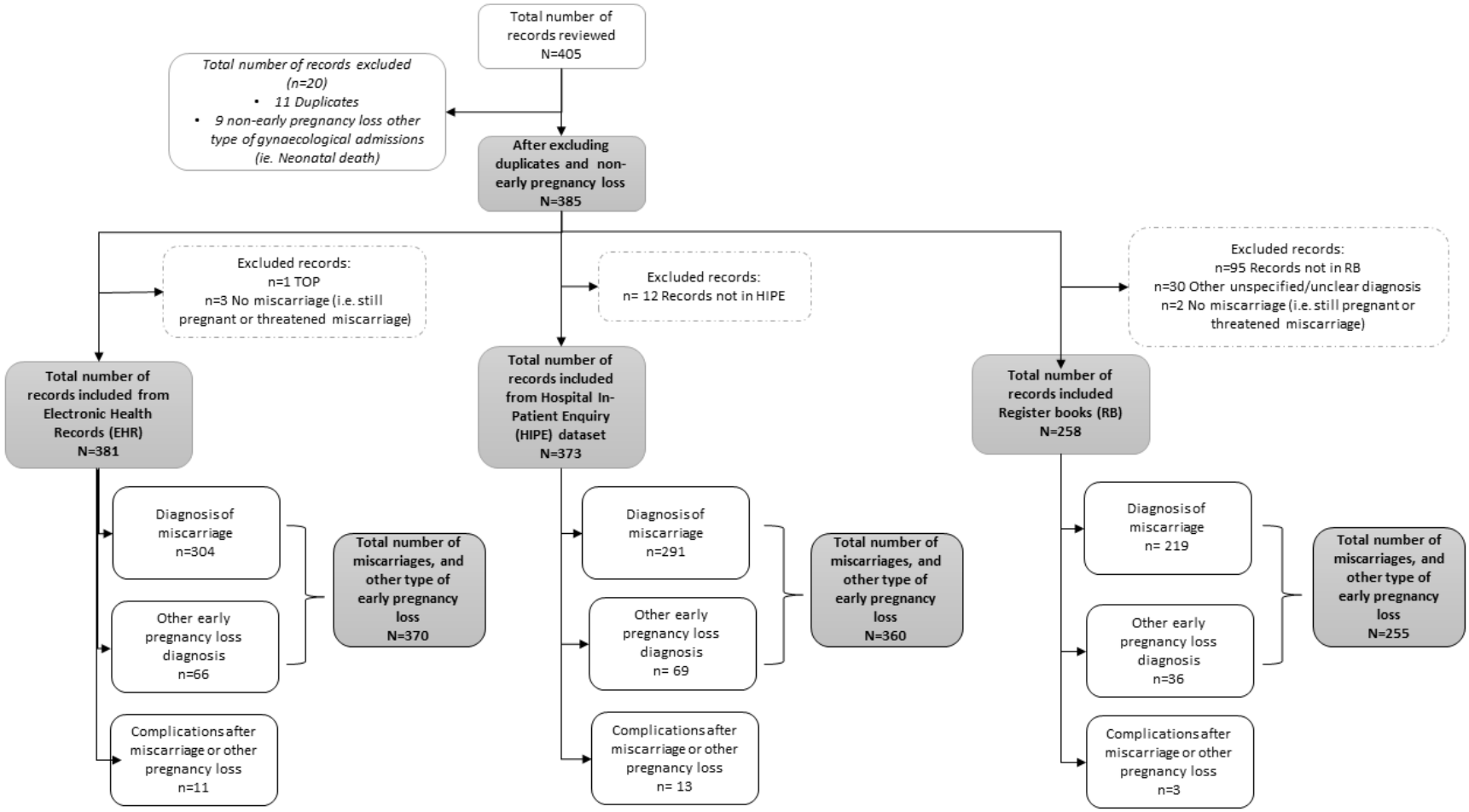


Figure 3.1. Flowchart of included and excluded records from the three data sources

Note: Excluded records are identified by dotted line in the boxes

3.4.1 Comparing EHR and HIPE

When comparing EHR and HIPE, 369 records were identified in both sources, 287 inpatient admissions for miscarriage were recorded by the two sources, eight recorded in EHR alone, and two recorded in the HIPE alone. The remaining 72 admissions were recorded as not being diagnoses of miscarriage by both sources. Using the EHR as a gold standard, HIPE had a sensitivity of 96.3%, specificity of 97.3%, PPV 98.3%, of NPV 90.0%; with a very good strength of agreement (k=0.92; p-value < 0.001). The observed level of agreement was 97.3% and the expected level of agreement was 67.0% (Table 3.1).

Table 3.1. Comparison of diagnosis of miscarriage between HIPE and EHR

		Diagnosis of miscarriage in EHR		**Total**
		Yes	No	
Diagnosis of miscarriage in HIPE	Yes	287	2	289
	No	8	72	80
Total		295	74	369
Kappa =0.92 p-value < 0.001 Sensitivity =96.3 % Specificity = 97.3% PPV = 98.3% NPV = 90.0% Observed level of agreement =97.29% Expected level of agreement = 66.96%				

3.4.2 Comparing EHR and register books

When comparing EHR and register books, 257 records were identified in both sources, 210 inpatient admissions for miscarriage were recorded by the two sources, six

recorded in EHR alone, and eight recorded in register books alone. The remaining 33 admissions were recorded as not being diagnoses of miscarriage by both sources. Using EHR as a gold standard, register books had a sensitivity of 97.2%, specificity of 80.5%, PPV of 96.3%, NPV of 84.6% with a good strength level of agreement (k=0.79; p-value < 0.001). The observed level of agreement was 94.6% and the expected level of agreement was 73.7% (Table 3.2).

Table 3.2. Comparison of diagnosis of miscarriage between EHR and register books

		Diagnosis of miscarriage in EHR		**Total**
		Yes	No	
Diagnosis of miscarriage in register books	Yes	210	8	218
	No	6	33	39
Total		216	41	257
Kappa =0.79 p-value < 0.001 Sensitivity = 97.2% Specificity = 80.5% PPV = 96.3% NPV = 84.6% Observed level of agreement = 94.6% Expected level of agreement = 73.7%				

3.4.3 Comparing EHR, HIPE and register books

When comparing the three data sources (N=385), three (0.78) records were rated by one database (rater), 133 (34.5%) records were rated by two databases, and 249 (64.7%) by the three databases (raters). More than half of the records were rated as being admitted to the hospital because of a diagnoses of miscarriage by the three databases (n=199; 51.7%); 27% (n=102) of records had two positive diagnosis of miscarriage, 4.2% (n=16) records had only one positive diagnosis of miscarriage, and

17.7% (n=68) were identified as having no diagnosis of miscarriage at admission to the maternity hospital. This study obtained a very good level of agreement when comparing the three data sources (k=0.84; p-value < 0.001).

3.4.4 Classification of type of miscarriage by three sources

A considerable discrepancy was identified with the classification of the type of miscarriage across the three data sources (Table 3.3). For example, percentages of missed miscarriage recorded in HIPE (n=16; 4.2%) were considerably lower than the percentage classified as missed miscarriage by EHR (n=173; 44.9%) and in the register books (n=150; 39.9%). In fact, sixty percent of admissions were classified as incomplete miscarriage according to HIPE (n=231; 60.0%; Table 3.3). A higher number of ectopic pregnancies were identified in HIPE (n=58, 15.1%) compared to the EHR (n=44; 11.4%) or the register books (n=32; 8.3%). The number of molar pregnancies were almost identical between the EHR and the register books, but this number increased moderately in the HIPE database (n=6, 1.6%; n=4; 1.0% and n=11, 2.9% for EHR, register books and HIPE, respectively; Table 3.3).

3.4.5 Classification of late miscarriage

Less discrepancy was found between the three data sources when classifying late (second trimester) miscarriage. Both HIPE and register books identified 28 (7.3%) inpatient admissions for late miscarriage compared to 37 (9.6%) identified by EHR.

3.4.6 Classification of missing records

A total of 95 records were not recorded or missing in the register books but were recorded in the EHR or the register books (Table 3.4). Of these, the most frequent classifications in EHR were missed miscarriage (n=44; 46.3%), ectopic pregnancies (n=20; 21.1%) and incomplete miscarriages (n=14; 14.7%). Of these 95 cases, the most frequent classifications in HIPE were incomplete miscarriage (n=50; 52.6), ectopic pregnancy (n=29; 30.5%) and missed miscarriage (n=5; 5.3%). Of the 12 records identified in the EHR, but not identified in HIPE, four (33.3%) were classified as incomplete miscarriage, three (25.0%) were classified as late miscarriage and another three (25.0%) were classified as ectopic pregnancy (Table 3.4). Of the 12 records identified in the register books, but not identified in HIPE, three (25.0%) were classified as missed miscarriage, three (25.0%) were classified as late miscarriage and another three (25.0%) were classified as ectopic pregnancy (Table 3.4). Of the 30 records identified in the EHR and HIPE but not in the register books, the most frequent classification in EHR was missed miscarriage (n=15; 57.7%) and the most frequent classification in the HIPE database was incomplete miscarriage (n=24; 80%; Table 3.4).

Table 3.3. Summary of number and percentages of classification of the type of records by each data source

		EHR		HIPE		Register books	
		n	**%**	**n**	**%**	**n**	**%**
Type of miscarriages		**304**	**78.9**	**291**	**75.7**	**219**	**57**
Early miscarriage	Missed miscarriage	173	44.9	16	4.2	150	39.0
	Incomplete	81	21.0	231	60.0	11	2.9
	Complete	13	3.4	16	4.2	11	2.9
Late miscarriage		37	9.6	28	7.3	28	7.3
Unspecified Miscarriage		0	0.0	0	0.0	19	4.9
Other type of pregnancy loss		**66**	**17.2**	**69**	**18**	**36**	**9.3**
Ectopic pregnancy		44	11.4	58	15.1	32	8.3
Molar pregnancy		6	1.6	11	2.9	4	1.0
PUL		16	4.2	0	0.0	0	0.0
Complications after miscarriage, ectopic or molar pregnancy		**11**	**2.9**	**13**	**3.4**	**3**	**0.8**
Complications following miscarriage and ectopic and molar pregnancy		11	2.9	13	3.4	3	0.8
Other type of records and missing values*		**4**	**1.1**	**12**	**3.1**	**123**	**32**
TOP (Termination of pregnancy)		1	0.3	0	0.0	0	0.0
No miscarriage (i.e. threatened miscarriage)		3	0.8	0	0.0	2	0.5
Records not in HIPE but in EHR and register books		0	0.0	12	3.1	0	0.0
Records in EHR and HIPE but not in register books		0	0.0	0	0.0	95	24.7
Missing diagnosis of miscarriage		0	0.0	0	0.0	30	7.7
Total		385	100.0	385	100.0	385	100.0

* Records excluded in the Kappa analysis

Table 3.4. Comparison of excluded records by the three data sources

	Records in EHR and HIPE but not in register books *		**Records not in HIPE but in EHR and register books***		**Missing diagnosis of miscarriage in the register books***	
	EHR n (%)	**HIPE n (%)**	**EHR n (%)**	**Register books n (%)**	**EHR n (%)**	**EHR n (%)**
Missed miscarriage	44 (46.3)	5 (5.3)	1 (8.3)	3 (25.0)	15 (57.7)	1 (3.3)
Incomplete	14 (14.7)	50 (52.6)	4 (33.3)	1 (8.3)	8 (26.7)	24 (80.0)
Complete	2 (2.1)	4 (4.2)	1 (8.3)	0 (0.0)	0 (0.0)	1 (3.3)
Late miscarriage	1 (1.1)	1 (1.1)	3 (25.0)	3 (25.0)	3 (10.0)	1 (3.3)
Ectopic pregnancy	20 (21.1)	29 (30.5)	3 (25.0)	3 (25.0)	0 (0.0)	1 (3.3)
Molar pregnancy	2 (2.1)	3 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Complications following miscarriage and ectopic and molar pregnancy	2 (2.1)	3 (3.2)	0 (0.0)	0 (0.0)	3 (10.0)	2 (6.7)
PUL	8 (8.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.3)	0 (0.0)
TOP (Termination of pregnancy)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
No miscarriage (i.e. threatened miscarriage)	2 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Unspecified miscarriage	0 (0.0)	0 (0.0)	0 (0.0)	2 (16.7)	0 (0.0)	0 (0.0)
Total	95 (100)	95 (100)	30 (100)	12 (100)	30 (100)	30 (100)

3.5 Discussion

3.5.1 Main findings

In this retrospective concordance study, EHR records confirmed 98.3% of HIPE and 96.3% of register books diagnosis of miscarriage. Level of agreement between each pair of data sources was found to be good or very good and level of agreement between the three data sources was found to be very good. However, a considerable discrepancy between identification of the type of miscarriage was found between the three data sources. EHR and register books were more likely to classify missed miscarriages compared to the HIPE dataset. This could be explained by the fact that HIPE does not include a standardised definition for missed miscarriage in their codebook. However, EHR often identified more late (second trimester) miscarriages compared to HIPE and register books. There is a lack of standardisation in definitions of late miscarriage between the three data sources, explaining the considerable misclassification when comparing this specific type of miscarriage. According to our analysis, this study recommends EHR and HIPE as the preferred sources of reliable data sources to report number of inpatient admissions of miscarriage. However, the authors believed that EHR is the preferred sources of reliable information to identify the type of miscarriage given that HIPE uses different definitions to classify types of miscarriage.

3.5.2 Comparison with other studies

Only three studies were identified that assessed the concordance of the outcome of miscarriage at hospital settings in the literature. Of the three studies which we found in the literature review, the first study compared diagnosis of miscarriage between the Danish National Registry of Patients (DNRP) and discharge records from hospital files

between 1980 and 2008.[266] Diagnosis of miscarriage were confirmed in 114/117 hospital files, with a PPV of 97.4%. As a result, this study concluded that DNRP is an accurate source of information to report a diagnosis of miscarriage in Denmark. Another Danish study validated the diagnosis of second trimester miscarriage compared between the DNRP and the Danish Medical Birth Registry from 1997 to 2012. This time, 91% of late miscarriage recorded in DNPR were identified by the medical records.[271] The third study assessed the concordance of the diagnosis of missed miscarriage using the ICD-9 diagnosis code from hospital electronic medical records in the Emergency Department in the United States for over one year (June 2011 to May 2012). The authors concluded that the code for missed miscarriage "632" had low sensitivity for identifying stable women with a missed miscarriage (41.9%), with high specificity (98.6%) and moderately high PPV (75%).[270] Therefore, true cases of stable miscarriage were correctly identified using ICD-9 code "632" with a low rate of false positives. Some of the reasoning of such a low sensitivity was that other similar codes were used to diagnose miscarriage such as threatened miscarriage or haemorrhage complications.

In keeping with our findings, the lack of a standardised definition of type of miscarriage, or the lack of training to identify types of miscarriage will introduce variation in the hospital data records. Therefore, it may affect reliability and accuracy of these data in epidemiological studies.

3.5.3 Strengths and limitations

To our knowledge, this is the first study validating the diagnosis of miscarriage using three sources in Ireland. In this study, a team of trained administration staff was in

charge of the coding process at HIPE. As a consequence, our findings might not be extended to other hospitals where care providers are responsible for coding the diagnosis of miscarriage themselves. However, it also implies less variability between people who assigned ICD-10-AM codes as a profession compared to health professionals, and our findings could be generalised to other hospitals where medical coders are in charge of the coding process of miscarriage. Secondly, the lack of standardised definitions of miscarriage and type of miscarriage in the literature nationally and internationally might have influenced the variation in the classification of the type of miscarriages between our sources. The discrepancies between the cut-offs of weeks of gestation does not affect the overall diagnoses of miscarriage (e.g. miscarriage yes or no), but influences the classification of early and late miscarriage. This will effect on the type of the treatment and investigations associated to the type of miscarriage; therefore, it influences the hospital activity and costs, national rates and morbidity investigated.

3.5.4 Implications for practice and/or policy

Reporting reliable prevalence and trends in incidence rates provide information about the burden of miscarriage at national and international levels. Although the level of agreement to identify the diagnosis of miscarriage was found to be good or very good between the three data sources, this study found a high variability when comparing the classification of the type of miscarriage. This might be explained by the fact that the process of miscarriage is a continuum where the diagnosis might evolve during the stay at the hospital. For example, a woman can be diagnosed with an incomplete miscarriage at the beginning of the hospitalisation process, but she could also be diagnosed as having a complete miscarriage before discharge and after expulsion or

retrieving the RPOC. Identifying the correct type of miscarriage during the hospitalisation process is very important because pathways of treatments available are intrinsically related to the type of miscarriage (i.e. incomplete, complete, or missed miscarriage). There is a need to standardise definitions of miscarriage between data sources not only in the ROI, but also in an international level. An effort needs to be done to modify the definitions used by HIPE, in Ireland, in accordance with the Irish legislation. In doing so, the classification of miscarriage and data reliability of miscarriage may improve.

This study found a considerable number of records missing in the register books compared to EHR and HIPE. It is well reported that doctors, midwives and nurses experience the high levels of stress at the workplace and burnout in Ireland and in Europe[277,278]. The introduction of the EHR represents a change in the way data are routinely entered in the maternity services in Ireland, and it may have increased the workload of the healthcare professionals. Currently, entering patients' information for both electronic and paper based records is required. The duplication of information might result in subsequent human error as healthcare professionals have to enter the same clinical information into two different databases at the same time. Maybe it is time to evolve to only electronic records to decrease the amount of workload for health professionals in the maternity services. It is also time to enable access to the electronic health records for simple data analysis such as numbers of miscarriage. Consequently, ensuring reliable data on type of miscarriage would allow investigation of the implications and morbidity of different management strategies. It might also influence future changes in the supports available to women who miscarry nationally and internationally. Finally, it is becoming more common that women who miscarry are

managed and medically treated at the outpatient department, and in outpatient early pregnancy units. In order to improve protocols and care of women who experience miscarriage, both outpatient and inpatient data should be available in the national health systems.

3.6 Conclusion

In conclusion, using electronic health records (EHR) as a "gold standard", this study found a good and very good level of agreement between HIPE and register books (paper-based records) for identifying inpatient admissions for miscarriage in a tertiary maternity hospital in Ireland. However, the high number of missing records or unclear diagnosis limited the usefulness for monitoring and reporting the prevalence of miscarriage based on the register books. In addition, identification of the type of diagnosis of miscarriage varied significantly between the three data sources. According to the statistical analysis, EHR and HIPE are sufficiently reliable and valid databases for monitoring and reporting prevalence and trends in inpatient admissions of miscarriage at a national level, but some improvements are needed. However, the authors believe that EHR is the preferred source for obtaining types of diagnosis of miscarriage when it is assessed by an experienced and specialised professional in pregnancy loss.

3.7 Implications for practice, policy and research

Implications for practice

- Our study found that EHR and HIPE are reliable and valid databases for monitoring and reporting prevalence of inpatient admissions for miscarriage in Ireland
- However, only EHR was found to be a reliable database for reporting types of hospitalisation of miscarriage (e.g. late, early, incomplete, complete and missed miscarriage)

Implications for policy

- There is a need to standardise the gestational cut-offs for miscarriage definitions and the types of miscarriage (e.g. late, early, incomplete, complete and missed miscarriage) at national level
- There is a need for training on data entry about pregnancy loss for healthcare professionals using the EHR at national level

Implications for research

- Identification of the type of inpatient admissions of miscarriage varied significantly between the three data sources (e.g. EHR, HIPE and register books)
- There is a need to unify outpatient and inpatient systems to estimate the overall burden of miscarriage at national level

3.8 Supplementary Tables

Supplementary Table 3.1. Description of main ICD-10 AM of diagnosis of early pregnancy loss in HIPE

ICD-10 codes	Diagnosis in HIPE
	Total
	Classification of diagnosis of miscarriage
O021	Missed abortion
O030	Spontaneous abortion: incomplete; complicated by genital tract and pelvic infection
O031	Spontaneous abortion: incomplete; complicated by delayed or excessive haemorrhage
O033	Spontaneous abortion: incomplete; with other and unspecified complications
O034	Spontaneous abortion: incomplete; without complication
O035	Spontaneous abortion: complete; complicated by genital tract and pelvic infection
O036	Spontaneous abortion: complete; complicated by delayed or excessive haemorrhage
O039	Spontaneous abortion: complete; without complication
	Other type complication following abortion and ectopic and molar pregnancy
O080	Genital tract and pelvic infection following abortion and ectopic and molar pregnancy
O081	Delayed or excessive haemorrhage following abortion and ectopic and molar pregnancy
O088	Other complications following abortion and ectopic pregnancy and molar pregnancy
O075	Other and unspecified failed attempted abortion; complicated by genital tract and pelvic infection
	Other type of early pregnancy loss
O001	Tubal pregnancy
O008	Other ectopic pregnancy
O009	Ectopic pregnancy, unspecified
O010	Classical hydatidiform mole
O011	Incomplete and partial hydatidiform mole

Supplemental Table 3.2. Data collection form

	MRN:		**Initials:**		**Age:**	
			Gravity:		**Parity:**	
	ADMDATE:		**DISCDATE:**		**LOS:**	
	DATE SEARCH:		HIPE (1)	☐	EHR (2)	☐
			Register books (3)	☐		
	DIAGNOSIS					
EHR & RB	**UNSPECIFIED (0):**	☐				
	EARLY (1):	☐	Complete (0)	☐	Incomplete (1)	☐
			Missed (2)	☐		
	LATE (2):	☐				
	OTHER PREGNANCY LOSS (3):	☐				
HIPE	**COMPLETE (0):**	☐	with infection (1)	☐	haemorrhage (2)	☐
	other complications. (3)	☐	without complications (4)	☐	Other (5)	
	INCOMPLETE (1):	☐	with infection (1)	☐	haemorrhage (2)	☐
	other complications (3)	☐	without complications (4)	☐	Other (5)	
	MISSED (2)	☐				
	OTHER PREGNANCY LOSS (3)	☐				
	WEEKS OF GESTATION					
EHR & RB	By USS (0):	☐	Weeks gest.		Days gest.	
	By dates (1):	☐	Weeks gest.		Days gest.	
	Unknown (888):		Weeks gest.		Days gest.	
HIPE	5-13 weeks (0)	☐	14-19 weeks (1)	☐	20-25 weeks (2)	☐
	TREATMENT					
	CONSERVATIVE		No (0)	☐	Yes (1)	☐
	SURGICAL		No (0)	☐	Yes (1)	☐
	MEDICAL		No (0)	☐	Yes (1)	☐
SURGICAL	**ERPC**		No (0)	☐	Yes (1)	☐
	ERPC consent form		No (0)	☐	Yes (1)	☐
	Antenatal (0)	☐	Postnatal (1)	☐		
	D&C (1)	☐	Suction curret (2)	☐	Blunt curret (3)	☐
	Sponge forceps	☐	Polyp force	☐	Other (3)	
	General Anaesthesia		No (0)	☐	Yes (1)	☐
	Delivery spontaneously		No (0)	☐	Yes (1)	☐
	Time:		Position:			
	VE		No (0)	☐	Yes (1)	☐
	EVA		No (0)	☐	Yes (1)	☐
	MROP		No (0)	☐	Yes (1)	☐
	Other surgical or invasive intervention					
	Anti-D given		No (0)	☐	Yes (1)	☐
	Analgesia		No (0)	☐	Yes (1)	☐
MEDICAL	**Drug name**		**Dose**	**Frequency**	**Where**	**When**
	Misoprostol (0)	☐				
	Mifepristone (1)	☐				
	Oxytocin (2)	☐				
	Other					
	Histological report		No (0)	☐	Yes (1)	☐
	Post-mortem exam		No (0)	☐	Yes (1)	☐
	SIGN AND SYMPTOMS					
	Vaginal bleeding	None	Minimal	Moderate	Heavy	Acute
	Cloths		No (0)	☐	Yes (1)	☐
	Blood transfusion		No (0)	☐	Yes (1)	☐
	Pain	None	Mild	Moderate	Acute	

Supplementary Table 3.3 Example of a 2x2 table comparing data sources

	Miscarriage recorded in source one	**Miscarriage not recorded in source one**	**Total**
Miscarriage recorded in source two	a	b	a + b
Miscarriage not recorded in source two	c	d	c + d
Total	a + c	b + d	n= a + b + c + d

Formulas

Prevalence = (a + c)/n

Cohen's Kappa statistics (k) = (po-pe)/(1-pe), with po and pe meaning observed and expected agreement by chance

Sensitivity = a/(a+c)

specificity= d/(b+d)

PPV = a/(a+b)

NPV = d/(c+d)

Interpretations of the Cohen's Kappa statistics (k) were carried out using the strength of agreement by Altman, 1991:

- poor if $k < 0.20$
- fair if $0.21 \leq k \leq 0.40$
- moderate if $0.41 \leq k \leq 0.60$
- good if $0.61 \leq k \leq 0.80$
- very good if $k > 0.81$

Chapter IV.

Risk factors for miscarriage among women attending an Early Pregnancy Assessment Unit (EPAU): A prospective cohort study

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4.1 Abstract

Background: Miscarriage is the most common adverse outcome in early pregnancy; however, high proportion of miscarriages are classified as unexplained. In addition, pregnant women attending early pregnancy assessment units might be more vulnerable. **Aims:** The purpose of this study was to explore the risk factors that might be associated with miscarriage among women attending an early pregnancy assessment unit (EPAU). **Methods**: A prospective cohort study was undertaken. The study was conducted on women attending an EPAU at a large, tertiary hospital. A detailed lifestyle questionnaire was completed. In addition, data from validated psychometric scales were collected. Participants were followed up to determine pregnancy outcome. The relative risk was calculated to estimate the probability of having a miscarriage for all independent variables. **Results**: A total sample of 293 women were included in this study. Well-established risk factors for miscarriage were found in this group including advanced maternal age and high-risk pregnancy (i.e. threatened miscarriage and recurrent miscarriage). In addition, lack of emotional well-being did contribute to an increased risk of miscarriage. Conversely, presenting with nausea or low-medium energy levels early in pregnancy were associated with a decreased risk of miscarriage. Finally, our results did not find any association between stressful life events, general health and lifestyle factors in this group. **Conclusions**: Our findings indicated that maternal, psychological and obstetric factors may have an influence on miscarriage among women attending an EPAU. The insight of a relationship between emotional wellbeing and miscarriage opens a window for prevention in this area.

Keywords: Early pregnancy assessment unit; Miscarriage; Perceived stress; Pregnancy history.

4.2 Introduction

Miscarriage is considered the most common adverse outcome in early pregnancy. It is defined as the spontaneous demise of a pregnancy from the time of conception until 24 weeks gestation[15]. It can be clinically classified as first-trimester miscarriage (within 12 weeks gestation) or second-trimester miscarriage (after 12 and before 24 completed weeks gestation)[15,16]. Miscarriage is a public health issue that affects women all around the world. When a pregnancy loss is based on decreasing serum or urinary human chorionic gonadotropin (hCG or β-hCG), it is defined as biochemical pregnancy loss. The number of biochemical miscarriages are estimated to be at least 30%[6] When a miscarriage is confirmed by ultrasound or histology it is defined as clinical miscarriage[15]. It is estimated that one out of four women will experience a clinically recognised miscarriage during the first-trimester in their reproductive life[4], and less than 1% will experience a second-trimester miscarriage[34]. Approximately, 1% of couples trying to conceive will experience three or more consecutive miscarriages, also defined as a recurrent miscarriage[106].

Half of all miscarriages are attributed to chromosomal abnormalities and a high proportion of miscarriages are classified as unexplained[62]. Without a putative cause and without an available treatment most pregnancy losses are considered unpreventable[179]. Consequently, identifying risk factors and effective interventions to prevent miscarriage has become a priority for both clinicians and researchers[149]. Well-documented risk factors include advanced maternal age, previous miscarriage, previous infertility and heavy smoking[150]. Nevertheless, controversy remains when investigating the effect of lifestyles and psychological wellbeing as modifiable and preventable factors[152] as these studies were limited by their design

and how they measured confounding and multifactorial variables[172]. For example, extremes of maternal weight, which are defined as a body max index (BMI) less than 18.5kg/m^2 or above 25kg/m^2, have been associated with an increased risk of miscarriage[175]; whereas other studies have not shown any association[171]. Similarly, caffeine intake and alcohol consumption have generally, but not consistently, been associated with an increased risk of miscarriage[171]. Other risk factors which have been explored in the literature are exercise, lifting more than 20 kg daily, work schedule and occupational status during pregnancy[150].

The psychological morbidity among women who experience miscarriage and their partners have been extensively studied worldwide[215]. However, the impact that antenatal maternal psychological distress might have on adverse obstetrics and fetal outcomes is less clear[279]. Evidence in this topic is controversial depending on the psychological stressor which is investigated (i.e. depression, anxiety, life events factors, stress at work, perceived stress, physiological stress) and the design of the study. For example, few studies found an association between depression or anxiety and risk of miscarriage[280]. While there are a considerable number of studies that reported an association between life events, work stressors or perceived stress and miscarriage[150,281], others did not[191,192]. Similarly, though much less investigated, some studies reported an increased risk of miscarriage after measuring physiologic stress factors (i.e. urinary cortisol or salivary alpha-amylase)[193], whereas others did not find any association[194].

The introduction of Early Pregnancy Assessment Units (EPAU) has improved the quality of antenatal care for women with complications in early pregnancy[282]. The most common reasons for attending EPAU are seeking reassurance of viability of the ongoing pregnancy among women with a history of pregnancy loss, but also those women who present with vaginal bleeding or pelvic pain[282]. Although several epidemiological studies have explored the association of risk factors and miscarriage in the general population of pregnant women[150,171], to our knowledge, no studies have assessed the risk factor for this targeted group of women who attend the EPAU. Therefore, we carried out a prospective cohort study to determine the relationships between risk factors that might be associated with miscarriage among women attending an EPAU.

4.3 Methods

4.3.1 Study design

This prospective cohort study was conducted at Cork University Maternity Hospital, a large, tertiary maternity hospital with approximately 8,000 deliveries annually. Eligible participants included pregnant women attending the EPAU in their first weeks of pregnancy, generally between 10 and 14 weeks of gestation. The EPAU is a custom designed unit in the hospital that provides care to pregnant women who present with complications in early pregnancy.

4.3.2 Recruitment and follow-ups

The EPAU is an appointment only clinic from 8am to 1pm Monday to Friday. Pregnant women were approached by the research midwife on randomly-selected

days (*n*=45) from the beginning of April to the end of July in 2012. Upon agreement to participate, the women's age, gestation at recruitment, parity and marital status were determined from her obstetric case-notes. Women were then asked to complete a detailed self-completed lifestyle questionnaire. Weight and height were self-reported questions (i.e. *what was your weight before you become pregnant? what is your height without shoes?*). After filling the questionnaire in, participants returned the survey on site or by post in a stamped, addressed envelope. Women were followed-up, whereby hospital records were reviewed after 20 weeks by the research midwife through to delivery in order to ascertain pregnancy outcome. Follow-ups were completed by the end of November of 2012.

4.3.3 Outcome measures

Our primary outcome of interest was miscarriage. This was defined as any pregnancy loss which occurred before 24 weeks gestation in a fetus weighing less than 500 grams[16].

4.3.4 Risk factors

This study explored the following potential risk factors for miscarriage: socioeconomic characteristics, past reproductive history, diet and lifestyle factors, physical activity and partners' characteristics. They survey was developed through a review of the literature. For example, demographic questions reflected those collected by other national collections or census by the Central Statistics Office (CSO). Questions about diet and lifestyle factors were selected using the Pregnancy

Risk Assessment Monitoring System (PRAMS) – Ireland [283]. The remaining sections were not collected using validated questionnaires. Nevertheless, all the questions were reviewed by a multidisciplinary team of experts in pregnancy loss. In addition, all the questions were reviewed by the Clinical Research Ethics Committee of the Cork Teaching Hospital to assess appropriateness. This study also included information on a range of traumatic events, e.g. loss of job, separation or divorce, serious accident or illness, death of someone close, previous miscarriage, stillbirth and death of a child, based on a list developed by Maconochie et al. (2007)[150]. Women were asked to indicate if they experienced a traumatic event in the last 12 months, more than 12 months ago, or not at all.

In the context of this study, women were categorised as either at high or low-risk for miscarriage. High-risk was defined as a woman who presented to the clinic with a threatened miscarriage or/and a history of recurrent miscarriage, i.e. three or more consecutive miscarriages. Women who did not meet these criteria were defined as low-risk for miscarriage. Confirmation of risk status was determined through review of the women's obstetric chart.

Psychometric scales were also used to assess women's psychological state during early pregnancy. The item perceived stress scale (PSS) was developed by Cohen, Kamarck, and Mermelstein to measure the degree to which situations in one's life are appraised as stressful[284]. The PSS is not a diagnostic instrument, but intended to make comparisons of subjects' perceived stress related to current, objective events. In this study, the PSS-4 was used as a simple psychological instrument to comprehend and score general queries about relatively current levels of perceived

stress. Using a 5-point Likert scale ranging from never to very often, women were asked to indicate how often feelings, thoughts or life situations were perceived as uncontrollable, unpredictable and stressful in the past month[284]. A total score ranging between zero and 16 was obtained by summing across all four items, after appropriate items were reversed. Higher summary scores indicate greater perceived stress. The internal consistency in our study (Cronbach's alpha) was 0.70.

The Research And Development (RAND) 36-Item Health Survey is one of the most widely used instruments to assess health-related quality of life[285]. It is comprised of eight health concepts: physical functioning, role limitations caused by physical health problems, role limitations caused by emotional problems, social functioning, emotional well-being, energy/fatigue, pain, and general health perceptions[285]. It includes the same items as the SF-36 but with different scoring algorithm. In this study, the RAND-36 scale was used to calculate aggregate scores to measure participant's energy/fatigue balance and emotional wellbeing. Women were asked to report how often they had felt happy, tired, worn out, nervous, downhearted or sad over the past four weeks. Responses for energy/fatigue balance were measured on a 6-point scale ranging from 'all of the time' (score of 100) to 'none of the time' (score of zero). For example, a score of 100 represented high energy with no fatigue; therefore, a lower score of 40% suggests the participant is experiencing a loss of energy and is experiencing some fatigue[286]. The internal consistency (Cronbach's alpha) was 0.84. Responses for emotional balance were measured on a 6-point scale ranging from 'all of the time' (score of zero) to 'none of the time' (score of 100). The internal consistency (Cronbach's alpha) was 0.76. Higher summary scores indicate a more favourable state of emotional wellbeing.

Social support was evaluated using the Maternity Social Support Scale (MSS). This six-item scale measures support from the woman's spouse, family and their wider social network on a five-point scale ranging from 'never' (score of one) to always (score of five). The total possible score was obtained by summing the response categories selected by the participants. Possible scores range from six to 30 points, with higher summary scores indicating higher levels of social support[287]. The internal consistency (Cronbach's alpha) was 0.63.

Finally, the Revised Life Orientation Test (LOT-R) is a measure of dispositional optimism. Studies indicate that having a positive outlook is beneficial for physical and psychological well-being and therefore has important health implications[288]. The scale assesses individual differences in generalised optimism versus pessimism. The LOT-R is a 10 item scale whereby women chose from a five point scale ranging from strongly disagree (score of zero) to strongly agree (score of four). Higher summary scores are indicative of an optimistic rather than a pessimistic outlook. The internal consistency (Cronbach's alpha) was 0.77.

4.3.5 Statistical analysis

Cronbach's alpha was used to assess the internal consistency of the psychometric scales in the study[4]. The PSS-4 and the psychometric scales are not diagnostic instruments and no predetermined cut-off scores points have been differentiated. Instead, psychological scales were divided into equally weighted tertiles (low, medium and high scores). BMI was calculated using the self-reported height and weight variables using the formula BMI=weight (kg) / height^2 (metre).

Binary logistic regression was performed to determine if there was a relationship between levels of stress and miscarriage. The relationship between psychometric scales, general health and lifestyles factors and miscarriage was also explored using logistic regression. The odds ratio was calculated to estimate the probability of having a miscarriage for all independent variables with their corresponding 95% confidence intervals. The first model included univariate analysis of all variables included in the study. The second model adjusted all variables by well-known confounder factors such as maternal age (continuous), body mass index (continuous), previous pregnancy loss (dichotomous), nausea and vomiting (dichotomous) and high or low risk presentation for miscarriage (dichotomous) upon recruitment at the AEPU. All the analyses were performed using SPSS 21.0 (IBM).

4.3.6 Sample size calculations

Sample size calculations were made using Power and Sample Size software (PASS 13). The main association under investigation was between levels of stress and miscarriage. We categorised stress scores into three equal groups (i.e. low, medium and high levels of stress). A sample size of 85 participants in each group allowed us to detect an odds ratio of 2.5 between two groups (i.e. high versus low stress) in relation to the outcome of miscarriage, with 80% power and 5% significance.

4.3.7 Ethical approval

This study received ethical approval from the Clinical Research Ethics Committee of the Cork Teaching Hospital on ECM 4 (iii) 10/01/2012.

4.4 Results

A total sample of 293 women were included in this analysis. The average age of the women was 31.9 years (SD 5.8). The majority of women presented to the EPAU with either a threatened miscarriage (46.1%, *n*=135) or to seek a reassurance scan (47.4%, *n*=139) with just 6.5% (*n*=19) of women attending with a history of recurrent miscarriage. Approximately 46% of women (*n*=134) had a confirmed miscarriage. Only 29% (*n*=40) of women who attended for a reassurance scan miscarried; however, two thirds of women who presented with threatened miscarriage and half of women with a history of recurrent miscarriage had a miscarriage (62%; *n*=82 & 53%; *n*=10, respectively). Women who attended the EPAU for threatened miscarriage and/or because of previous recurrent miscarriage had four times the risk of miscarrying compared to those attending for a reassurance scan (OR 4.1; 95% CI95% CI 2.0-8.3; Table 4.1).

Women who miscarried were older than those who continued the pregnancy (mean 33.5 years old ± 6.1 versus 30.5 ± 5.2, respectively). Women who were 38 years or older had almost four times the risk of having a miscarriage compared to women younger than 38 years (OR 3.9; 95% CI 2.0-7.8) (Table 4.1). Women who had a previous pregnancy loss were more likely to have a miscarriage (OR 1.7; 95% CI 1.0-2.8); however, this association was not significant after adjusting for confounders (Table 4.2).

Table 4.1. Odds Ratios for miscarriage (<24 weeks): Socioeconomic characteristics.

	Pregnancy *n* (%)	**Miscarriage *n* (%)**	**Model I OR (95% CI)**	**P-value**	**Model II OR (95% CI)**	**P-value**
Total (*n*)	159	134				
Age (*n*)	107	97				
Age, mean (SD)	30.5 (5.2)	33.5 (6.1)	1.1 (1.0, 1.2)	0.011	1.1 (1.1, 1.2)	0.001
Under 38 years	94 (56.6)	72 (43.4)	1.0		1.0	
38 years or more	13 (34.2)	25 (65.8)	2.5 (1.2, 5.2)	0.014	3.9 (2.0, 7.8)	0.000
Ethnicity (*n*)	158	134				
White Irish	132 (55.2)	107 (44.8)	1.0		1.0	
Other ethnic background	26 (49.1)	27 (50.9)	1.3 (0.7, 2.3)	0.415	0.9 (0.4, 2.3)	0.874
Country of birth (*n*)	159	134				
Republic of Ireland	125 (56.1)	98 (43.9)	1.0		1.0	
Outside Ireland	34 (48.6)	36 (51.4)	1.4 (0.8, 2.3)	0.274	1.2 (0.5, 2.9	0.686
Marital Status (*n*)	158	134				
Married	95 (52.8)	85 (47.2)	1.0		1.0	
Non married	63 (56.3)	49 (43.8)	0.9 (0.6, 1.4)	0.563	1.1 (0.5, 2.5)	0.742
Education (n*)*	157	133				
Undergraduate or postgraduate degree	57 (59.4)	39 (40.6)				
Some primary/Certificate and/or higher diploma	100 (51.5)	94 (48.5)	1.4 (0.8, 2.3)	0.209	2.0 (0.9, 4.3)	0.079
Household income (*n*)	152	126				
40,000 or more	68 (59.1)	47 (40.9)	1.0		1.0	
Below 20,000 till 39,999	84 (51.5)	79 (48.5)	1.4 (0.8, 2.2)	0.211	0.6 (0.3, 1.3)	0.191
Current employment status (*n*)	159	134				
Full-time paid work	77 (52.7)	69 (47.3)	1.0		1.0	

Part-time/unemployed/ student	82 (55.8)	65 (44.2)	0.9 (0.6, 1.4)	0.601	1.0 (0.5, 2.1)	0.988
BMI	149	123				
Mean (SD)	26.9 (5.01)	30.1 (22.80)	1.0 (0.99, 1.08)	0.093	1.1 (1.02-1.14)	0.013
Previous miscarriage (*n*)	150	121				
No	68 (63.0)	40 (37.0)	1.0		1.0	
Yes	82 (50.3)	81 (49.7)	1.7 (1.0-2.8)	0.041	1.6 (0.8-3.2)	0.190
Nauseas and vomiting (*n*)	152	123				
No	40 (44.0)	51 (56.0)	1.0		1.0	
Yes	112 (60.9)	72 (39.1)	0.5 (0.3-0.8)	0.008	0.6 (0.3-1.2)	0.131
Presentation (*n*)	159	134				
Low risk presentation	99 (71.2)	40 (28.8)	1.0		1.0	
High risk presentation	60 (39.0)	94 (61.0)	3.9 (2.4, 6.3)	0.000	4.1 (2.0, 8.3)	0.000

Model I: Univariate unadjusted model. Model II: Multivariate model adjusted for maternal age (continuous), presentation (dichotomous), previous miscarriage (dichotomous), nausea and vomiting (dichotomous), Body Mass Index (continuous).

Similarly, women who had three or more miscarriages had almost three times the risk of having a miscarriage without adjusting for confounder factors (OR 2.6; 95% CI 1.1-6.7). Those women who were in their first pregnancy (primigravida) and who reported to have taken three months or more to conceive had a higher risk of miscarriage compared to those who got pregnant in less than three months in the univariate analysis (OR 4.0; 95% CI 1.2-13.5) (Table 4.2). In addition, presenting with nausea and vomiting in the early stages of pregnancy was protective (OR 0.5; 95% CI 0.3-0.8), but not after adjusting for confounders (Table 4.2).

Women who had high levels of perceived stress or who self-reported having high energy with no fatigue were more likely to have a miscarriage, but only before adjusting for confounder factors (OR 1.9; 95% CI 1.13.5 & OR 1.9; 95% CI 1.1-3.3, respectively; Table 4.3). Conversely, those who had an emotional balance were less likely to have a miscarriage in the multivariate model (OR 0.4; 95% CI 0.2-1.0) (Table 4.3). No differences were found in relation to maternal social support or for life orientation (Table 4.3).

Table 4.2. Odds Ratios for miscarriage (<24 weeks): past reproductive history.

	Pregnancy *n* (%)	**Miscarriage *n* (%)**	**Model I OR (95% CI)**	**P-value**	**Model II OR (95% CI)**	**P-value**
Age at first period (*n*)	141	115				
More than 13 years old	46 (57.5)	34 (42.5)	1.0		1.0	
13 years old or younger	95 (54.0)	81 (46.0)	1.2 (0.7-2.0)	0.600	1.6 (0.7-3.6)	0.222
Age at first period, mean (SD)	13.0 (1.4)	12.6 (1.9)	0.9 (0.7-1.0)	0.056	0.8 (0.6-1.0)	0.082
Age at first delivery (*n*)	100	84				
30 years old or younger	66 (60)	44 (40)	1.0		1.0	
More than 30 years old	34 (45.9)	40 (54.1)	1.8 (1.0-3.2)	0.062		
Age at first delivery, mean (SD)	26.3 (6.7)	28.0 (6.2)	1.0 (1.0-1.1)	0.072	1.0 (0.9-1.1)	0.889
Live births (*n*)	153	125				
No	54 (57.4)	40 (42.6)	1.0		1.0	
Yes	99 (53.8)	85 (46.2)	1.2 (0.7-1.9)	0.564	0.7 (0.3-1.5)	0.347
Stillbirth (*n*)	100	84				
No	137 (55.0)	112 (45.0)	1.0		1.0	
Yes	7 (58.3)	5 (41.7)	0.9 (0.3-2.8)	0.822	0.6 (0.1-2.6)	0.465
Weeks of gestation at delivery: first child (*n*)	100	84				
Term	89 (53.0)	79 (47.0)	1.0		1.0	
Preterm	11 (68.8)	5 (31.3)	0.5 (0.2-1.5)	0.233	0.6 (0.1-2.3)	0.426
Weeks of gestation at delivery: second child (*n*)	35	38				
Term	32 (48.5)	34 (51.5)	1.0		1.0	
Preterm	3 (42.9)	4 (57.1)	1.3 (0.3-6.0)	0.777	4.2 (0.3-77.9)	0.332
Type of delivery: first child (*n*)	100	84				
Assisted/Caesarean delivery	52 (52.5)	47 (47.5)	1.0		1.0	

Normal delivery	48 (56.5)	37 (43.5)	1.2 (0.7-2.1)	0.592	0.8 (0.3-1.8)	0.553
Type of delivery: second child (*n*)	35	37				
Normal delivery	24 (44.4)	30 (55.6)	1.0		1.0	
Assisted/Caesarean delivery	11 (61.1)	7 (38.9)	0.5 (0.2-1.5)	0.224	0.2 (0.02-1.1)	0.058
Delivery early in previous pregnancies (*n*)	82	64				
No	62 (59.6)	42 (40.4)	1.0		1.0	
Yes	20 (47.6)	22 (52.4)	1.6 (0.8-3.3)	0.188	1.7 (0.6-4.7)	0.314
Previous miscarriage (*n*)	150	121				
No	68 (63.0)	40 (37.0)	1.0		1.0	
Yes	82 (50.3)	81 (49.7)	1.7 (1.0-2.8)	0.041	1.6 (0.8-3.2)	0.190
Number of miscarriages (*n*)	150	121				
Zero	68 (63.0)	40 (37.0)	1.0		1.0	
One	53 (50.5)	52 (49.5)	1.7 (1.0-2.9)	0.067	0.7 (0.2-2.8)	0.561
Two	20 (57.1)	15 (42.9)	1.3 (0.6-2.8)	0.539	1.2 (0.3-5.2)	0.823
Three or more	9 (39.1)	14 (60.9)	2.6 (1.1-6.7)	0.039	0.7 (0.1-3.9)	0.716
Type of treatment first miscarriage (*n*)	78	78				
Conservative treatment	40 (51.3)	38 (48.7)	1.0		1.0	
Medical or surgical treatment	38 (48.7)	40 (51.3)	1.1 (0.6-2.1)	0.749	0.6 (0.2-1.6)	0.305
Bleeding during sexual intercourse (*n*)	110	86				
Never	83 (58.0)	60 (42.0)	1.0		1.0	
Sometimes/rarely	27 (50.9)	26 (49.1)	1.3 (0.7-2.5)	0.374	0.8 (0.3-2.1)	0.586
Time to conceive (primigravida, *n*)*	30	20				
Less than 3 months	19 (76.0)	6 (24.0)	1.0		1.0	
Three months or more	11 (44.0)	14 (56.0)	4.0 (1.2-13.5)	0.024	-	-
Interpregnancy interval	117	99				

(multiparas, *n*)						
Less than 3 months	20 (62.5)	12 (37.5)	1.0		1.0	
Three months or more	97 (52.7)	87 (47.3)	1.5 (0.7-3.2)	0.307	1.3 (0.4-3.8)	0.639
Nauseas and vomiting (*n*)	152	123				
No	40 (44.0)	51 (56.0)	1.0		1.0	
Yes	112 (60.9)	72 (39.1)	0.5 (0.3-0.8)	0.008	0.6 (0.3-1.2)	0.131
Pre-eclampsia previous pregnancy (*n*)	107	88				
No	103 (55.7)	82 (44.3)	1.0		1.0	
Yes	4 (40)	6 (60)	1.9 (0.5-6.9)	0.339	2.2 (0.3-15.8)	0.446
Family history of pre-eclampsia (*n*)	130	113				
No	127 (54.7)	105 (45.3)	1.0		1.0	
Yes	13 (61.9)	8 (38.1)	0.8 (0.5-1.5)	0.528	1.7 (0.4-7.1)	0.442
Folic acid (n)	155 (54.8)	128 (45.2)				
No	36 (52.9)	32 (47.1)	1.0		1.0	
Yes	119 (55.3)	96 (44.7)	0.9 (0.5-1.6)	0.728	1.4 (0.7-3.2)	0.360
Fertility treatment recent pregnancy (*n*)	150	121				
No	142 (55.3)	115 (44.7)	1.0		1.0	
Yes	8 (57.1)	6 (42.9)	0.9 (0.3-2.8)	0.890	1.5 (0.3-8.6)	0.643

Model I: Univariate unadjusted model. Model II: Multivariate model adjusted for maternal age (continuous), presentation (dichotomous), previous miscarriage (dichotomous), nausea and vomiting (dichotomous), Body Mass Index (continuous). * Excluded from multivariate model as a highly imprecise odds ratio was reported.

Table 4.3. Odds Ratios for miscarriage (<24 weeks): Perceived stress and psychometric scales.

	Pregnancy *n* (%)	**Miscarriage *n* (%)**	**Model I OR (95% CI)**	**P-value**	**Model II OR (95% CI)**	**P-value**
Total						
Perceived Stress (*n*)	152	127				
Low (0-4)	57 (58.8)	40 (41.2)	1.0		1.0	
Medium (5-7)	60 (60.0)	40 (40.0)	0.9 (0.5-1.7)	0.860	0.9 (0.4-2.1)	0.735
High (≥8)	35 (42.7)	47 (57.3)	1.9 (1.1-3.5)	0.033	2.4 (1.0-5.8)	0.063
Maternal Social Support (*n*)	146	121				
Low support (7-23)	42 (59.2)	29 (40.8)	1.0		1.0	
Medium support (24-25)	45 (54.2)	38 (45.8)	1.2 (0.6-2.3)	0.538	1.2 (0.4-3.1)	0.773
High support (26-30)	63 (52.5)	57 (47.5)	1.3 (0.7-2.4)	0.372	1.6 (0.6-3.9)	0.0.325
Life orientation (*n*)	147	127				
Pessimistic (0-12)	38 (54.3)	32 (45.7)	1.0		1.0	
Neutral (13-15)	44 (54.3)	37 (45.7)	0.99 (0.5-2.0)	0.997	0.8 (0.3-2.1)	0.675
Optimistic (16-24)	65 (52.8)	58 (47.2)	1.1 (0.6-1.9)	0.847	0.7 (0.3-1.7)	0.715
Energy fatigue balance (*n*)	158	130				
Low energy with lot of fatigue (0-35)	60 (65.2)	32 (34.8)	1.0		1.0	
Medium energy with some fatigue (36-45)	26 (50.9)	26 (49.1)	1.8 (0.9-3.6)	0.093	1.1 (0.4-3.2)	0.881
High energy with no fatigue (46-100)	71 (49.7)	72 (50.3)	1.9 (1.1-3.3)	0.020	1.8 (0.8-4.2)	0.160
Emotional wellbeing (*n*)	158	129				
Little emotional balance (0-60)	32 (41.6)	45 (58.4)	1.0		1.0	
Some emotional balance (61-76)	58 (62.4)	35 (37.6)	0.4 (0.2-0.8)	0.007	0.4 (0.1-0.9)	0.034
Emotional balance (77-100)	68 (58.1)	49 (41.9)	0.5 (0.3-0.9)	0.025	0.4 (0.2-1.0)	0.042

Model I: Univariate unadjusted model. Model II: Multivariate model adjusted for maternal age (continuous), presentation (dichotomous), previous miscarriage (dichotomous), nausea and vomiting (dichotomous), Body Mass Index (continuous).

Women who had a higher BMI had a slightly higher risk of miscarriage (OR 1.1; 95% CI 1.02-1.14). Women who self-reported that their workplace was stressful had almost four times the risk of having a miscarriage compared to those who report that they had never had a stressful workplace (OR 3.4 95% CI 1.0-11.1) (Supplementary Table 4.1). Women who worked with a computer screen were more likely to have a miscarriage (OR 1.6; 95% CI 1.0-2.8), but this association was not significant after adjusting for confounders. No differences were found among any other general health factor or lifestyle behaviours (Supplementary Table 4.1). However, women whose partner was unemployed or worked part-time had twice the risk of having a miscarriage compared to those who worked full-time (OR 2.3; 95% CI 1.0-5.2) (Supplementary Table 4.2). In the univariate analysis women whose partner was 35 years or older had a higher risk of miscarriage than those whom had a partner younger than 35 years (OR 1.8; 95% 1.1-2.9); however, this analysis were not significant in the multivariate analysis (Supplementary Table 4.2). Finally, no differences were found in relation to traumatic and stressful life events (Supplementary Table 4.3).

4.5 Discussion

4.5.1 Main findings

In this prospective cohort study almost half of the women went on to have a miscarriage (46%). The main objective was to examine the relationship between risk factors and miscarriage among women who attended an EPAU. Advanced maternal age and high-risk pregnancy were associated with an increased risk of miscarriage in this targeted group. For instances, being 38 years old or older was

associated with four-fold higher risk of having a miscarriage. Interestingly, this study did not find an association between advanced paternal age and miscarriage. Some work conditions were found to have an influence in the risk of miscarriage. For example, women who reported having a stressful workplace had a higher risk of miscarriage. Contrary to other studies, working with a computer screen was not found to be associated with miscarriage in this study. In addition, women whose partners had a part-time job or were unemployed did also have a higher risk of miscarriage in this sample. When looking at women's emotional and psychological wellbeing, this study found that women who self-reported having balanced emotional wellbeing were at a lower risk of miscarriage. However, this study did not find any association between stressful life events, high levels of stress, and high energy levels with no fatigue and miscarriage. Similarly, we did not find an association between an increased risk of miscarriage and women's general health, lifestyle factors or past reproductive history. Finally, the only protective factor which was found in this study was nausea and vomiting, which were associated with a decreased risk of miscarriage.

4.5.2 Interpretation

One explanation of our higher incidence rate of miscarriage may be that the majority of women who are referred to the EPAUs have a history of poor obstetric outcomes, which are associated with higher risk of miscarriage[289]. For instance, similar to our results, a study evaluating the value of introducing EPAUs in Canada found that 47.7% (691/1448) of women who attended the EPAU had a miscarriage[289]. Our results reaffirm previous findings of well-established obstetric risk factors for miscarriage, such as advanced maternal age[29,150,152] and high-risk

pregnancy, including threatened and recurrent miscarriage[290]. The delaying of the time of conception and its relationship with an increase of adverse pregnancy outcomes is a well-known public health issue; however, little is known about the underlying causes of this relationship[156]. Some authors claim that advanced maternal age can be considered a "preventable" factor, although cultural and social conditions, which influence this tendency, might limit its modification[152].

In line with our findings, previous evidence has shown that women who present with bleeding and/or pain in emergency departments have a higher risk of miscarriage[290]. However, contradictory results are also found in the literature[44]. Stressful life events and work stress have also been associated with miscarriage by several studies[150]. However, in this study only perceiving work as a stressful was found to be associated with an increased risk of miscarriage. The only partner' characteristic which was found to be associated with an increased risk of miscarriage was to have a part-time job or being unemployed. Previous studies have found an association between higher risk of pregnancy loss and economic disparities[183]. For instance, Bruckner et al. (2016) found that at least 15% of pregnancy losses were statistically attributable to women's unexpected high unemployment rate in the previous month[183]. In addition, our results did not find any association between general health and lifestyle factors and miscarriage. Smoking and alcohol during pregnancy are considered well-recognized risk factors for miscarriage[165]. However, contradictory evidence has also been published[291]. One explanation may be that women who had already had previous miscarriages or other types of pregnancy complications might be more motivated to improve their lifestyle behaviour to increase the chances of successful pregnancies[152].

In contrast with previous studies, our results did not find an increased risk of miscarriage after previous pregnancy loss when adjusting for confounding factors[150,152]. Similarly, the presence of nausea and vomiting[150] have been previously associated with a decreased risk of miscarriage, but this study did not find an association after adjusting for confounders. This might suggest that the variables which were used as a confounding factor including maternal age, body mass index, and high or low risk presentation might have a stronger predictor factor than previous pregnancy loss or nausea in our sample population.

There is a growing trend in the literature focusing on the effect of psychological wellbeing on subsequent pregnancy loss. Our results suggest that having balanced emotional wellbeing was the only psychological factor which was associated with a decreased risk of miscarriage after adjusting for confounding factors. In contrast to our results, the presence of pregnancy symptoms such low/medium energy[292] have been previously associated with a decreased risk of miscarriage. Several studies have evaluated and reviewed the impact of stress on pregnancy loss[281]. In addition, psychological stress has been associated with an increased risk of preterm labour, low birth weight and unsuccessful outcomes for in vitro fertilisation (IVF)[293]. Immunological imbalances have been linked to miscarriage in women who reported high perceived stress[281] and women who reported feeling stressed, anxious, depressed, out of control or overwhelmed in their first trimester had higher odds of miscarriage[150]. Very recently, a systematic review and meta-analysis concluded that maternal psychological stress and traumatic life events are risk factors for miscarriage[190]. Nevertheless, the effect of maternal stress on miscarriage

has not been publicly accepted yet by well-known and reputable medical and health institutions[294]; maybe because of the contradictory evidence in the field.

Reasons why obtaining conclusive evidence about risk of stress for miscarriage is challenging might be related to the wide range of scales for measuring different type of stress responses (perceived levels of stress, life events, and work stress). Also, the difficulty in distinguishing between the effect of other mental disorders, such as anxiety and depression, or between other lifestyle behaviours, such as smoking or alcohol consumption, which are also associated with an increased risk of poor pregnancy outcomes[190]. It is of note that only 2 of the 8 studies identified in a systematic review[190] used a specific scale for measuring perceived levels of stress; and that they obtained contradictory results[192,295].

4.5.3 Strengths and Limitations

Most of the studies published in the research area are retrospective cohort studies or case-control studies. The study design of this prospective study is one of its main strengths and all risk factors were collected before the event (miscarriage) occurred. Although this study was undertaken in 2012 in a single EPAU at a maternity hospital which limits the generalisability of the findings for the general population, our sample size of almost 300 women is larger than most previous studies in this area and it gave the study power to detect relatively uncommon risk factors. A limitation of this study is that it was not possible to collect information on psychosocial factors for women who did not return the lifestyle questionnaire or who did not want to participate. This study did not keep a log of women who declined to participate before agreeing to take part in the study, neither it keep a log

of women who did not send back the questionnaire. Therefore, we were unable to compare responders with non-responders in this regard. In addition, this study did not include stable psychological variables or biological predictors of stress (i.e. cortisol) and our results are limited by self-reported data. Bias from self-reported data is well documented as some health behaviours are either sensitive or difficult to recall. However, studies have indicated that maternal recall regarding health behaviours during pregnancy is reliable. Another strength of this study is that we used validated questionnaires for assessing perceived stress; but our study also incorporated a wide range of psychological stressors such as life events, stress at work and emotional wellbeing.

4.5.4 Implications and conclusions

Women who attend EPAUs might need specific care because of a complex obstetric history. Identification of risk factors in this targeted group might help clinicians to recognise and monitor with extra care those women who are at higher risk of subsequent miscarriage[281]. Although this study identifies some well-established risk factors (advanced age, threatened miscarriage, recurrent miscarriage), the options to encourage their prevention are limited. Nearly half of the participants attended the EPAU for a reassurance scan (48%). Therefore, it could be argued that women who had a positive scan showing a healthy ongoing pregnancy may have a reduction in stress and anxiety compared to women who were attending the EPAU with a history of recurrent miscarriage or who were experiencing a threatened miscarriage. However, to our knowledge, no studies have investigated the effect of a positive reassurance scan and the potential benefits for pregnant women's psychological wellbeing who have a history of pregnancy loss.

Nevertheless, the insight of a relationship between emotional wellbeing and miscarriage opens a window for prevention in this area. To date, few studies have examined interventions aimed at reducing stress or promoting emotional wellbeing in pregnant populations with a history of miscarriage[296]. For instance, a recent systematic review did not find any randomised controlled study which examined non-pharmacological interventions aimed at reducing stress, anxiety or depression in pregnant women with a history of miscarriage[297]. The findings of our study suggest that such studies are warranted. Further work to develop and evaluate targeted interventions which could improve coping skills before getting pregnant or during pregnancy might be effective in lowering the risk of miscarriage among women who have a history of pregnancy loss.

4.5.5 Conclusion

Despite the prevalence of miscarriage, chromosomal abnormalities only account for 50% of the cases. Therefore, identifying preventable and modifiable risk factors for miscarriage is becoming an area of interest worldwide. The results of this study reinforced that well-established risk factors such as advanced maternal age and high-risk pregnancies are associated with an increased risk of miscarriage in our targeted population. In addition, this study has provided evidence that contributes to the growing body of research by assessing the association of a large number of early maternal, psychological and obstetric factors and the potential risk of miscarriage. These conclusions underscore the need for supportive care in early pregnancy, particularly with women who may be more vulnerable.

4.6 Implications for practice, policy and research

Implications for practice

- Although this study identifies some well-established risk factors, the alternatives to encourage their prevention are limited
- The insight into the relationship between perceived levels of stress and miscarriage opens a window for prevention in this area

Implications for policy

- More funding is needed in order to carry out large scale cohort studies that assess the effects of previous miscarriages on psychological, physical and life styles among women in their subsequent pregnancy

Implications for research

- Targeted interventions to reduce stress and increase mental wellbeing are needed among this population
- Future development of questionnaires which assess the risk factors of miscarriage should involve patient advocacy and/or students advocacy
- A full-scale prospective study is needed in pregnant women without any complication to provide control background data on psychological, sleep patterns and support during pregnancy

4.7 Supplementary Tables

Supplementary Table 4.1. Odds Ratios for miscarriage (<24 weeks): General health and lifestyles behaviours.

	Pregnancy *n* **(%)**	**Miscarriage** *n* **(%)**	**Model I** **OR (95% CI)**	**P-value**	**Model II** **OR (95% CI)**	**P-value**
BMI (kg/m^2)*	n=148	n=123				
BMI (mean, SD)	26.9 (5.0)	30.1 (22.8)	1.0 (0.99-1.08)	0.093	1.1 (1.02-1.14)	0.013
General Health	n=159	n=134				
Very good/good	152 (55.5)	122 (44.5)	1.0		1.0	
Fair/poor	7 (36.8)	12 (63.2)	2.1 (0.8-5.6)	0.122	1.1 (0.3-4.3)	0.848
Medical illness	n=156	n=129				
No	127 (55.9)	100 (44.1)	1.0		1.0	
Yes	29 (50.0)	29 (50.0)	1.3 (0.7-2.3)	0.417	1.5 (0.7-3.5)	0.327
Diagnosis of anxiety	n=95	n=73				
No	83 (57.2)	62 (42.8)	1.0		1.0	
Yes	12 (52.2)	11 (47.8)	1.3 (0.5-3.0)	0.649	2.4 (0.6-9.5)	0.223
Diagnosis of depression	n=96	n=73				
No	74 (56.5)	57 (43.5)	1.0		1.0	
Yes	22 (57.9)	16 (42.1)	0.9 (0.5-2.0)	0.878	0.9 (0.3-2.8)	0.914
Regular medication	n=153	n=126				
No	115 (58.1)	83 (41.9)	1.0		1.0	
Yes	38 (46.9)	43 (53.1)	1.6 (0.9-2.6)	0.090	1.5 (0.7-3.2)	0.281
Flight abroad in early pregnancy	n=127	n=155	1.1 (0.56-2.1)			
No	131 (57.2)	98 (42.8)	1.0		1.0	

Yes	24 (45.3)	29 (54.7)	1.6 (0.9-2.9)	0.118	1.5 (0.6-3.7)	0.394
Physical activity**	n=153	n=128				
Unchanged	85 (55.9)	67 (44.1)	1.0		1.0	
Decreased	68 (52.7)	61 (47.3)	1.1 (0.7-1.8)	0.591	1.0 (0.5-2.1)	0.944
Hours per day watching TV	n=159	n=132				
Less than 2 hours	53 (54.1)	45 (45.9)	1.0		1.0	
2 or more hours	106 (54.9)	87 (45.1)	1.4 (0.7-1.8)	0.591	1.0 (0.5-2.1)	0.971
Workplace stressful	n=118	n=98				
Never	28 (73.7)	10 (26.3)	1.0		1.0	
Sometimes/often	90 (50.6)	88 (49.4)	2.7 (1.3-5.9)	0.011	3.4 (1.0-11.1)	0.046
Work hours	n=120	n=96				
Less than 40 hours	100 (58.1)	72 (41.9)	1.0		1.0	
40 hours or more	20 (45.5)	24 (54.5)	1.7 (0.9-3.2)	0.133	1.5 (0.6-4.1)	0.412
Physically demanding job	n=141	n=110				
No	93 (55.4)	75 (44.6)	1.0		1.0	
Yes	48 (57.8)	35 (42.2)	1.1 (0.7-1.9)	0.710	0.9 (0.4-1.9)	0.847
Working with a computer screen	n=142	n=112				
No	63 (63.6)	36 (36.4)	1.0		1.0	
Yes	79 (51.0)	76 (49.0)	1.6 (1.0-2.8)	0.048	1.6 (0.7-3.6)	0.255
No. of hours working with computer per week	n=82	n=73				
20 hours or less	42 (52.5)	38 (47.5)	1.0		1.0	
More than 20 hours	40 (53.3)	35 (46.7)	1.0 (0.5-1.8)	0.917	0.9 (0.3-2.5)	0.881
Mean, SD	21.1 (13.6)	20.2 (13.7)	1.0 (1.0-1.0)	0.699	0.9 (0.3-2.5)	0.881
Lifting between 11 – 20 kg at a time	n=138	n=107				
No	106 (55.8)	84 (44.2)	1.0		1.0	

Yes	32 (58.2)	23 (41.8)	1.1 (0.6-1.1)	0.753	0.9 (0.4-2.3)	0.910
Lifting between 11 to 20 kg at work (times)	n=32	n=21				
4 times or less	21 (67.7)	10 (32.3)	1.0		1.0	
More than 4 times	11 (50.0)	11 (50.0)	2.1 (0.7-6.4)	0.196	0.7 (0.1-5.4)	0.737
Mean, SD			1.0 (0.9-1.1)	0.927	1.0 (0.8-1.3)	0.763
Lifting more than 20 kg at a time	n=131	n=102				
No	123 (56.4)	95 (43.6)	1.0		1.0	
Yes	8 (53.3)	7 (46.7)	0.9 (0.3-2.5)	0.816	0.8 (0.1-5.7)	0.862
Lifting more than 20 kg at work (times)* **	n=6	n=6				
3 times or less	2 (28.6)	5 (71.4)	1.0		1.0	
More than 3 times	4 (80.0)	1 (20.0)	0.1 (0.006-1.6)	0.099	-	-
Mean, SD			0.6 (0.3-1.3)	0.201	-	-
Frequency of practicing physical activities	n=159	n=134				
No exercise	30 (50.8)	29 (49.2)	1.0		1.0	
At least once per week (any exercise)	129 (55.1)	105 (44.9)	0.8 (0.5-1.5)	0.556	0.5 (0.2-1.2)	0.115
Exercise per week (minutes)	n=117	n=93				
1-60 minutes	89 (57.1)	67 (42.9)	1.0		1.0	
61 minutes or more	28 (51.9)	26 (48.1)	1.2 (0.7-2.3)	0.508	1.1 (0.4-2.9)	0.907
Mean (SD)	41.7 (72.9)	48.8 (69.7)	1.0 (1.0-1.0)	0.292	1.0 (1.0-1.0)	0.773
Drinking coffee	n=156	n=130				
No, never	67 (55.8)	53 (44.2)	1.0		1.0	
Yes, current or before preg.	89 (53.6)	77 (46.4)	1.1 (0.7-1.8)	0.710	1.4 (0.7-2.9)	0.331
Coffee before getting pregnant	n=88	n=72				
Less than 4 cups/day	75 (56.4)	58 (43.6)	1.0		1.0	
4 cups/day or more	13 (48.1)	14 (51.9)	1.4 (0.6-3.1)	0.434	0.6 (0.2-2.2)	0.443
Coffee early in pregnancy	n=88	n=76				

No, I don’t	38 (55.9)	30 (44.1)	1.0		1.0	
Yes, I drink coffee early in preg.	50 (52.1)	46 (47.9)	1.2 (0.6-2.1)	0.631	1.3 (0.6-3.4)	0.546
Drinking tea	n=156	n=126				
No, never	30 (49.2)	31 (50.8)	1.0		1.0	
Yes, current or before preg.	126 (57.0)	95 (43.0)	0.7 (0.4-1.3)	0.277	1.0 (0.4-2.5)	0.954
Tea before getting pregnant	n=123	n=95				
Less than 4 cups/day	93 (55.0)	76 (45.0)	1.0		1.0	
4 cups/day or more	30 (61.2)	19 (38.8)	0.8 (0.4-1.5)	0.442	0.7 (0.3-1.8)	0.450
Tea early in pregnancy	n=127	n=96				
No, never	17 (58.6)	12 (41.4)	1.0		1.0	
Yes, I drink tea early in preg.	110 (56.7)	84 (43.3)	1.1 (0.5-2.4)	0.846	1.1 (0.3-4.3)	0.896
Drinking cola	n=155	n=130				
No, never	90 (50.6)	88 (49.4)	1.0		1.0	
Yes, current or before preg	65 (60.7)	42 (39.3)	0.7 (0.4-1.1)	0.095	0.7 (0.3-1.4)	0.281
Cola before getting pregnant	n=57	n=38				
Less than 4 cups/day	50 (59.5)	34 (40.5)	1.0		1.0	
4 cups/day or more	7 (63.6)	4 (36.4)	0.7 (0.2-3.1)	0.794	1.0 (0.1-8.0)	0.983
Cola early in pregnancy	n=60	n=39				
No, never	29 (65.9)	15 (34.1)	1.0		1.0	
Yes, I drink tea	31 (56.4)	24 (43.6)	1.5 (0.7-3.4)	0.335	1.8 (0.6-6.0)	0.326
Vegetables eaten	n=158	n=130				
Once every day or more times	109 (54.0)	93 (46.0)	1.0		1.0	
Most day or less than a week	49 (57.0)	37 (43.0)	0.9 (0.5-1.5)	0.638	0.8 (0.4-1.7)	0.562
Fruit eaten	n=158	n=132				
Once every day or more times	99 (52.1)	91 (47.9)	1.0		1.0	
Most day or less than a week	59 (59.0)	41 (41.0)	0.8 (0.5-1.2)	0.263	0.9 (0.4-1.9)	0.736

Drinking behaviour	n=157	n=129				
Never drink	21 (56.8)	16 (43.2)	1.0		1.0	
Drinking now or before pregnancy	136 (54.6)	113 (45.4)	1.1 (0.6-2.2)	0.807	1.2 (0.4-3.5)	0.742
Units per week early pregnancy	n=60	n=58				
2 units or less per week	52 (51.5)	49 (48.5)	1.0		1.0	
More than 2 units per week	8 (47.1)	9 (52.9)	1.2 (0.5-3.3)	0.736	1.0 (0.2-5.9)	0.999
Binge drinking	n=68	n=59				
No, never	54 (54.5)	45 (45.5)	1.0		1.0	
Yes, more than 5 drinks/day	14 (50.0)	14 (50.0)	1.2 (0.5-2.8)	0.670	0.9 (0.3-3.4)	0.866
Smoking behaviour	n=154	n=124				
Never smoke	79 (54.9)	65 (45.1)	1.0		1.0	
Smoking now or before pregnancy	75 (56.0)	59 (44.0)	1.0 (0.6-1.5)	0.853	0.8 (0.4-1.6)	0.477
Smoking behaviour	n=26	n=24				
4 or less cigarettes per day	6 (54.5)	5 (45.5)	1.0		1.0	
More than 4 cigarettes per day	20 (51.3)	19 (48.7)	1.2 (0.3-4.4)	0.848	0.7 (0.06-7.8)	0.770
Drug use	n=158	n=127				
Never took drug	156 (55.7)	124 (44.3)	1.0		1.0	
Drug use now or before pregnancy	2 (40.0)	3 (60.0)	1.9 (0.3-11.5)	0.490	-	-

* Only one case was underweight, so we excluded it from the analysis; ** Physical activity changed during most recent pregnancy: no participants reported to increase their levels of physical activity; *** Excluded from multivariate model as a highly imprecise odds ratio was reported. Model I: Univariate unadjusted model. Model II: Multivariate model adjusted for maternal age (continuous), presentation (dichotomous), previous miscarriage (dichotomous), nausea and vomiting (dichotomous), BMI (continuous).

Supplementary Table 4.2. Odds Ratios for miscarriage (<24 weeks): Partners' characteristics.

	Pregnancy *n* **(%)**	**Miscarriage** *n* **(%)**	**Model I** **OR (95% CI)**	**P-value**	**Model II** **OR (95% CI)**	**P-value**
Partners' age	n=150	n=125				
Less than 35 years old	87 (61.7)	54 (38.3)	1.0		1.0	
35 years old or older	63 (47.0)	71 (53.0)	1.8 (1.1-2.9)	0.015	1.9 (0.9-4.1)	0.119
Mean, SD	33.5 (6.0)	34.6 (5.8)	1.0 (1.0-1.1)	0.123	1.1 (1.0-1.1)	0.247
Partners' ethnicity	n=152	n=125				
White background (Irish/other)	141 (55.1)	115 (44.9)	1.0		1.0	
Other background	11 (52.4)	10 (47.6)	1.1 (0.5-2.7)	0.811	1.7 (0.4-7.5)	0.509
Partners employment	n=120	n=147				
Full-time paid job	105 (56.1)	82 (43.9)	1.0		1.0	
Part-time/unemployed/student	42 (52.5)	38 (47.5)	1.2 (0.7-2.0)	0.583	2.3 (1.0-5.2)	0.048
Partner drink behaviour	n=123	n=151				
No, never	23 (56.1)	18 (43.9)	1.0		1.0	
Yes, he drinks	128 (54.9)	105 (45.1)	2.1 (0.7-6.4)	0.202	1.2 (0.4-3.2)	0.726
Partners units per week	n=84	n=101				
2 units per week or less	21 (56.8)	16 (43.2)	1.0		1.0	
More than 2 units per week	80 (54.1)	68 (45.9	1.1 (0.6-2.3)	0.768	1.2 (0.4-3.1)	0.773
Partner binge drinking	n=93	n=114				
No	47 (53.4)	41 (46.6)	1.0		1.0	
Yes	67 (56.3)	52 (43.7)	0.9 (0.5-1.5)	0.679	1.5 (0.6-3.3)	0.392
Partners smoking	n=146	n=123				
No, never	96 (55.2)	78 (44.8)	1.0		1.0	
Yes, smokers (now or before pregnancy)	50 (52.6)	45 (47.4)	1.1 (0.7-1.8)	0.689	1.3 (0.6-2.8)	0.522

Partner smoking frequency	n=40	n=46				
Some days	10 (71.4)	4 (28.4)	1.0		1.0	
Everyday	36 (50.0)	36 (50.0)	0.4 (0.1-1.4)	0.150	0.2 (0.02-2.2)	0.206
Partner smoking behaviour	n=42	n=41				
Never smokes around me	26 (57.8)	19 (42.2)	1.0		1.0	
Occasionally/Usually smokes around me	15 (39.5)	23 (60.5)	2.1 (0.9-5.0)	0.099	2.5 (0.5-12.3)	0.261

Model I: Univariate unadjusted model. Model II: Multivariate model adjusted for maternal age (continuous), presentation (dichotomous), previous miscarriage (dichotomous), nausea and vomiting (dichotomous), BMI (continuous).

Supplementary Table 4.3. Odds Ratios for miscarriage (<24 weeks): traumatic and stressful life events.

Total	All *n*	Miscarriage *n* (%)	Pregnancy *n* (%)	Model I OR (95% CI)	Model II OR (95% CI)
Job generally demanding	280	67 (42.4)	91 (57.6)	0.8 (0.5-1.3)	0.5 (0.3-1.1)
Job insecurity	279	20 (46.5)	23 (53.3)	1.1 (0.6-2.0)	1.2 (0.4-3.1)
Husband lost job	280	29 (40.3)	43 (59.7)	0.8 (0.5-1.3)	0.9 (0.4-2.1)
Separation/divorce	279	7 (53.8)	6 (46.2)	1.4 (0.5-4.4)	1.6 (0.3-8.5)
Financial problems	280	22 (47.8)	24 (52.2)	1.2 (0.6-2.2)	1.2 (0.5-3.0)
Accident	280	11 (50.0)	11 (50.0)	1.2 (0.5-3.0)	1.1 (0.3-4.1)
Serious illness	280	9 (52.9)	8 (47.1)	1.4 (0.5-3.7)	1.3 (0.3-5.5)
Illness of someone close	280	32 (51.6)	30 (48.4)	1.4 (0.8-2.4)	1.2 (0.5-2.7)
Death of someone close	280	38 (45.8)	45 (54.2)	1.1 (0.6-1.8)	1.2 (0.6-2.7)
Death of a child	277	3 (50.0)	3 (50.0)	1.2 (0.2-6.3)	0.5 (0.07-3.4)
Stillbirth	276	6 (54.5)	5 (45.5)	1.5 (0.4-5.0)	0.6 (0.1-2.7)
Other stressful/trauma situations	276	20 (44.4)	25 (55.6)	1.0 (0.5-1.9)	0.8 (0.3-2.3)

Model I: Univariate unadjusted model. Model II: Multivariate model adjusted for maternal age (continuous), presentation (dichotomous), previous miscarriage (dichotomous), nausea and vomiting (dichotomous), BMI (continuous).

Chapter V

University students' awareness of causes and risk factors of miscarriage: a cross-sectional study.

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5.1 Abstract

Background: Spontaneous miscarriage is the most common complication of pregnancy, occurring in up to 20% of pregnancies. Despite the prevalence of miscarriage, little is known regarding peoples' awareness and understanding of causes of pregnancy loss. The aim of this study was to explore university students' understanding of rates, causes and risk factors of miscarriage. **Methods:** A cross-sectional study including university students. An online questionnaire was circulated to all students at the University College Cork using their university email accounts in April and May 2016. Main outcomes included identification of prevalence, weeks of gestation at which miscarriage occurs and causative risk factors for miscarriage. **Results:** A sample of 746 students were included in the analysis. Only 20% (n=149) of students correctly identified the prevalence of miscarriage, and almost 30% (n=207) incorrectly believed that miscarriage occurs in less than 10% of pregnancies. Female were more likely to correctly identify the rate of miscarriage compared to men (21.8% versus 14.5%). However, men tended to underestimate the rate and females overestimate it. Students who did not know someone who had a miscarriage underestimated the rate of miscarriage, and those who were aware of some celebrities who had a miscarriage overestimated the rate. Almost 43% (n=316) of students correctly identified fetal chromosomal abnormalities as the main cause of miscarriage. Females, older students, those from Medical and Health disciplines and those who were aware of a celebrity who had a miscarriage were more likely to identify chromosomal abnormalities as a main cause. However, more than 90% of the students believed that having a fall, consuming drugs or the medical condition of the mother was a causative risk factor for miscarriage. Finally, stress was identified as a risk factor more frequently than

advanced maternal age or smoking. **Conclusion:** Although almost half of the participants identified chromosomal abnormalities as the main cause of miscarriage, there is still a lack of understanding about the prevalence and most important risk factors among university students. University represents an ideal opportunity for health promotion strategies to increase awareness of potential adverse outcomes in pregnancy.

Key words: Miscarriage, University students, Awareness, Prevalence, Risk factors

5.2 Background

Miscarriage is one of the most common complications in pregnancy[246]. It is estimated that one out of four clinically recognised pregnancies will end in miscarriage during the first-trimester, and approximately 1% of pregnant women will experience a second-trimester miscarriage[4]. Despite the prevalence of miscarriage, 50% are attributed to chromosomal abnormalities[298], and a considerable percentage are classified as unexplained[9]. Therefore, identifying risk factors and effective interventions to prevent miscarriage has become a priority in the medical and scientific community[149]. Well-known risk factors include advanced maternal and paternal age, heavy smoking, alcohol consumption, infertility and previous miscarriage[151,161,164,167,299].

Preconception health care aims to identify and increase awareness to reduce risk factors before pregnancy that might affect the future maternal, child and family health[300-302]. An effort has been made to develop effective intervention plans and to include preconception risk factors in prenatal prevention programs

internationally[303-307]. One of the main recommendations is to promote effective preconception health care interventions to develop curricula of preconception risk factors at undergraduate and postgraduate level[304]. Insight into students' awareness of miscarriage might help to assess the effectiveness of preconception care education at a university level, but also to highlight the gaps of knowledge among this targeted population. Therefore, a cross-sectional study was conducted to explore university students' understanding of prevalence, causes and risk factors of miscarriage.

5.3 Methods

5.3.1 Study design and data source

A cross sectional study was carried at University College Cork (UCC). Cork is one of the three cities in the Republic of Ireland with the highest full-time enrolments in the academic year 2016/2017[308]. UCC currently has 20,000 full-time students of whom 14,000 are undergraduate[308]. It has over 3,000 international students from 100 countries around the world. There are over 120 degree and professional programmes in Medicine, Dentistry, Pharmacy, Nursing and the Clinical Therapies, along with the Humanities, Business, Law, Architecture, Science, Food and Nutritional Sciences, available at UCC. Students were asked to select their area of study at UCC from a list of six options. For the purpose of this study, this list was grouped into four categories in accordance with the organisation of the Colleges within the University (i.e. The College of Medicine and Health, The College of Arts and Social Science, The College of Engineering & Food Science and The College of Business and Commerce & Law)[309]. For example, the College of Medicine and

Health includes the Schools of Medicine, Dental School, Clinical Therapies, Nursing and & Midwifery, Pharmacy and Public Health.

An online questionnaire was circulated to all students at UCC using their university email accounts, in April and May 2016. The questionnaire was compiled using SurveyMonkey®, which is a user-friendly site to develop and administer online surveys. The questionnaire was anonymous and voluntary. An informed consent form explaining the objectives of the survey had to be completed before accessing the questionnaire. The main questionnaire consisted of twenty-six questions utilised to assess students' understanding of the topic of miscarriage. Topics included general demographic and educational characteristics (i.e. sex, age, marital status, discipline and level of study), general knowledge and risk factors for miscarriage (i.e. agree, disagree and unsure of both well-known and spurious risk factors), identification of previous experience of miscarriage among themselves or their partners, and awareness of family member, friends or a celebrity who had a miscarriage. Students were asked to select the most common causes of miscarriage from a list of six options including lifestyle of mother (i.e. smoking and alcohol), medical condition or medical problem with the mother; genetic problem with the baby; psychological problems during pregnancy (i.e. stress, depression) and incidents during pregnancy (i.e. fall, injury, accident). In addition, students were asked to provide rates of miscarriage in Ireland (i.e. "*In your opinion, what percentage of pregnancies in Ireland ends in a miscarriage? Please insert a number anywhere from 0 to 100 %")* and weeks of gestation at which miscarriage occurs ("*when can a miscarriage occur? Between week "x" to week "x" of a pregnancy*").

Definitions of miscarriage vary significantly between countries and jurisdictions[12]. For the purposes of this study, miscarriage is defined as the spontaneous demise of a pregnancy from the time of conception up to 24 completed weeks of gestation[15,16,310]. This study also reported the number of students who were only aware of first trimester miscarriage, which is defined as the loss of a pregnancy up to 12 weeks of gestation[15,16,310]. It is estimated that approximately one fifth of clinical pregnancies will end in a miscarriage in Ireland[16]. Therefore, a rate of 20% of miscarriage was selected as the cut-off rate in this study.

5.3.2 Statistical analysis

Descriptive analysis was carried out using mean and standard deviation (SD) for continuous variables and percentages for categorical variables. Age was categorised using tertiles (i.e. 33.3% of the students were 21 years old or younger and 66.7% were 23 years old or younger). Three categories were created to calculate the number of students who underestimated (i.e. below the correct answer), correctly estimated or overestimated (i.e. above the correct answer) the rate of miscarriage. Information regarding the university students' knowledge about contributory risk factors of miscarriage was assessed using a 5-point Likert scale ranging from strongly agree to strongly disagree. In the context of this study, answers were categorised as agree, unsure and disagree.

Chi-square tests were performed to assess the relationship between general demographic and educational characteristics, and knowing someone who had a miscarriage and identifying the correct rate of miscarriage. Chi-square tests were also calculated to investigate the relationship between independent variables and

awareness of the most common causes of miscarriage. Binary logistic regression was calculated to estimate the probability of selecting risk factors for miscarriage (i.e. agree versus disagree) and general demographic and educational characteristics, knowing or not someone who had a miscarriage (i.e. themselves, partners, family, friends or celebrities) and whether the rate of miscarriage was correct, underestimated or overestimated. A high number of university students were unsure of their answers, and therefore, we also explored the relationship between agree versus unsure in the identification of risk factors for miscarriage; however, only those results which showed statistically significant differences and which added extra information to the comparison were reported.

A total number of 25 possible causes of miscarriage were alphabetically ordered in the questionnaire. For the purpose of this study we only analysed the Odds Ratios for those risk factors with a strong association with miscarriage (i.e. age, chromosomal abnormalities, smoking, alcohol and medical condition of mother) and for some spurious risk factors for miscarriage (i.e. flu vaccine, flying, hair dye, verbal arguments and vitamin C). Unadjusted and adjusted odds ratios (OR and aOR respectively) were calculated for all independent variables with their corresponding 95% confidence intervals (CI). All the analyses were performed using SPSS 21.0 (IBM).

5.3.3 Ethical approval and consent to participate

This study received ethical approval from the Clinical Research Ethics Committee of the Cork Teaching Hospital on ECM 6 (rrrr) 12/04/16. Consent to participate was implied through completed surveys.

5.4 Results

Overall, 872 students responded to the online survey. Of those, 126 were excluded from the analysis because they did not complete more than half of the survey or they had highly extreme answers in demographic characteristic such as age. Therefore, a total sample of 746 university students were included in our analysis. The mean age was 24.3 years (SD=6.58), and most of students were between 21 and 22 years old (n=284; 38.1%) or were 23 years old or older (n=289; n=38.7%) ranging between 18 and 60 years old. More than half of the respondents were females (n=577; 77.3%), and approximately 80% were single (n=617). The discipline with the lowest response rate was Business and Commerce and Law (n=104; 13.9%) and with the highest response rate was Medicine and Health (n = 280; 31.9%).

Male students were more likely to report that they did not know anyone who had a miscarriage compared to female students (23.9% versus 9.6%; $p < 0.001$). Students aged 23 years old or older were more likely to report they knew someone who had a miscarriage; however, students of 20 years of age or younger were more likely to report they were aware of a celebrity who had had a miscarriage ($p < 0.05$). Single students were also more likely not to know anyone who had a miscarriage compared to those who had a partner, were married, were cohabiting or divorced (14.1% versus 5.8%; $p < 0.05$). Females were more likely to be aware of a celebrity who had a miscarriage than male students (16.9% versus 7.0%; Table 5.1). Students from Engineering and Food Science (n=34; 18.3%) or Business and Commerce and Law (n=14; 14.9%) disciplines were more likely to report that they did not know anyone with a miscarriage. Medicine and Health (n=159; 74%), and Arts and Social

Science (n=130; 72.6%) were more likely to know someone who had a miscarriage (Table 5.1).

Table 5.1. University students' characteristics by type of relationship with someone who had a miscarriage.

		Do not know anyone, n (%)	**Myself, partner, family or friend, n (%)**	**Celebrities, n (%)**	**p-value**
Total*	674	85 (12.6)	489 (72.6)	100 (14.8)	
Sex					
Female	532	51 (9.6)	391 (73.5)	90 (16.9)	<0.001
Male	142	34 (23.9)	98 (69.0)	10 (7.0)	
Age					
≤20	152	20 (13.2)	103 (67.8)	29 (19.1)	0.005
21-22	257	44 (17.1)	175 (68.1)	38 (14.8)	
≥23	265	21 (7.9)	211 (79.6)	33 (12.5)	
Marital status					
Single	554	78 (14.1)	394 (71.1)	82 (14.8)	0.045
Other (married, cohabiting…)	120	7 (5.8)	95 (79.2)	18 (15.0)	
Discipline					
Medicine and Health	215	21 (9.8)	159 (74.0)	35 (16.3)	0.023
Arts and Social Science	179	16 (8.9)	130 (72.6)	33 (18.4)	
Engineering & Food Science	186	34 (18.3)	135 (72.6)	17 (9.1)	
Business and Commerce & Law	94	14 (14.9)	65 (69.1)	15 (16.0)	
Level of study					
Undergraduate	535	76 (14.2)	378 (70.7)	81 (15.1)	0.035
Postgraduate	139	9 (6.5)	111 (79.9)	19 (13.7)	

* Missing data (n=72)

Only 20% (n=149) of students identified a mean rate of 20% for miscarriage. The remaining students underestimated or overestimated the rate of miscarriage (Table 5.2). Female students, older students and those who knew someone who had a miscarriage were more likely to identify the 20% rate of miscarriage. Students from Arts and Social Science (n=45, 22.5%) and Medicine and Health (n=52, 21.9) were

more likely to estimate the correct rate of miscarriage (Table 5.2). A total of 96 (12.9%) students correctly responded that miscarriage happens up to 12 weeks of gestation (early miscarriage) or up to 24 weeks of gestation (late miscarriage). Overall, only 54 (6.2%) students were aware that miscarriage can happen from conception until 24 weeks of gestation. A quarter of all students (n=179; 24%) thought miscarriage could happen at any stage of pregnancy.

Table 5.2. Grade of correct, underestimated and overestimated rate of miscarriage.

Rate	Underestimated, n (%)	Correct (20%), n (%)	Overestimated, n (%)	p-value
Total	295 (39.9)	149 (20.1)	296 (40.0)	
Sex				
Female	192 (33.4)	125 (21.8)	257 (44.8)	<0.001
Male	103 (62.0)	24 (14.5)	39 (23.5)	
Age				
≤20	66 (38.6)	32 (18.7)	73 (42.7)	0.803
21-22	118 (41.8)	54 (19.1)	110 (39.0)	
≥23	111 (38.7)	63 (22.0)	113 (39.4)	
Discipline				
Medicine and Health	92 (38.8)	52 (21.9)	93 (39.2)	0.207
Arts and Social Science	68 (34.0)	45 (22.5)	87 (43.5)	
Engineering & Food Science	95 (47.3)	33 (16.4)	73 (36.3)	
Business and Commerce & Law	40 (39.2)	19 (18.6)	43 (42.2)	
Known someone*				
Do not know anyone	50 (58.8)	9 (10.6)	26 (30.6)	<0.001
Myself, partner, family or friends	181 (37.2)	114 (23.4)	192 (39.4)	
Celebrities	29 (29.0)	16 (16.0)	55 (55.0)	

* Missing data (n=72)

The most common cause of miscarriage identified by the university students was chromosomal abnormalities in the baby, (n=316; 42.4%), followed by medical conditions (n=177; 23.7%) and lifestyles (n=109; 14.6%). Chromosomal abnormalities of the baby were identified as the most common cause of miscarriage in a higher percentage of female students, older students (i.e. 23 years old or older),

students who reported being married, divorced or cohabiting, students from Medicine and Health and for those students who knew a celebrity who had a miscarriage. Male students, younger and single students, students from Engineering and Food Science and Business and Commerce and Law, and students who reported that they did not know anyone who had a miscarriage were more likely to report lifestyles and the medical condition of the mother as the most common cause of miscarriage (Table 5.3).

Students who correctly estimated the rate of miscarriage were more likely to select chromosomal abnormalities as the main cause of miscarriage (n=72; 48.3% for correct rate of miscarriage, n=136; 45.9% for overestimated rate and n=107; 36.3% for underestimated rate; Table 5.3). Conversely, students who correctly identified the rate of miscarriage were less likely to select psychological problems as the main cause of miscarriage. Students who overestimated the rate of miscarriage were less likely to identify medical conditions of the mother as a cause of miscarriage, whereas those who underestimated were more likely to select it. Approximately 15% (underestimated rate n=42; correct rate n=22 and overestimated rate n=44) of students selected lifestyle behaviour as the main cause of miscarriage independently of the selected rate of miscarriage (Table 5.3).

Table 5.3. University Students' awareness of most common cause of miscarriage

	Total	**Lifestyle, n (%)**	**Medical condition of mother, n (%)**	**Chromosomal abnormalities, n (%)**	**Psychological problems during pregnancy, n (%)**	**Incident during pregnancy, n (%)**	**Other, n (%)**	**p-value**
Total	746	109 (14.6)	177 (23.7)	316 (42.4)	43 (5.8)	85 (11.4)	16 (2.1)	
Sex								
Female	577	78 (13.5)	127 (22.0)	251 (43.5)	34 (5.9)	73 (12.7)	14 (2.4)	0.060
Male	169	31 (18.3)	50 (29.6)	65 (38.5)	9 (5.3)	12 (7.1)	2 (1.2	
Age								
≤20	173	38 (22.0)	43 (24.9)	54 (31.2)	12 (6.9)	23 (13.3)	3 (1.7)	<0.001
21-22	284	48 (16.9)	75 (26.4)	96 (33.8)	25 (8.8)	37 (13.0)	3 (1.1)	
≥23	289	23 (8.0)	59 (20.4)	166 (57.4)	6 (2.1)	25 (8.7)	10 (3.5)	
Marital status								
Single	617	103 (16.7)	152 (24.6)	232 (37.6)	38 (6.2)	79 (12.8)	13 (2.1)	<0.001
Other (married, cohabiting…)	129	6 (4.7)	25 (19.4)	84 (65.1)	5 (3.9)	6 (4.7)	3 (2.3)	
Discipline								
Medicine and Health	238	29 (12.2)	33 (13.9)	143 (60.1)	10 (4.2)	20 (8.4)	3 (1.3)	<0.001
Arts and Social Science	201	26 (12.9)	50 (24.9)	84 (41.8)	9 (4.5)	28 (13.9)	4 (2.0)	
Engineering & Food Science	203	32 (15.8)	63 (31.0)	64 (31.5)	17 (8.4)	22 (10.8)	5 (2.5)	
Business and Commerce & Law	104	22 (21.2)	31 (29.8)	25 (24.0)	7 (6.7)	15 (14.4)	4 (3.8)	
Known someone								
Do not know anyone	85	15 (17.6)	30 (35.3)	27 (31.8)	4 (4.7)	9 (10.6)	0 (0.0)	0.056
Myself, partner, family or friends	489	69 (14.1)	105 (21.5)	214 (43.8)	30 (6.1)	61 (12.5)	10 (2.0)	
Celebrities	100	12 (12.0)	19 (19.0)	52 (52.0)	3 (3.0)	10 (10.0)	4 (4.0)	
Rate of miscarriage								
Underestimate rate	295	42 (14.2)	89 (30.2)	107 (36.3)	19 (6.4)	34 (11.5)	4 (1.4)	0.022
Correct rate	149	22 (14.8)	30 (20.1)	72 (48.3)	3 (2.0)	18 (12.1)	4 (2.7)	
Over-estimate rate	296	44 (14.9)	54 (18.2)	136 (45.9)	21 (7.1)	33 (11.1)	8 (2.7)	

The most reported risk factors for miscarriage were accident or fall, drugs, medical condition of the mother, alcohol, stress, age, smoking and being underweight. Most students disagreed that sexual intercourse, hair dye, vitamin C and exercise were risk factors for miscarriage (Figure 5.1).

Overall, the majority of college students correctly selected age (n=566; 88%) and medical conditions of the mother (n=682; 98%) as contributory risk factors for miscarriage. No statistically significant differences between agree or disagree responses for age or for medical conditions of mother were found between groups (Supplementary Table 5.1). However, students from Arts and Social Science were more likely to be unsure about age as a risk factor (aOR 2.78; 95% CI 1.52-5.09). Students of 21 years of age or older were more likely to identify chromosomal abnormalities as a causative factor for miscarriage than those aged 20 years old or younger (students aged 21-22: aOR 0.27; 95% CI 0.12-0.61 and students aged 23 years old or older: aOR 0.48; 95% CI 0.24-0.96; Supplementary Table 5.1). Students from Arts and Social Science or Business and Commerce and Law more frequently did not identify chromosomal abnormalities as a potential causative factor compared to college students from Medical and Health (aOR 2.40; 95% CI 1.01-5.73 and aOR 3.0; 95% CI 1.16-7.73 respectively; Supplementary Table 5.1).

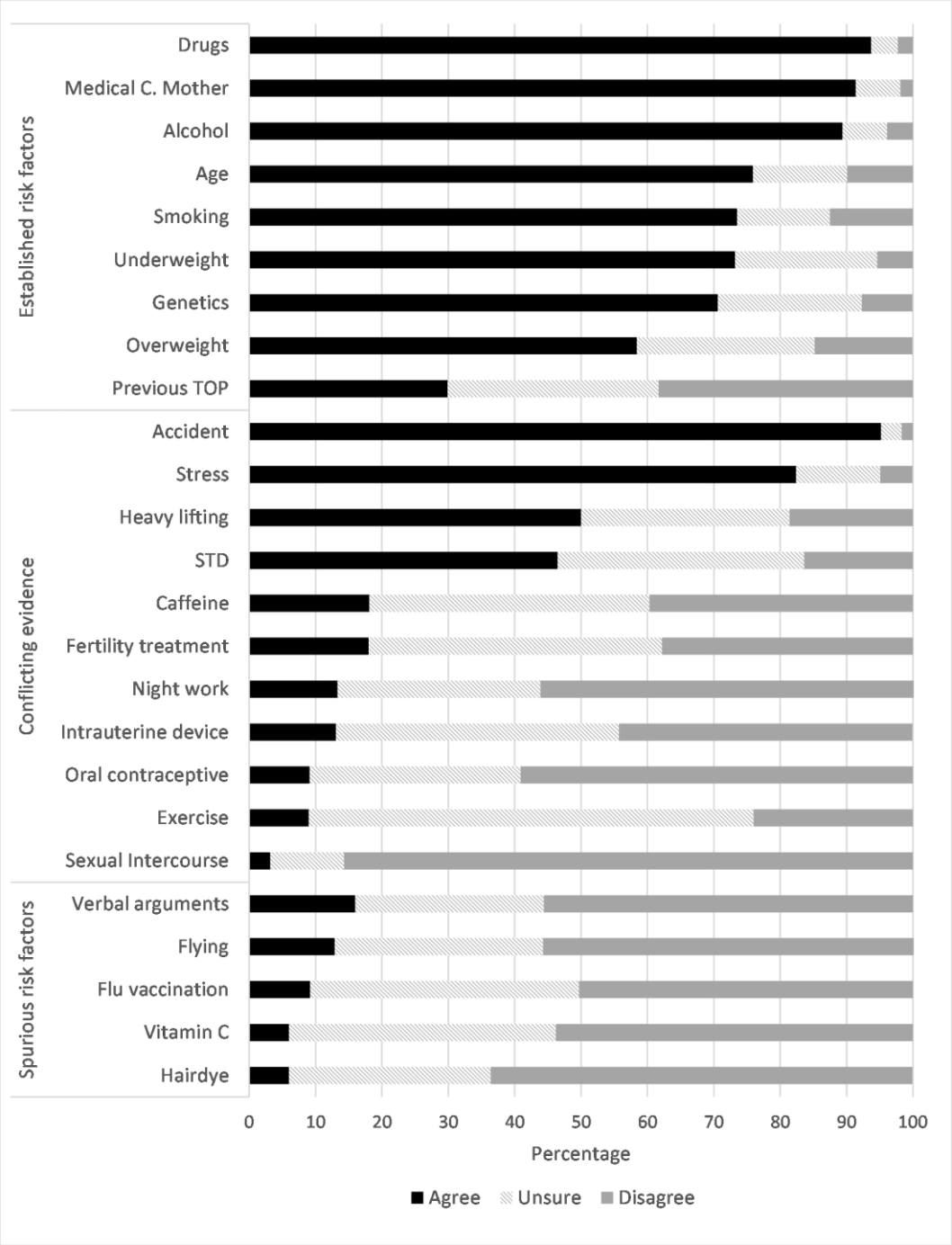


Figure 5.1. Percentage of most selected risk factors for miscarriage.

Note: Medical condition of mother (Medical C. Mother); Termination of pregnancy (TOP); Sexual transmitted disease (STD)

Male students were more likely to agree that smoking was a risk factor for miscarriage compared to female students (aOR 0.47; 95% CI 0.24-0.94). Older students (i.e. 23 years old or older) disagreed more frequently that smoking was a

risk factor for miscarriage compared to students who were 20 years old or younger (aOR 2.09; 95% CI 1.08-4.07). Compared to students from Medicine and Health, the remaining disciplines disagreed more frequently that smoking was a risk factor. For alcohol, older students and those from Business and Commerce and Law were more likely to disagree that it was a risk factor for miscarriage (Supplementary Table 5.1).

Students from Arts and Social Science were more likely to identify flu vaccination as a risk factor for miscarriage (n=25; 26.9%; Supplementary Table 5.2). Students from Engineering and Food Science and Business and Commerce and Law were more likely to identify verbal arguments as a risk factor for miscarriage (aOR 0.56; 95% CI 0.31-0.99 and aOR 0.42; 95% CI 0.21-0.82). Students between 21 and 22 years old were more likely to be unsure that vitamin C was a risk factor for miscarriage compared to younger students (aOR 2.85; 95% CI 1.21-6.72). Only students who were 23 years old or older were more likely to identify vitamin C as a spurious risk factor compared to students who were 20 years old or younger (aOR 2.34; 95% CI 1.03-5.34; Supplementary Table 5.2).

Among the remaining potential causative risk factors for miscarriage, male students were less likely to identify working night shifts and previous termination of pregnancy (TOP) as risk factors (aOR 0.45; 95% CI 0.25-0.80and aOR 0.44; 95% CI 0.26-0.72). Older students (i.e. 23 years old or older) were less likely to identify caffeine as a risk factor (aOR 2.61; 95% CI 1.45-4.70). Compared to students from the college of Medicine and Health, those from Business and Commerce and Law were less likely to identify sexually transmitted disease, previous TOP and being

underweight as contributory risk factors for miscarriage (aOR 3.39; 95% CI 1.77-6.51 and aOR 2.20; 95% CI 1.13-4.25 and aOR 2.79; 95% CI 1.10-7.03). Students from Engineering and Food Science were less likely to identify night work as a risk factor, but were more likely to consider stress as a contributory risk factor for miscarriage compared to Medicine and Health students (aOR 2.06; 95% CI 1.08-3.93 and aOR 0.36; 95% CI 0.13-0.98). The odds of not identifying oral contraceptive as a cause of miscarriage were lower for students who overestimated the rate of miscarriage compared to those who correctly identified the rate (OR: 0.30; 95% CI 0.12-0.75). Finally, only students from Arts and Social Science were more likely to identify heavy lifting as a risk factor.

5.5 Discussion

5.5.1 Main findings

This cross-sectional study provides insight into university students' awareness of prevalence and risk factors of miscarriage. The findings of this study illustrate that common misunderstandings still prevail regarding the etiology of miscarriage, suggesting a deficiency in formal information and access to information related to reproductive health. For example, only 20% of the students correctly identified the prevalence of miscarriage at 20%, and almost 30% incorrectly believed the prevalence of miscarriage is less common than 10%. Female students were more likely to identify the correct rate, but also to overestimate it, and male students tended to underestimate it. Almost one-quarter of the students believed miscarriage can happen from conception until birth, and 87% of the students erroneously selected the weeks of gestation at which miscarriage occurs. Females students, older

students, those from Medicine and Health, those who were aware of a celebrity who had a miscarriage, and those who identified the correct rate of miscarriage were more likely to identify chromosomal abnormalities as the most common cause of miscarriage. However, this was only identified by 43% of the total sample.

5.5.2 Strengths and limitations

The nature of the study design implies that data were collected at one point in time. Previous studies have found an association between ethnicity and religion and the perception of risk factors for miscarriage[239], however we did not include this information in our survey and no comparison can be made. One of the main limitations is that a higher percentage of female students responded to the survey compared to male students. Although similar gender distributions were reported at UCC in the academic year 2006/2007 (36% male and 64% females)[311], recent overall data shows a more equal gender distribution for third-level graduates in the Republic of Ireland in 2016, with 52.2% of the students being female[312]. This percentage is similar to the European Union (EU-28) in 2015[313]. Nevertheless, our sample seems to be representative of the overall distribution of male and females by discipline. In 2016, women represented more than three out of four (76.4%) graduates in Health compared to more than four out of five (82.4%) graduates in Engineering were male[312] in the Republic of Ireland.

No standardised instrument of relevance was found in the literature for the purpose of this study; and therefore our survey was not validated. A multidisciplinary team specialised in pregnancy loss developed and reviewed all questions. In addition, a patient advocate for women who experience pregnancy loss also reviewed the

questionnaire to ensure clarity. To our knowledge, this is one of the largest studies exploring the knowledge of rates and risk factors for miscarriage among college students from multiple disciplines, representing the main strength of this study.

5.5.3 Comparison with other studies

Our study is in keeping with the results of two previous studies[239,240]. In a cross-sectional study including 1084 adults located in 49 states within the United States, Bardos et al. (2015) found that half of the participants believed that miscarriage was uncommon, occurring in 5% or less of all pregnancies. Similar to our results, it also found that approximately one fifth of the respondents incorrectly believed that lifestyle behaviours such as consumption of drugs, alcohol or tobacco were the only cause of miscarriage. In addition, men were more likely to identify lifestyle behaviours as a contributing risk factor for miscarriage. Also, participants with a higher educational degree identified chromosomal abnormalities more frequently as a cause of miscarriage compared to less educated respondents[239]. It is important to note that approximately 80% of these participants attended some college or medical school. Interestingly, in our study, male students were also more likely to identify smoking as a contributing risk factor. In another study, Delgado et at assessed awareness among undergraduate students related to preconception health and pregnancy. Results showed a low to moderate level of knowledge of miscarriage, with women having a slightly higher knowledge than men[240].

Assessing the reasons behind overestimating or underestimating the risk of miscarriage is difficult to understand[314]. It could be possible that students who overestimate the risk of miscarriage were under unnecessary stress or anxiety at the

time of this study. Some studies have shown a link between psychological distress and anticipatory representations of possible future threats or overestimating the risk of a disease[315,316]. No studies have evaluated college students' psychological and lifestyles factors and perception of risk of pregnancy loss; therefore, more research needs to be done to assess which are the underlying factors that might impact on a population's perception of risk of pregnancy loss.

5.5.4 Implications

Despite the high occurrence of miscarriage, some studies highlight the potential barriers that might influence the lack of awareness of this topic among the general public. For example, the existence of guilt, shame or feeling responsible for the pregnancy loss might have reinforced the reclusion of the topic exclusively to the close family or friends, or in some cases, only among the couple who experience miscarriage[207,317]. This has led to miscarriage being a "taboo" or "unspoken" topic in some cultures, increasing the chance of the causes of miscarriage being surrounded by myths and folklore[239,318]. The potential benefits of promoting healthy behaviours, lifestyle, mental and social factors during women and men's reproductive years has been increasingly accepted in the medical and scientific community[302,319].In this context, preconception health care offers a unique opportunity to increase personal responsibility and awareness of risk factors and adverse pregnancy outcomes during the reproductive years of this targeted population[305].

Universities are underused settings for improving preconception health among the community. They provide an opportunity to reach a population with a diverse

socioeconomic and gender background. In a scoping review of 29 preconception health care interventions that were evaluated, six of them were delivered at a School, college or university settings[306]. All of them reported an improvement in preconception health knowledge[240,320-323]; however, most of the interventions were provided to women who were identified as being at-risk of developing adverse maternal outcomes, and men were not generally included in the interventions[320]. Although the Republic of Ireland has one of the highest birth rates in Europe[324], to our knowledge, there are no preconception healthcare intervention programmes or clinical practice guidelines focused on improved preconception healthcare in higher education settings.

5.6 Conclusion

According to our results and the little evidence available, misunderstanding of causes and risk factors for miscarriage is a public health issue. The findings of this study highlight an opportunity for public health interventions to improve reproductive health education. Universally preconception healthcare programmes successfully provide health promotion strategies to increase awareness of potential adverse outcomes in pregnancy. In particular, University settings are an ideal opportunity to reach a targeted population.

5.7 Implications for practice, policy and research

Implications for practice

- University represents an ideal opportunity for health promotion strategies to increase awareness of potential adverse outcomes in pregnancy

Implications for policy

- There is a need to promote and initiate education programmes that include reproductive health education about miscarriage in the community in order to increase the knowledge of risk factors and features of miscarriage among the population

Implications for research

- Future research should involve students advocates (e.g. students union) in order to assess reproductive health programmes at high schools or at Universities
- Future development of questionnaires which assess the knowledge of risk factors for miscarriage should include students advocates

5.8. Supplementary Tables

Supplementary Table 5.1. Odds Ratios of agreement with strong risk factors for miscarriage.

Age	**Agree n (%)**	**Disagree n (%)**	**OR (95% CI)**	**p-value**	**aOR (95% CI)**	**p-value**
Total	566 (88.4)	74 (11.6)				
Sex						
Female	435 (88.4)	57 (11.6)	1	(ref.)	1	(ref.)
Male	131 (88.5)	17 (11.5)	0.99 (0.56-1.8)	0.97	0.84 (0.42-1.71)	0.84
Age						
≤20	131 (87.3)	19 (12.7)	1	(ref.)	1	(ref.)
21-22	211 (89.4)	25 (10.6)	0.82 (0.43-1.54)	0.53	1.14 (0.55-2.34)	0.73
≥23	224 (88.2)	30 (11.8)	0.92 (0.50-1.71)	0.80	1.34 (0.65-2.74)	0.42
Discipline						
Medicine and Health	190 (88.0)	26 (12.0)	1	(ref.)	1	(ref.)
Arts and Social Science	140 (88.1)	19 (11.9)	0.99 (0.53-1.86)	0.98	1.10 (0.56-2.16)	0.77
Engineering & Food Science	165 (93.2)	12 (6.8)	0.53 (0.26-1.09)	0.08	0.46 (0.21-1.10)	0.07
Business and Commerce & Law	71 (80.7)	17 (19.3)	1.75 (0.90-3.42)	0.10	1.96 (0.95-4.03)	0.07
Known someone	515 (88.6)	66 (11.4)				
Do not know anyone	68 (88.3)	9 (11.7)	1	(ref.)	1	(ref.)
Myself, partner, family or friends	378 (90.4)	40 (9.6)	0.80 (0.37-1.72)	0.57	0.74 (0.33-1.65)	0.46
Celebrities	69 (80.2)	17 (19.8)	1.86 (0.78-4.47)	0.16	1.60 (0.63-4.03)	0.32
Rate of miscarriage						
Correct rate	118 (92.9)	9 (7.1)	1	(ref.)	1	(ref.)
Over-estimate fertility	221 (86.3)	35 (13.7)	2.08 (0.97-4.47)	0.06	1.98 (0.90-4.34)	0.09
Underestimate miscarriage	224 (88.5)	29 (11.5)	1.70 (0.78-3.70)	0.18	1.65 (0.72-3.78)	0.23
Chromosomal abnormalities	**Agree n (%)**	**Disagree n (%)**	**OR (95% CI)**	**p-value**	**aOR (95% CI)**	**p-value**
Total	527 (90.2)	57 (9.8)				

Sex						
Female	404 (90.4)	43 (9.6)	1	(ref.)	1	(ref.)
Male	123 (89.8)	14 (10.2)	1.07 (0.57-2.02)	0.84	1.20 (0.55-2.61)	0.65
Age						
≤20	110 (81.5)	25 (18.5)	1	(ref.)	1	(ref.)
21-22	202 (94.8)	11 (5.2)	**0.24 (0.11-0.51)**	**0.00**	**0.27 (0.12-0.61)**	**0.00**
≥23	215 (91.1)	21 (8.9)	**0.43 (0.23-0.80)**	**0.01**	**0.48 (0.24-0.96)**	**0.04**
Discipline						
Medicine and Health	187 (94.9)	10 (5.1)	1	(ref.)	1	(ref.)
Arts and Social Science	126 (86.3)	20 (13.7)	**2.97 (1.34-6.55)**	**0.01**	**2.40 (1.01-5.73)**	**0.05**
Engineering & Food Science	144 (91.1)	14 (8.9)	1.82 (0.79-4.21)	0.16	1.53 (0.61-3.87)	0.37
Business and Commerce & Law	70 (84.3)	13 (15.7)	**3.47 (1.46-8.28)**	**0.01**	**3.0 (1.16-7.73)**	**0.02**
Known someone	474 (90.6)	49 (9.4)				
Do not know anyone	56 (88.9)	7 (11.1)	1	(ref.)	1	(ref.)
Myself, partner, family or friends	346 (91.1)	34 (8.9)	0.80 (0.33-1.86)	0.58	0.67 (0.27-1.71)	0.40
Celebrities	72 (90.0)	8 (10.0)	0.90 (030-2.60)	0.83	0.70 (0.21-2.37)	0.60
Rate of miscarriage						
Correct rate	105 (89.7)	12 (10.3)	1	(ref.)	1	(ref.)
Over-estimate fertility	212 (90.6)	22 (9.4)	0.91 (0.43-1.91)	0.80	0.89 (0.40-1.97)	0.77
Underestimate miscarriage	207 (90.4)	22 (9.6)	0.93 (0.44-1.95)	0.85	0.76 (0.33-1.79)	0.53
Smoking	**Agree n (%)**	**Disagree n (%)**	**OR (95% CI)**	**p-value**	**aOR (95% CI)**	**p-value**
Total	548 (85.5)	93 (14.5)				
Sex						
Female	410 (83.8)	79 (16.2)	1	(ref.)	1	(ref.)
Male	138 (90.8)	14 (9.2)	**0.53 (0.29-0.96)**	**0.04**	**0.47 (0.24-0.94)**	**0.03**
Age						
≤20	131 (87.9)	18 (12.1)	1	(ref.)	1	(ref.)
21-22	211 (85.8)	35 (14.2)	1.21 (0.66-2.22)	0.54	1.66 (0.86-3.22)	0.13
≥23	206 (83.7)	40 (16.3)	1.41 (0.78-2.57)	0.26	**2.09 (1.08-4.07)**	**0.03**
Discipline						

Medicine and Health	197 (92.9)	15 (7.1)	1	(ref.)	1	(ref.)
Arts and Social Science	139 (79.9)	35 (20.1)	**3.31 (1.74-6.29)**	**0.00**	**3.53 (1.79-6.97)**	**0.00**
Engineering & Food Science	137 (81.5)	31 (18.5)	**2.97 (1.55-5.72)**	**0.00**	**3.46 (1.72-6.94)**	**0.00**
Business and Commerce & Law	75 (86.2)	12 (13.8)	2.10 (0.94-4.70)	0.07	**2.44 (1.04-5.74)**	**0.04**
Known someone	491 (85.1)	86 (14.9)				
Do not know anyone	63 (87.5)	9 (12.5)	1	(ref.)	1	(ref.)
Myself, partner, family or friends	355 (84.7)	64 (15.3)	1.26 (0.60-2.67)	0.54	1.15 (0.53-2.51)	0.73
Celebrities	73 (84.9)	13 (15.1)	1.25 (0.50-3.11)	0.64	1.16 (0.44-3.03)	0.77
Rate of miscarriage						
Correct rate	104 (85.2)	18 (14.8)	1	(ref.)	1	(ref.)
Over-estimate fertility	219 (94.9)	39 (15.1)	1.03 (0.56-1.89)	0.93	1.03 (0.54-1.96)	0.93
Underestimate miscarriage	220 (85.9)	36 (14.1)	0.95 (0.51-1.74)	0.86	1.05 (0.54-2.06)	0.88

Alcohol	**Agree n (%)**	**Disagree n (%)**	**OR (95% CI)**	**p-value**	**aOR (95% CI)**	**p-value**
Total	667 (95.8)	29 (4.2)				
Sex						
Female	510 (95.3)	25 (4.7)	1	(ref.)	1	(ref.)
Male	157 (97.5)	4 (2.5)	0.52 (0.18-1.52)	0.23	0.54 (0.17-1.68)	0.29
Age						
≤20	161 (98.2)	3 (1.8)	1	(ref.)	1	(ref.)
21-22	259 (96.6)	9 (3.4)	1.87 (0.50-7.00)	0.36	1.39 (0.35-5.56)	0.64
≥23	247 (93.6)	17 (6.4)	**3.70 (1.07-12.81)**	**0.04**	**3.74 (1.03-13.64)**	**0.05**
Discipline						
Medicine and Health	216 (95.6)	10 (4.4)	1	(ref.)	1	(ref.)
Arts and Social Science	183 (96.3)	7 (3.7)	0.83 (0.31-2.21)	0.70	0.89 (0.28-2.84)	0.85
Engineering & Food Science	185 (97.4)	5 (2.6)	0.58 (0.20-1.74)	0.33	0.95 (0.30-3.06)	0.93
Business and Commerce & Law	83 (92.2)	7 (7.8)	1.82 (0.67-4.94)	0.24	**3.02 (1.01-9.01)**	**0.05**
Known someone	603 96.0)	25 (4.0)				
Do not know anyone	75 (93.8)	5 (6.3)	1	(ref.)	1	(ref.)
Myself, partner, family or friends	442 (96.5)	16 (3.5)	0.54 (0.19-1.53)	0.25	0.43 (0.15-1.29)	0.13
Celebrities	86 (95.6)	4 (4.4)	0.70 (0.18-2.69)	0.60	0.55 (0.13-2.27)	0.40

Rate of miscarriage						
Correct rate	136 (95.1)	7 (4.9)	1	(ref.)	1	(ref.)
Over-estimate fertility	261 (96.0)	11 (4.0)	0.82 (0.31-2.16)	0.69	0.69 (0.24-1.95)	0.48
Underestimate miscarriage	265 (96.0)	11 (4.0)	0.81 (0.31-2.13)	0.66	0.75 (0.26-2.16)	0.60
Medical condition of mother	**Agree n (%)**	**Disagree n (%)**	**OR (95% CI)**	**p-value**	**aOR (95% CI)**	**p-value**
Total	682 (98.0)	14 (2.0)				
Sex						
Female	529 (98.1)	10 (1.9)	1	(ref.)	1	(ref.)
Male	153 (97.5)	4 (2.5)	1.38 (0.43-4.47)	0.59	0.66 (0.16-2.72)	0.57
Age						
≤20	152 (97.4)	4 (2.6)	1	(ref.)	1	(ref.)
21-22	265 (99.3)	2 (0.7)	0.29 (0.05-1.58)	0.15	0.29 (0.05-1.66)	0.17
≥23	265)97.1)	8 (2.9)	1.15 (0.34-3.87)	0.83	1.27 (0.34-4.73)	0.72
Discipline						
Medicine and Health	225 (98.7)	3 (1.3)	1	(ref.)	1	(ref.)
Arts and Social Science	179 (97.3)	5 (2.7)	2.10 (0.49-8.89)	0.32	1.74 (0.37-8.14)	0.49
Engineering & Food Science	185 (97.9)	4 (2.1)	1.62 (0.36-7.34)	0.53	1.76 (0.35-8.81)	0.49
Business and Commerce & Law	93 (97.9)	2 (2.1)	1.61 (0.27-9.81)	0.60	1.79 (0.28-11.62)	0.54
Known someone	618 (97.9)	13 (2.1)				
Do not know anyone	78 (96.3)	3 (3.7)	1	(ref.)	1	(ref.)
Myself, partner, family or friends	448 (98.5)	7 (1.5)	0.41 (0.10-1.61)	0.20	0.42 (0.10-1.82)	0.25
Celebrities	92 (96.8)	3 (3.2)	0.85 (1.67-4.32)	0.84	1.04 (0.18-6.05)	0.69
Rate of miscarriage						
Correct rate	139 (98.6)	2 (1.4)	1	(ref.)	1	(ref.)
Over-estimate fertility	272 (99.3)	2 (0.7)	0.51 (0.07-3.67)	0.50	0.45 (0.06-3.27)	0.43
Underestimate miscarriage	268 (96.4)	10 (3.6)	2.59 (0.56-12.0)	0.22	2.36 (0.48-11.62)	0.29

3

Supplementary Table 5.2. Odds Ratios of disagreement with spurious risk factors for miscarriage.

Flu vaccine	**Agree n (%)**	**Disagree n (%)**	**OR (95% CI)**	**p-value**	**aOR (95% CI)**	**p-value**
Total	69 (15.5)	375 (85.4)				
Sex						
Female	57 (17.0)	278 (83.0)	1	(ref.)	1	(ref.)
Male	12 (11.0)	97 (89.0)	1.66 (0.85-3.22)	0.14	**2.41 (1.00 -5.78)**	**0.05**
Age						
≤20	17 (17.7)	79 (82.3)	1	(ref.)	1	(ref.)
21-22	29 (18.0)	132 (82.0)	0.98 (0.51-1.90)	0.95	0.75 (0.35-1.59)	0.45
≥23	23 (12.3)	164 (87.7)	1.53 (0.78-3.04)	0.22	1.03 (0.48-2.24)	0.93
Discipline						
Medicine and Health	17 (9.9)	155 (90.1)	1	(ref.)	1	(ref.)
Arts and Social Science	25 (26.9)	68 (73.1)	**0.30 (0.15-0.59)**	**0.00**	**0.31 (0.15-0.64)**	**0.00**
Engineering & Food Science	14 (11.8)	105 (88.2)	0.82 (0.34-1.74)	0.61	0.79 (0.36-1.75)	0.56
Business and Commerce & Law	13 (21.7)	47 (78.3)	**0.40 (0.18-0.88)**	**0.02**	0.49 (0.20-1.22)	0.13
Known someone	60 (14.7)	347 (85.3)				
Do not know anyone	4 (7.3)	51 (92.7)	1	(ref.)	1	(ref.)
Myself, partner, family or friends	46 (15.7)	247 (84.3)	0.42 (0.15-1.22)	0.11	0.41 (0.14-1.22)	0.11
Celebrities	10 (16.9)	49 (83.1)	0.38 (0.11-1.31)	0.13	0.46 (0.13-1.62)	0.23
Rate of miscarriage						
Correct rate	13 (13.1)	86 (86.9)	1	(ref.)	1	(ref.)
Over-estimate fertility	26 (15.8)	139 (84.2)	0.81 (0.39-1.66)	0.56	0.79 (0.37-1.70)	0.55
Underestimate miscarriage	28 (15.8)	149 (84.2)	0.80 (0.40-1.64)	0.55	0.61 (0.28-1.35)	0.22
Flying	**Agree n (%)**	**Disagree n (%)**	**OR (95% CI)**	**p-value**	**aOR (95% CI)**	**p-value**
Total	96 (18.8)	416 (81.3)				
Sex						
Female	80 (20.5)	310 (76.5)	1	(ref.)	1	(ref.)
Male	16 (13.1)	106 (86.9)	1.71 (0.96-3.05)	0.07	1.65 (0.83-3.26)	0.15
Age						

≤20	22 (20.0)	88 (80.0)	1	(ref.)	1	(ref.)
21-22	36 (18.7)	157 (81.3)	1.10 (0.60-1.97)	0.77	1.10 (0.58-2.09)	0.77
≥23	38 (18.2)	171 (81.8)	1.13 (0.63-2.02)	0.69	1.13 (0.59-2.18)	0.71
Discipline						
Medicine and Health	33 (18.6)	144 (81.4)	1	(ref.)	1	(ref.)
Arts and Social Science	26 (20.3)	102 (79.7)	0.90 (0.51-1.60)	0.72	0.94 (0.51-1.73)	0.84
Engineering & Food Science	21 (15.3)	116 (84.7)	1.27 (0.70-2.31)	0.44	1.28 (0.66-2.46)	0.46
Business and Commerce & Law	16 (22.9)	54 (77.1)	0.77 (0.39-1.52)	0.46	0.96 (0.45-2.06)	0.92
Known someone	83 (17.8)	383 (82.2)				
Do not know anyone	7 (10.9)	57 (89.1)	1	(ref.)	1	(ref.)
Myself, partner, family or friends	62 (18.6)	272 (81.4)	0.54 (0.23-1.24)	0.15	0.62 (0.26-1.45)	0.27
Celebrities	14 (20.6)	54 (79.4)	0.47 (0.18-1.26)	0.14	0.60 (0.22-1.64)	0.32
Rate of miscarriage						
Correct rate	20 (20.6)	77 (79.4)	1	(ref.)	1	(ref.)
Over-estimate fertility	40 (20.2)	158 (79.8)	1.03 (0.56-1.87)	0.93	1.03 (0.54-1.94)	0.94
Underestimate miscarriage	35 (16.4)	179 (83.6)	1.33 (0.72-2.45)	0.36	1.20 (0.62-2.33)	0.60
Hair dye	**Agree n (%)**	**Disagree n (%)**	**OR (95% CI)**	**p-value**	**aOR (95% CI)**	**p-value**
Total	45 (8.7)	474 (91.3)				
Sex						
Female	38 (9.5)	363 (90.5)	1	(ref.)	1	(ref.)
Male	7 (5.9)	111 (94.1)	1.67 (0.72-3.82)	0.23	1.87 (0.61-5.76)	0.27
Age						
≤20	10 (8.4)	109 (91.6)	1	(ref.)	1	(ref.)
21-22	23 (11.6)	175 (88.4)	0.70 (0.32-1.52)	0.37	0.80 (0.34-1.90)	0.62
≥23	12 (5.9)	190 (94.1)	1.45 (0.61-3.47)	0.40	2.18 (0.79-6.04)	0.14
Discipline						
Medicine and Health	14 (8.2)	156 (91.8)	1	(ref.)	1	(ref.)
Arts and Social Science	17 (12.3)	121 (87.7)	0.64 (0.30-1.35)	0.24	0.85 (0.35-2.02)	0.70
Engineering & Food Science	8 (5.8)	131 (94.2)	1.47 (0.60-3.61)	0.40	1.77 (0.65-4.78)	0.26
Business and Commerce & Law	6 (8.3)	66 (91.7)	0.99 (0.36-2.68)	0.98	1.51 (0.45-5.07)	0.51
Known someone	35 (7.4)	441 (92.6)				

Do not know anyone	5 (7.1)	65 (92.9)	1	(ref.)	1	(ref.)
Myself, partner, family or friends	29 (8.7)	306 (91.3)	0.81 (0.30-2.18)	0.68	0.90 (0.32-2.54)	0.83
Celebrities	1 (1.4)	70 (98.6)	5.39 (0.61-47.32)	0.13	7.32 (0.80-66.86)	0.08
Rate of miscarriage						
Correct rate	7 (6.4)	102 (93.6)	1	(ref.)	1	(ref.)
Over-estimate fertility	24 (11.7)	181 (88.3)	0.52 (0.22-1.24)	0.14	0.68 (0.27-1.73)	0.42
Underestimate miscarriage	14 (6.9)	189 (93.1)	0.93 (0.36-2.37)	0.87	0.97 (0.35-2.69)	0.95
Verbal arguments	**Agree n (%)**	**Disagree n (%)**	**OR (95% CI)**	**p-value**	**aOR (95% CI)**	**p-value**
Total	119 (22.3)	415 (77.7)				
Sex						
Female	95 (22.6)	325 (77.4)	1	(ref.)	1	(ref.)
Male	24 (21.1)	90 (78.9)	1.10 (0.66-1.82)	0.72	0.96 (0.54-1.72)	0.90
Age						
≤20	26 (22.2)	91 (77.8)	1	(ref.)	1	(ref.)
21-22	54 (26.9)	147 (73.1)	0.78 (0.46-1.33)	0.36	0.65 (0.36-1.19)	0.17
≥23	39 (18.1)	177 (81.9)	1.30 (0.74-2.26)	0.36	1.03 (0.55-1.94)	0.93
Discipline						
Medicine and Health	30 (16.3)	154 (83.7)	1	(ref.)	1	(ref.)
Arts and Social Science	28 (21.5)	102 (78.5)	0.71 (0.40-1.26)	0.24	0.85 (0.45-1.60)	0.61
Engineering & Food Science	38 (25.9)	109 (74.1)	**0.56 (0.33-0.96)**	**0.03**	**0.56 (0.31-0.99)**	**0.05**
Business and Commerce & Law	23 (31.5)	50 (68.5)	**0.42 (0.23-0.80)**	**0.01**	**0.42 (0.21-0.82)**	**0.01**
Known someone	105 (21.6)	382 (78.4)				
Do not know anyone	11 (19.0)	47 (81.0)	1	(ref.)	1	(ref.)
Myself, partner, family or friends	75 (20.9)	284 (79.1)	0.89 (0.44-1.79)	0.74	0.69 (0.33-1.46)	0.33
Celebrities	19 (27.1)	51 (72.9)	0.63 (0.27-1.46)	0.28	0.51 (0.21-1.24)	0.14
Rate of miscarriage						
Correct rate	17 (16.8)	84 (83.2)	1	(ref.)	1	(ref.)
Over-estimate fertility	54 (24.4)	167 (75.6)	0.63 (0.34-1.15)	0.13	0.71 (0.37-1.34)	0.29
Underestimate miscarriage	48 (22.7)	163 (77.3)	0.69 (0.37-1.27)	0.23	0.75 (0.39-1.45)	0.39
Vitamin C	**Agree n (%)**	**Disagree n (%)**	**OR (95% CI)**	**p-value**	**aOR (95% CI)**	**p-value**

Total	45 (10.1)	401 (89.9)				
Sex						
Female	34 (10.1)	303 (89.9)	1	(ref.)	1	(ref.)
Male	11 (10.1)	98 (89.9)	1.00 (0.49-2.05)	0.99	0.63 (0.28-1.45)	0.28
Age						
≤20	17 (16.3)	87 (83.7)	1	(ref.)	1	(ref.)
21-22	14 (8.8)	146 (91.3)	2.04 (0.96-4.34)	0.07	2.14 (0.91-5.00)	0.08
≥23	14 (7.7)	168 (92.3)	**2.35 (1.10-4.98)**	**0.03**	**2.34 (1.03-5.34)**	**0.04**
Discipline						
Medicine and Health	14 (9.1)	140 (90.9)	1	(ref.)	1	(ref.)
Arts and Social Science	16 (15.7)	86 (94.3)	0.54 (0.5-1.16)	0.11	0.86 (0.36-2.01)	0.72
Engineering & Food Science	8 (6.5)	116 (93.5)	1.45 (0.59-3.58)	0.42	1.71 (0.67-4.37)	0.26
Business and Commerce & Law	7 (10.6)	59 (89.4)	0.84 (0.32-2.20)	0.73	1.23 (0.43-3.49)	0.70
Known someone	40 (9.9)	365 (90.1)				
Do not know anyone	3 (5.4)	53 (94.6)	1	(ref.)	1	(ref.)
Myself, partner, family or friends	31 (10.6)	262 (89.4)	0.48 (0.14-1.62)	0.24	0.47 (0.14-1.66)	0.24
Celebrities	6 (10.7)	50 (89.3)	0.47 (0.11-1.99)	0.31	0.49 (0.11-2.20)	0.35
Rate of miscarriage						
Correct rate	9 (9.8)	83 (90.2)	1	(ref.)	1	(ref.)
Over-estimate fertility	20 (12.0)	146 (88.0)	0.79 (0.35-1.82)	0.58	0.81 (0.34-1.92)	0.63
Underestimate miscarriage	16 (8.6)	170 (89.9)	1.15 (0.49-2.72)	0.75	1.20 (0.48-3.03)	0.69

Chapter VI

Reproductive health knowledge about miscarriage: a cross-sectional study of university students.

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6.1. Abstract

Objective. To assess university students' knowledge of reproductive health information about miscarriage. **Methods.** A single-centre, cross-sectional study was carried out using an online survey at a higher education institution in the Republic of Ireland between April-May of 2016. A total of 746 university students' responses were analysed. **Results**. Approximately 60% and 70% of college students correctly identified features of first and second trimester miscarriage. After adjusting for confounders, male students were two times more likely to have a poor knowledge of features of miscarriage compared to females (aOR 2.0 95% CI 1.3-3.0 & aOR 1.7 95% CI 1.1-2.6 for first and second trimester respectively). Poor knowledge of features of first trimester miscarriage was less common among older students and students who were married, cohabiting or in a relationship (aOR 0.4 95% CI 0.2-0.6 & aOR 0.4 95% CI 0.3-0.8 respectively). Students who studied Medicine and Health were more likely to identify any types of treatment for miscarriage compared to students who studied other disciplines. However, students who studied Arts and Social Science were more likely to overestimate the percentage of estimated sporadic miscarriages (i.e. 50-60%) compared to students who studied Medicine and Health. **Conclusion.** Our results provide additional information about the gap of knowledge in regards to reproductive health information about miscarriage, specifically among university students.

Keywords: University students, knowledge, miscarriage, features, reproductive health.

Significance

Despite the high occurrence of miscarriage, there is little evidence regarding the population's knowledge, especially among those who are at a prime age for interventions to enhance knowledge on reproductive health. This study highlights the lack of knowledge of essential reproductive health information about miscarriage among university students. Students reported poor knowledge of signs and symptoms of miscarriage and types of treatments. This study emphasises the need to implement health education programs in the university community as a public health strategy to promote population's pregnancy-decision-making.

6.2. Introduction

Miscarriage is one of the most common adverse outcomes in early pregnancy[37]. It is widely accepted that improving women's informed decision-making during the perinatal period benefits maternal health outcomes[325]. Being aware of the most common signs and symptoms of miscarriage, the type of treatment and health care support available may improve feelings of control and self-determination during a miscarriage event[326].

Despite the prevalence and emotional burden of miscarriage, data on the population's awareness and knowledge of miscarriage is limited. In a study from the United States, the general population's knowledge of the prevalence, causes and risk factors of miscarriage was low[239]. Another American study showed a low to moderate level of awareness of preconception health and pregnancy, with poor general knowledge of common risk factors for miscarriage among undergraduate students[240]. Neither of

these studies evaluated knowledge of prevalence, causes and risk factors for miscarriage, nor specific information about miscarriage. University students represent an ideal environment to increase knowledge about miscarriage. Therefore, a cross-sectional study was conducted to explore students' knowledge about first and second trimester miscarriage, and students' knowledge of the type of management and diagnostic tests available for women who miscarry.

6.3. Methods

A cross-sectional study was undertaken at a University in the Republic of Ireland. There are 20,000 full-time students, of whom 14,000 are undergraduate[327]. This University is multicultural with more than 3,000 international students from 100 countries[327]. Between April and May of 2016, an online questionnaire, using SurveyMonkey®, was circulated to a random sample of 10% of undergraduate and postgraduate students who were enrolled using their university email accounts. Participation was voluntary and anonymous. Students had to read an information sheet and complete a consent form before completing the survey.

The survey consisted of 26 questions related to socio-demographic and educational characteristics and questions related to reproductive health information, awareness and knowledge about miscarriage. These sections included questions related to knowledge about the features (i.e. symptoms and signs) of a miscarriage event in the first and second trimester, diagnostic tests, treatment available and the investigations of miscarriage. This study also explored the students' knowledge about the percentage of miscarriages that will have a cause identified. Finally, this study explored the preferred information sources used to seek information about miscarriage.

Features of first and second trimester miscarriage were categorised as correct and incorrect. Correct signs and symptoms of miscarriage were chosen according to the National Clinical Guidelines in Obstetrics and Gynaecology of the Royal College of Physicians of Ireland (RCPI)[16,45]. In addition, this study added other signs and symptoms that were not associated with a miscarriage event and were grouped as incorrect features. A detailed list of the features can be seen in Supplementary Table 1. A total score was calculated to measure students' knowledge of features for miscarriage. Correct identification of a feature was scored as a 1, and an incorrect identification of a feature as zero. The maximum score for features of first trimester miscarriage ranged was 11 and 12 for second trimester miscarriage. The median was used as a cut-off to create dichotomous variables. Whereby scores below the median indicated poor understanding of features of miscarriage, and scores equal or above the median illustrated a good knowledge of the features of miscarriage.

Approximately 50 to 60% of miscarriages are attributed to chromosomal abnormalities[298], leaving a considerable percentage classified as unexplained . In order to estimate the percentage of miscarriages that will have a cause identified, students could report any percentage between 0 and 100%. Student responses were categorised into three groups: firstly underestimated estimates (i.e. 0 - 49%), correct estimates (i.e. 50 - 60%) or overestimated estimates (i.e. 61 -100%).

6.3.1 Statistical analysis

Descriptive analysis was carried out using mean and standard deviation for continuous variables and percentages for categorical variables. Data were excluded from analysis

when extreme outliers in socio-demographic characteristics such as age were identified or when responses were missing for more than half of the questionnaire. Binary logistic regression was calculated to assess if independent variables (e.g. sex, age, marital status, discipline and being aware of someone who had a miscarriage or not) predict good or bad knowledge of features of first and second miscarriage, and type of knowledge of treatments, diagnostic tests and investigations for miscarriage. Good or bad knowledge were coded as zero and one respectively. Having some knowledge of types of treatments, diagnostic tests and investigations for miscarriage was coded as zero and having no knowledge as one. Therefore, higher odd ratios were interpreted as having a poorer knowledge of features for first and second trimester miscarriage compared to those who had higher odd ratios.

Multinomial logistic regression was calculated to estimate the probability of underestimation or overestimation of the percentage of miscarriages that have a cause identified compared to students who selected the correct percentage. Chi-square tests were performed to assess the relationship between socio-demographic and educational characteristics and the type information sources preferred by students to look for information about miscarriage. Fisher's exact test was calculated for cells with an expected count of less than five. All analyses were adjusted by sex, age, marital status, discipline and being aware of someone who had a miscarriage or not with their corresponding 95% confidence intervals. All the analyses were performed using SPSS 21.0 (IBM).

6.3.2 Ethical approval and consent to participate

This study received ethical approval from the Clinical Research Ethics Committee of the Cork Teaching Hospital (ref: ECM 6 (rrrr) 12/04/16).

6.4. Results

A total sample of 872 students responded to the online survey. After excluding for missing data or extreme outliers, a total of 746 university students were included in the analysis. More than half of the respondents were females (n=577, 77.3%). The average age was 24.3 years (SD=6.58). Almost 50% (n=277) of students between 21 and 22 years of age were single, and more than 80% (n=111) of students 23 years of age or older were married or cohabiting (Table 6.1).

The most common feature identified for first and second trimester miscarriage was cramping and abdominal pain (n=607, 81.4% for first trimester and n=595, 79.8% for second trimester; Figure 6.1 and Figure 6.2). The second most common feature identified was passing tissue or clots (n=435, 58.3% for first trimester and n=438, 58.7% for second trimester). Both light and heavy bleeding for first trimester miscarriage were identified by approximately half of the students (n=411, 55.1% for light bleeding and n=351, 47.1% for heavy bleeding); however, only heavy bleeding was frequently recognised as feature for second trimester (n=113, 15.1% for light bleeding and n=601, 80.6% for heavy bleeding). Only a minority were aware that miscarriage can happen with either minor or potentially no signs or symptoms (n=216, 24.8% for first trimester and n=30; 3.4% for second trimester), or experiencing rupture

of membranes (i.e. water breaking) (n=24, 2.8% for first trimester and n=123, 14.1% for second trimester; Figure 6.1 and Figure 6.2).

Table 6.1. University students' characteristics by sex and age.

	Total n (%)	**Female** n (%)	**Male** n (%)	**≤20** n (%)	**21-22** n (%)	**≥23** n (%)
Total	746(100)	577 (77.3)	169 (22.7)			
Age						
≤20	173 (23.2)	144 (83.2)	29 (16.8)			
21-22	284 (38.1)	224 (78.9)	60 (21.1)			
≥23	289 (38.7)	209 (72.3)	80 (27.7)			
Marital status						
Single	617 (82.7)	470 (76.2)	147 (23.8)	162 (26.3)	277 (44.9)	178 (28.8)
Other (married, cohabiting…)	129 (17.3)	107 (82.9)	22 (17.1)	11 (8.5)	7 (5.4)	111 (86.0)
Discipline						
Medicine and Health	238 (31.9)	188 (79.0)	50 (21.0)	34 (14.3)	82 (34.5)	122 (51.3)
Arts and Social Science	201 (26.9)	172 (85.6)	29 (14.4)	59 (29.4)	66 (32.8)	76 (37.8)
Engineering & Food Science	203 (27.2)	143 (70.4)	60 (29.6)	52 (25.6)	87 (42.9)	64 (31.5)
Business and Commerce & Law	104 (13.9)	74 (71.2)	30 (28.8)	28 (26.9)	49 (47.1)	27 (26.0)
Level of study						
Undergraduate	590 (79.1)	475 (77.5)	133 (22.5)	172 (29.2)	260 (44.1)	158 (26.8)
Postgraduate	156 (20.9)	120 (76.2)	36 (23.1)	1 (0.6)	24 (15.4)	131 (84.0)
Known someone*						
Do not know anyone	85 (11.4)	51 (60.0)	34 (40.0)	20 (23.5)	44 (51.8)	21 (24.7)
Myself, partner, family or friends	489 (65.5)	391 (80.0)	98 (20.0)	103 (21.1)	175 (35.8)	211 (43.1)
Celebrities	100 (13.4)	90 (90.0)	10 (10.0)	29 (29.0)	257 (38.0)	265 (33.0)

***** Total subsample (n=674) of students' awareness of someone who had a miscarriage or not (i.e. themselves, partners, family, friends or celebrities).

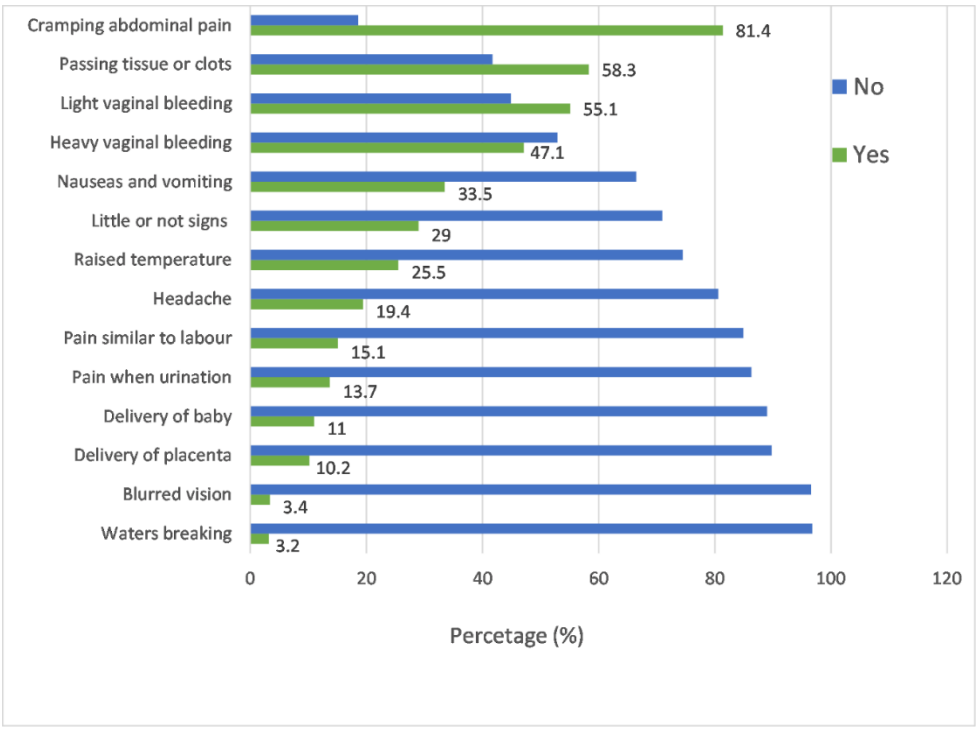


Figure 6.1. Identification of main features of first trimester miscarriage.

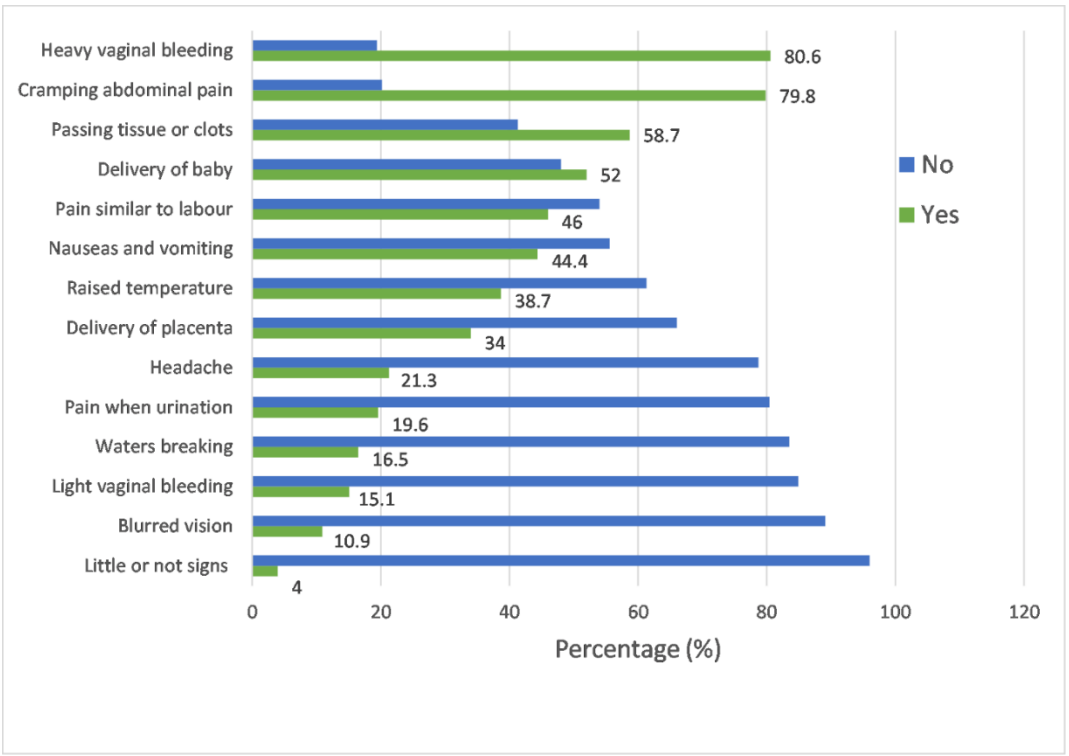


Figure 6.2. Identification of main features of second trimester miscarriage.

Students reported better knowledge of features for second trimester miscarriage, whereby 68.1% (n=508) had a good knowledge of the features of second trimester as opposed to only 60% (n=442) for first trimester miscarriage (Table 6.2). After adjusting for covariates, male students were less likely to identify features for first and second trimester than female students (aOR 2.0; 95% CI 1.3-3.0 & aOR 1.7; 95% CI 1.1-2.6, respectively; Table 6.2). Poor knowledge of features of first and second trimester miscarriage were less common among college students who were married or cohabiting than single students (aOR 0.4; 95% CI 0.3-0.8 & aOR 0.5; 95% CI 0.3-0.9, respectively; Table 6.2). Students who studied in the School of Arts and Social Science or Business and Commerce & Law were more likely to have poor knowledge of the features of second trimester miscarriage than those who studied in the School of Medicine and Health (aOR 1.9; 95% CI 1.2-3.1 & aOR 2.7; 95% CI 1.5-4.6, respectively; Table 6.2).

Table 6.2. Good and poor knowledge of features of first and second trimester miscarriage among university students.

		First trimester			Second trimester		
	Total n	**Good knowledge n (%)**	**Unadjusted uOR (95% CI)**	**Adjusted aOR (95% CI)**	**Good knowledge n (%)**	**Unadjusted uOR (95% CI)**	**Adjusted aOR (95% CI)**
Total	746	442 (59.2)			508 (68.1)		
Sex							
Female	577	364 (63.1)	1.0 (ref.)	1.0 (ref.)	411 (71.2)	1.0 (ref.)	1.0 (ref.)
Male	169	78 (46.2)	**2.0 (1.4-2.8)**	**2.0 (1.3-3.0)**	97 (57.4)	**1.8 (1.3-2.6)**	**1.7 (1.1-2.6)**
Age							
≤20	173	80 (46.2)	1.0 (ref.)	1.0 (ref.)	100 (57.8)	1.0 (ref.)	1.0 (ref.)
21-22	284	150 (52.8)	0.8 (0.5-1.1)	0.7 (0.5-1.1)	187 (65.8)	0.7 (0.5-1.1)	0.7 (0.5-1.1)
≥23	289	212 (73.4)	**0.3 (0.2-0.5)**	**0.4 (0.2-0.6)**	221 (76.5)	**0.4 (0.3-0.6)**	0.6 (0.4-1.0)
Marital status							
Single	617	340 (55.1)	1.0 (ref.)	1.0 (ref.)	404 (65.5)	1.0 (ref.)	1.0 (ref.)
Other (married, cohabiting…)	129	102 (79.1)	**0.3 (0.2-0.5)**	**0.4 (0.3-0.8)**	104 (80.6)	**0.5 (0.3-0.7)**	**0.5 (0.3-0.9)**
Discipline							
Medicine and Health	238	161 (67.7)	1.0 (ref.)	1.0 (ref.)	184 (77.3)	1.0 (ref.)	1.0 (ref.)
Arts and Social Science	201	118 (58.7)	1.5 (1.0-2.2)	1.5 (1.0-2.4)	130 (64.7)	**1.9 (1.2-2.8)**	**1.9 (1.2-3.1)**
Engineering & Food Science	203	112 (55.2)	**1.7 (1.2-2.5)**	1.4 (0.9-2.2)	138 (68.0)	**1.6 (1.1-2.5)**	1.5 (0.9-2.5)
Business and Commerce & Law	104	51 (49.0)	**2.2 (1.4-3.5)**	1.6 (0.9-2.6)	56 (53.8)	**2.9 (1.8-4.8)**	**2.7 (1.5-4.6)**
Known someone*							
Do not know anyone	85	43 (50.6)	1.0 (ref.)	1.0 (ref.)	58 (68.2)	1.0 (ref.)	1.0 (ref.)
Myself, partner, family or friends	489	314 (64.2)	**0.6 (0.4-0.9)**	0.8 (0.5-1.3)	354 (72.4)	0.8 (0.5-1.4)	1.0 (0.6-1.7)
Celebrities	100	58 (58.0)	0.7 (0.4-1.3)	1.0 (0.5-1.9)	72 (72.0)	0.8 (0.4-1.6)	1.0 (0.5-2.0)

***** Total subsample (n=674); uOR = Unadjusted OR; aOR = adjusted OR for all the variables included in the table (e.g. sex, age, marital status, discipline and known someone); uOR, aOR and their respective 95% Confidence Intervals (CIs) in bold are significant $p < 0.005$.

Almost half of the participants identified medical and surgical treatment as a treatment for miscarriage (n=338, 45.3% and n=351, 47.1% respectively; Table 6.3); however, only 35.7% (n=266) knew that expectant treatment (i.e. no treatment or conservative management) is an alternative option to medical and surgical treatments for miscarriage. Students who studied in any discipline other than Medicine and Health were more likely not to be aware of any type of treatment for miscarriage (aOR 2.3; 95% CI 1.3-4.3, aOR 2.1; 95% CI 1.2-3.7 & aOR 2.5; 95% CI 1.5-4.8 for Arts and Social Science, Engineering & Food Science and Business and Commerce & Law respectively; Table 6.3).

When students were asked to estimate the percentage of sporadic miscarriages that will have an identified cause for the miscarriage, only 30% (n=207) of students identified the correct percentage (i.e. 50 to 60%), and more than half of the students underestimated the percentage (n=400, 53.6%; Table 6.4). However, the odds of overestimating the percentage of miscarriage were lower for students who themselves or their partners had a miscarriage or who knew a relative or a friend who had a miscarriage, but also among students who knew a celebrity who had a miscarriage (aOR 0.3; 95% CI 0.2-0.6 & aOR 0.3; 95% CI 0.1-0.8, respectively; Table 6.4). Students who studied Arts and Social Science were more likely to overestimate the percentage compared to students who studied Medicine and Health (aOR 2.5; 95% CI 1.2-5.1; Table 6.4).

The diagnostic tests for miscarriage most frequently identified among university students were ultrasound scan (n=540, 72.4%) and physical examination (n=385, 51.6%; Supplementary Table 6.2). Almost 13% (n=97) of students did not know how

miscarriage was diagnosed. After adjusting for confounding factors, male students and students who studied Business and Commerce & Law were more likely to report that they did not know any type of diagnostic tests of miscarriage compared to female students and students who studied Medicine and Health (aOR 1.9; 95% CI 1.1-3.3 & aOR 2.4; 95% CI 1.5-5.0, respectively; Supplementary Table 6.2). Almost half of the students knew that a placental examination is a type of investigation available for women who miscarry (n=369, 49.5%; Supplementary Table 6.3); However, only 35.7% (n=266) of students knew that post-mortem examination is an option for investigating miscarriage (Supplementary Table 6.3).

The majority of students reported Google as a preferred source of information about miscarriage (n=596; 80%), followed by their General Practitioner (GP) (n=414, 55.5%) and the hospital (n=198, 26.5%; Supplementary Table 6.4). The least preferred information sources were Wikipedia and mobile applications (n=102, 13.7%, and n=21, 2.8% respectively; Supplementary Table 6.4). Female students sought information about miscarriage more frequently at the GP (n=332, 80.2% versus n=82, 19.8%; $p < 0.05$) or on Wikipedia (n=60, 58.8% versus n=42, 41.2%; $p < 0.001$) than male students. Students aged 23 years or older sought information about miscarriage at the GP or hospital more frequently than younger students ($p < 0.05$). However, they were also more likely to look for information on mobile phone applications than younger students (Supplementary Table 6.4).

Table 6.3. University students' awareness of treatment available for women who miscarry.

		Type of treatment selected			Knowledge of treatment for miscarriage			
	Total n	**Conservative treatment n (%)**	**Medical treatment n (%)**	**Surgical treatment n (%)**	**Some knowledge n (%)**	**No knowledge n (%)**	**Unadjusted uOR (95% CI)**	**Adjusted aOR (95% CI)**
Total	746	266 (44.3)	338 (56.2)	351 (58.4)	601 (80.6)	145 (19.4)		
Sex								
Female	577	208 (36.0)	274 (47.5)	283 (49.0)	468 (81.1)	109 (18.9)	1.0 (ref.)	1.0 (ref.)
Male	169	58 (34.3)	64 (37.9)	68 (40.2)	133 (78.7)	36 (21.3)	1.2 (0.8-1.8)	1.3 (0.8-2.0)
Age								
≤20	173	37 (21.4)	63 (36.4)	72 (41.6)	132 (76.3)	41 (23.7)	1.0 (ref.)	1.0 (ref.)
21-22	284	80 (28.2)	128 (45.1)	111 (39.1)	217 (76.4)	67 (23.6)	1.0 (0.6-1.6)	1.0 (0.6-1.6)
≥23	289	149 (51.6)	147 (50.9)	168 (58.1)	252 (87.2)	37 (12.8)	**0.5 (0.3-0.8)**	**0.5 (0.3-0.9)**
Marital status								
Single	617	195 (31.6)	282 (45.7)	281 (45.5)	491 (79.6)	126 (20.4)	1.0 (ref.)	1.0 (ref.)
Other (married, cohabiting…)	129	71 (55.0)	56 (43.4)	70 (54.3)	110 (85.3)	19 (14.7)	0.7 (0.4-1.1)	1.0 (0.5-1.8)
Discipline								
Medicine and Health	238	130 (54.6)	141 (59.2)	142 (59.7)	214 (89.9)	24 (10.1)	1.0 (ref.)	1.0 (ref.)
Arts and Social Science	201	48 (23.9)	78 (38.8)	96 (47.8)	157 (78.1)	44 (21.9)	**2.5 (1.5-4.3)**	**2.3 (1.3-4.0)**
Engineering & Food Science	203	63 (31.0)	78 (38.4)	69 (34.0)	153 (75.4)	50 (24.6)	**2.9 (1.7-4.9)**	**2.1 (1.2-3.7)**
Business and Commerce & Law	104	25 (24.0)	41 (39.4)	44 (42.3)	77 (74.0)	27 (26.0)	**3.1 (1.7-5.8)**	**2.5 (1.5-4.8)**
Known someone*								
Do not know anyone	85	24 (28.2)	30 (35.3)	32 (37.6)	60 (70.6)	25 (29.4)	1.0 (ref.)	1.0 (ref.)
Myself, partner, family or friends	489	186 (38.0)	239 (48.9)	242 (49.5)	390 (79.8)	99 (20.2)	0.6 (0.4-1.0)	0.8 (0.4-1.3)
Celebrities	100	39 (39.0)	48 (48.0)	58 (58.0)	87 (87.0)	13 (13.0)	**0.4 (0.2-0.8)**	**0.4 (0.2-0.9)**

***** Total subsample (n=674); uOR = Unadjusted OR; aOR = adjusted OR for all the variables included in the table (e.g. sex, age, marital status, discipline and known someone); uOR, aOR and their respective 95% Confidence Intervals (CIs) in bold are significant $p < 0.005$.

Table 6.4. Estimation of the percentage of miscarriages that will have a cause identified for the pregnancy loss (N=745)

Rate	**Correct (50-60%) n (%)**	**Underestimated n (%)**	**Unadjusted uOR (95% CI)**	**Adjusted aOR (95% CI)**	**Overestimated n (%)**	**Unadjusted uOR (95% CI)**	**Adjusted aOR (95% CI)**
Total	207 (27.7)	400 (53.6)			138 (18.5)		
Sex							
Female	153 (26.6)	323 (56.1)	1.0 (ref.)	1.0 (ref.)	100 (17.4)	1.0 (ref.)	1.0 (ref.)
Male	54 (32.0)	77 (45.6)	0.7 (0.5-1.0)	**0.6 (0.4-0.8)**	38 (22.5)	1.1 (0.7-1.8)	0.8 (0.4-1.4)
Age							
≤20	49 (28.3)	77 (44.5)	1.0 (ref.)	1.0 (ref.)	47 (27.2)	1.0 (ref.)	1.0 (ref.)
21-22	91 (32.2)	139 (49.1)	0.9 (0.6-1.5)	0.9 (0.6-1.5)	53 (18.7)	0.6 (0.4-1.0)	0.6 (0.3-1.0)
≥23	67 (23.2)	184 (63.7)	**1.7 (1.1-2.8)**	1.4 (0.9-2.4)	38 (13.1)	0.6 (0.3-1.0)	0.6 (0.3-1.2)
Marital status							
Single	25 (19.4)	84 (65.1)	1.0 (ref.)	1.0 (ref.)	20 (15.5)	1.0 (ref.)	1.0 (ref.)
Other (married, cohabiting…)	182 (29.5)	316 (51.3)	**1.9 (1.2-3.1)**	1.6 (0.9-2.8)	118 (19.2)	1.2 (0.7-2.3)	1.6 (0.7-3.6)
Discipline							
Medicine and Health	60 (25.2)	151 (63.4)	1.0 (ref.)	1.0 (ref.)	27 (11.3)	1.0 (ref.)	1.0 (ref.)
Arts and Social Science	51 (25.5)	99 (49.5)	0.8 (0.5-1.2)	0.8 (0.5-1.2)	50 (25.0)	**2.2 (1.2-4.0)**	**2.5 (1.2-5.1)**
Engineering & Food Science	64 (31.5)	102 (50.2)	**0.6 (0.4-0.9)**	0.7 (0.4-1.1)	37 (18.2)	1.3 (0.7-2.4)	1.4 (0.7-2.9)
Business and Commerce & Law	32 (30.8)	48 (46.2)	0.6 (0.4-1.0)	0.7 (0.4-1.3)	24 (23.1)	1.7 (0.8-3.3)	2.2 (1.0-4.9)
Known someone*							
Do not know anyone	20 (23.5)	42 (49.4)	1.0 (ref.)	1.0 (ref.)	23 (27.1)	1.0 (ref.)	1.0 (ref.)
Myself, partner, family or friends	142 (29.0)	286 (58.5)	1.0 (0.5-1.7)	0.7 (0.4-1.3)	61 (12.5)	**0.4 (0.2-0.7)**	**0.3 (0.2-0.6)**
Celebrities	35 (35.4)	48 (48.5)	0.7 (0.3-1.3)	**0.5 (0.2-0.9)**	16 (16.2)	**0.4 (0.2-0.9)**	**0.3 (0.1-0.8)**

* Total subsample (n=674); uOR = Unadjusted OR; aOR = adjusted OR for all the variables included in the table (e.g. sex, age, marital status, discipline and known someone); uOR, aOR and their respective 95% Confidence Intervals (CIs) in bold are significant $p < 0.005$.

6.5. Discussion

This cross-sectional study highlights university student's lack of knowledge of essential reproductive health information regarding miscarriage. Although students correctly identified heavy bleeding, cramping and pain as common features for miscarriage, they were not aware that miscarriage can sometimes occur without any signs or symptoms. In addition, this study explored factors that predict good or poor knowledge about features and type of treatments, diagnostic tests and investigations for miscarriage. Students outside of disciplines from Medicine and Health were more likely to have a poor knowledge of second trimester miscarriage, treatment and investigations of miscarriage. Surprisingly, only 44.3% of students knew that expectant treatment is an alternative management option for women who miscarry. Google was the preferred source for information related to miscarriage.

Although our overall response rate was low (39.6%), students were randomly selected, which increases the external validity of our results. Nevertheless, our study design involved some limitations. Firstly, a validated questionnaire was not available meaning a questionnaire was developed by a multidisciplinary team of professionals in the area of pregnancy loss. Data were collected at one point in time from a single University. However, our findings can be used to gain insight into students' knowledge of miscarriage as cross-sectional studies are the best study designs for estimating the prevalence of behaviour in a population[328].

Based on limited published evidence, it appears that there is a poor awareness of causes and risk factors of miscarriage[239,240]. One study reported that more than half of

the respondents stated that miscarriage was uncommon, occurring in less than 6% of all pregnancies[239]. Respondents also incorrectly believed that lifestyle factors were the single most common cause of miscarriage, even more common than genetic or medical causes[239]. Similar to our findings, Delgado et al. (2008) found that female students had a significantly higher knowledge of preconception health compared to male students. This finding could be explained by the fact that approximately 50% of females were enrolled in the School of Medicine and Health in our study. In addition, it is internationally accepted that men have been traditionally excluded from being targeted for reproductive health initiatives[329,330] and preconception health websites[331].

Promoting reproductive health education has the potential to increase well informed pregnancy-related decisions[332], and prove empowering for all women and men of reproductive age[306]. Nevertheless, a study published in the United Kingdom reported that nearly half of the women who experience a miscarriage did not feel well informed at the time of event, only 30% felt emotionally well supported, and almost 80% did not received aftercare[333]. Furthermore, another study showed that women felt that the information provided by healthcare professionals was vague or difficult to understand[334]. However, given that miscarriage is common, educating and informing the population about miscarriage as part of public health initiative in the community in a stress-free and favourable environment may help women and men in two different ways: firstly to be more prepared for what to expect when a miscarriage occurs and secondly to be aware of where to seek reliable health information following a miscarriage. In fact, the need to be repeatedly informed about preconception health and fertility has been addressed by adolescents themselves in a previous study[335].

The Internet is becoming the most accessed health information source worldwide[336]. In a survey carried out in the UK in 2014, the second highest country for Internet health searches, Google was more commonly used to look for symptoms than booking an appointment with a GP or visiting a pharmacy for advice[337]. Therefore, it is not surprising that our study population preferred Google as a first choice, as opposed to visiting a GP or the hospital for information about miscarriage. However, the quality of the information provided by an array of health websites is not always reliable[338]. In a review assessing the quality of information about miscarriage on the Internet, only 19 of 120 hits had relevant information[338]. Health care providers need to be aware of the good quality websites that are available for women looking for information about miscarriage[339].

6.6. Conclusion

In keeping with the limited evidence in the field, our results highlight university students' lack of knowledge and common misunderstandings around basic reproductive health information relating to miscarriage. Universities have an ideal opportunity to target a group of adults in an early reproductive stage to enhance their knowledge and promote awareness about miscarriage.

6.7 Implications for practice, policy and research

Implications for practice

- University represents an ideal opportunity for health promotion strategies to increase awareness of potential adverse outcomes in pregnancy

Implications for policy

- There is a need to promote and initiate education programmes that include reproductive health education about miscarriage in the community in order to increase the knowledge of risk factors and features of miscarriage among the population

Implications for research

- Further research projects might apply for the Science Foundation Ireland (SFI) Education and Public Engagement programme in order to be carry out studies that promote the awareness and engagement of the Irish public with the topic of pregnancy loss
- Future development of questionnaires which assess the knowledge of risk factors for miscarriage should include students advocates

6.8. Supplementary Tables

Supplementary Table 6.1. List of features in first and second trimester of miscarriage

	CORRECT	INCORRECT
FIRST TRIMESTER MISCARRIAGE	• Cramping abdominal pain • Heavy vaginal bleeding • Light vaginal bleeding, similar to menstruation • Little to no physical signs • Passing tissue or clot-like material • Waters breaking	• Blurred vision • Headache • Painful urination
	CORRECT	**INCORRECT**
SECOND TRIMESTER MISCARRIAGE	• Cramping abdominal pain • Heavy vaginal bleeding • Light vaginal bleeding, similar to menstruation • Passing tissue or clot-like material • Delivery of baby, though small in size • Delivery of placenta • Pain similar to labour pains • Little to no physical signs • Waters breaking	• Blurred vision • Headache • Painful urination

Supplementary Table 6.2. University students' knowledge of how a miscarriage can be diagnosed.

		Type of diagnostic test selected				Knowledge of diagnostic tests for miscarriage			
	Total	**Physical exam n (%)**	**Blood test n (%)**	**Scan n (%)**	**Surgery n (%)**	**Some knowledge n (%)**	**No knowledge n (%)**	**Unadjusted uOR (95% CI)**	**Adjusted aOR (95% CI)**
Total	746	385 (51.6)	203 (27.2)	540 (72.4)	13 (1.7)	649 (87.0)	97 (13)		
Sex									
Female	577	307 (53.2)	163 (28.2)	430 (74.5)	10 (1.7)	508 (88.0)	69 (12.0)	1.0 (ref.)	1.0 (ref.)
Male	169	78 (46.2)	40 (23.7)	110 (65.1)	3 (1.8)	141 (83.4)	28 (16.6)	**1.7 (1.0-2.8)**	**1.9 (1.1-3.3)**
Age									
≤20	173	86 (49.7)	42 (24.3)	103 (59.5)	1 (0.6)	137 (79.2)	36 (20.8)	1.0 (ref.)	1.0 (ref.)
21-22	284	141 (49.6)	68 (23.9)	207 (72.9)	7 (2.5)	244 (85.9)	40 (14.1)	**0.5 (0.3-0.9)**	**0.5 (0.3-0.9)**
≥23	289	158 (54.7)	93 (32.2)	230 (76.9)	5 (1.7)	268 (92.7)	21 (7.3)	**0.3 (0.1-0.5)**	**0.3 (0.1-0.6)**
Marital status									
Single	617	323 (52.4)	163 (26.4)	435 (70.5)	11 (1.8)	529 (85.7)	88 (14.3)	1.0 (ref.)	1.0 (ref.)
Other (married, cohabiting…)	129	62 (48.1)	40 (31.0)	105 (81.4)	2 (1.6)	120 (93.0)	9 (7.0)	**0.4 (0.2-0.9)**	0.7 (0.3-1.6)
Discipline									
Medicine and Health	238	115 (48.3)	79 (33.2)	200 (84.0)	5 (2.1)	219 (92.0)	19 (8.0)	1.0 (ref.)	1.0 (ref.)
Arts and Social Science	201	114 (56.7)	46 (22.9)	129 (64.2)	6 (3.0)	172 (85.6)	29 (14.4)	**2.1 (1.1-3.9)**	1.9 (0.9-3.6)
Engineering & Food Science	203	106 (52.2)	47 (23.2)	147 (72.4)	1 (0.5)	178 (87.7)	25 (12.3)	1.7 (0.9-3.3)	1.3 (0.6-2.5)
Business and Commerce & Law	104	50 (48.1)	31 (29.8)	64 (61.5)	1 (1.0)	80 (76.9)	24 (23.1)	**3.1 (1.6-6.3)**	**2.4 (1.2-5.0)**
Known someone**									
Do not know anyone	85	41 (48.2)	22 (25.9)	62 (72.9)	3 (3.5)	71 (83.5)	14 (16.5)	1.0 (ref.)	1.0 (ref.)
Myself, partner, family or friends	489	265 (54.2)	142 (29.0)	369 (75.5)	7 (1.4)	425 (86.9)	64 (13.1)	0.8 (0.4-1.4)	1.0 (0.5-1.9)
Celebrities	100	58 (58.0)	27 (27.0)	78 (78.0)	1 (1.0)	90 (90.0)	10 (10.0)	0.6 (0.2-1.3)	0.7 (0.3-1.7)

**Total subsample (n=674); uOR = Unadjusted OR; aOR = adjusted OR for all the variables included in the table (e.g. sex, age, marital status, discipline and known someone); uOR, aOR and their respective 95% Confidence Intervals (CIs) in bold are significant $p < 0.005$.

Supplementary Table 6.3. University students' awareness of investigations available for women who miscarry.

		Type of investigations selected			Knowledge of investigations for miscarriage			
	Total n	**Blood tests n (%)**	**Placenta exam n (%)**	**Post-mortem exam n (%)**	**Some knowledge n (%)**	**No knowledge n (%)**	**Unadjusted uOR (95% CI)**	**Adjusted aOR (95% CI)**
Total	746	312 (41.8)	369 (49.5)	266 (35.7)	518 (69.4)	228 (30.6)		
Sex								
Female	577	248 (43.0)	292 (50.6)	203 (35.2)	396 (68.6)	181 (31.4)	1.0 (ref.)	1.0 (ref.)
Male	169	64 (37.9)	77 (45.6)	63 (37.3)	122 (72.2)	47 (27.8)	1.0 (0.6-1.4)	0.9 (0.6-1.4)
Age								
≤20	173	70 (40.5)	78 (45.1)	50 (28.9)	123 (71.1)	50 (28.9)	1.0 (ref.)	1.0 (ref.)
21-22	284	122 (43.0)	142 (50.0)	101 (35.6)	196 (69.0)	88 (31.0)	1.0 (0.7-1.6)	1.1 (0.7-1.8)
≥23	289	120 (41.5)	149 (51.6)	115 (39.8)	199 (68.9)	90 (31.1)	1.0 (0.6-1.5)	1.1 (0.7-1.8_
Marital status								
Single	617	266 (43.1)	309 (50.1)	219 (35.5)	435 (70.5)	182 (29.5)	1.0 (ref.)	1.0 (ref.)
Other (married, cohabiting…)	129	46 (35.7)	60 (46.5)	47 (36.4)	83 (64.3)	46 (35.7)	1.3 (0.8-1.9)	1.2 (0.8-2.0)
Discipline								
Medicine and Health	238	122 (51.3)	149 (62.6)	127 (53.4)	194 (81.5)	44 (18.5)	1.0 (ref.)	1.0 (ref.)
Arts and Social Science	201	75 (37.3)	88 (43.8)	48 (23.9)	124 (61.7)	77 (38.3)	**3.0 (1.9-4.8)**	**3.0 (1.9-4.8)**
Engineering & Food Science	203	80 (39.4)	95 (46.8)	62 (30.5)	138 (68.0)	65 (32.0)	**2.2 (1.4-3.5)**	**2.2 (1.4-3.6)**
Business and Commerce & Law	104	35 (33.7)	37 (35.6)	29 (27.9)	62 (59.6)	42 (40.4)	**3.1 (1.8-5.3)**	**3.2 (1.9-5.6)**
Known someone**	674							
Do not know anyone	85	41 (48.2)	43 (50.6)	30 (35.3)	58 (68.2)	27 (31.8)	1.0 (ref.)	1.0 (ref.)
Myself, partner, family or friends	489	205 (41.9)	249 (50.9)	186 (38.0)	327 (66.9)	162 (33.1)	1.1 (0.6-1.7)	1.1 (0.6-1.8)
Celebrities	100	43 (43.0)	57 (57.0)	38 (38.0)	75 (75.0)	25 (25.0)	0.7 (0.4-1.4)	0.7 (0.4-1.4)

** Total subsample (n=674); uOR = Unadjusted OR; aOR = adjusted OR for all the variables included in the table (e.g. sex, age, marital status, discipline and known someone); uOR, aOR and their respective 95% Confidence Intervals (CIs) in bold are significant $p < 0.005$.

Supplementary Table 6.4. Preferences of university students' sources to look for information about miscarriage.

	Total n	**GP n (%)**	**Hospital n (%)**	**Google n (%)**	**Wikipedia n (%)**	**Mobile app n (%)*** **	**Other n (%)*** **
	746	414 (55.5)	198 (26.5)	596 (79.9)	102 (10.4)	21 (2.8)	47 (6.3)
Sex							
Female	577	332 (57.5)*	154 (26.7)	468 (81.1)	60 (10.4)*	14 (2.4)	34 (5.9)
Male	169	82 (48.5)	44 (26.0)	128 (75.7)	42 (24.9)	7 (4.1)	13 (7.7)
Age							
≤20	173	81 (46.8)*	37 (21.4)*	132 (76.3)	16 (9.2)	2 (1.2)	8 (4.6)
21-22	284	157 (55.3)	65 (22.9)	235 (82.7)	44 (15.5)	8 (2.8)	15 (5.3)
≥23	289	176 (60.9)	96 (33.2)	229 (79.2)	42 (14.5)	11 (3.8)	24 (8.3)
Marital status							
Single	617	331 (53.6)*	157 (25.4)	499 (80.9)	92 (14.9)*	20 (3.2)	35 (5.7)
Other (married, cohabiting…)	129	83 (64.3)	41 (31.8)	97 (75.2)	10 (7.8)	1 (0.8)	12 (9.3)
Discipline							
Medicine and Health	238	132 (55.5)	97 (40.8)*	187 (78.8)	35 (14.7)	9 (3.8)	23 (9.7)*
Arts and Social Science	201	123 (61.2)	50 (24.9)	151 (75.1)	21 (10.4)	2 (1.0)	14 (7.0)
Engineering & Food Science	203	99 (48.8)	36 (17.7)	171 (84.2)	32 (15.8)	4 (4.0)	9 (4.4)
Business and Commerce & Law	104	60 (57.7)	15 (14.4)	87 (83.7)	14 (13.5)	6 (5.8)	1 (1.0)
Known someone**							
Do not know anyone	85	43 (50.6)	19 (22.4)	72 (84.7)	19 (22.4)	3 (3.5)	5 (5.9)
Myself, partner, family or friends	489	290 (59.3)	141 (28.8)	408 (83.4)	62 (12.7)	12 (2.5)	26 (5.3)
Celebrities	100	63 (63.0)	28 (28.0)	87 (87.0)	16 (16.0)	4 (4.0)	9 (9.0)

* Statistically significant p <0.05; ** Total subsample (n=674); *** Fisher's exact test correction was calculated for cells with an expected count less than five

Chapter VII

Psychological distress and general health during pregnancy among women with a history of miscarriage: a pilot prospective study.

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7.1 Abstract

Introduction. Miscarriage is one of the most common complications in early pregnancy. Nevertheless, little is known about how previous miscarriage might affect psychological and general health factors in subsequent pregnancies. The aim of this study was to examine the feasibility of a prospective cohort study, which aims to assess the change of perceived level of stress, anxiety, depression, life stressors, general health and quality of sleep over the course of pregnancy among women who have a history of miscarriages. **Material and methods.** A feasibility prospective cohort study was carried out in a tertiary maternity hospital in Ireland. Pregnant women, who have a history of miscarriage, were recruited from the Early Pregnancy Assessment Unit from August to December 2017. Using validated questionnaires, this feasibility study explored mean changes over the pregnancy of perceived levels of stress, anxiety and depression, as well as general health and quality of sleep. Descriptive analysis were carried using STATA statistical software. **Results.** Based on inclusion criteria, 58 women were eligible and gave consent to participate in the study. Of these, 35 (60%) responded to the first survey, 15 (43%) the second survey and 18 (51%) the third questionnaire. Responders were slightly older and were more likely to have two previous miscarriages compared to non-responders. Psychological and general health factors fluctuated over the pregnancy. **Conclusions.** Although miscarriage is one of the most common complications in early pregnancy, there is limited evidence on psychological variations in the next subsequent pregnancy. Therefore, there is a lack of evidence in the field among this targeted group. This study explored changes over the pregnancy of psychological and general health factors and discusses potential factors for screening, recruiting and retention among pregnant women who have a history of miscarriage.

Keywords: pregnancy, history of miscarriage, psychological factors, feasibility cohort study

7.1 Introduction

Miscarriage is one of the most common complications during pregnancy. It is estimated that miscarriage affects up to one-third of pregnancies[4,5]. Recently, the

effect of maternal stress during pregnancy has gained attention as an important factor for both the mother and the fetus[186,187,340]. Several studies have reported that women who miscarry are more likely to experience high levels of stress, anxiety and depression following miscarriage[212,341] and in their subsequent pregnancies[341-343]. However, little is known about the fluctuation of stress, anxiety and depression during pregnancy among women who have a history of miscarriage[344].

It is essential to design and implement prospective studies to measure the potential change of stress, anxiety and depression over the course of pregnancy. In addition, women who miscarry may be vulnerable to the potentially detrimental effect of maternal stress[186,215]. Hence, it is important to investigate the potential impact of stress, anxiety and depression on subsequent pregnancy outcomes; specifically to study which trimesters of pregnancy are more susceptible to psychological distress. More research is needed to understand which particular subgroups of pregnant women, under what circumstances and at which stages of gestation might be more vulnerable[186]. To our knowledge, this is the first feasibility study that looked at changes of psychological morbidity among women with a history of miscarriage. The overall main aim of this study was to examine the feasibility of a prospective study to assess the change of perceived level of stress, anxiety, depression, life stressors, and general health over the course of pregnancy among women who have a history of miscarriage.

7.4 Material and Methods

This was a feasibility prospective study at a large tertiary hospital with approximately 7,500 births annually. This maternity hospital serves patients primarily in the south of

the Republic of Ireland. The population under examination were pregnant women who had a history of miscarriage and were in their subsequent pregnancy. Inclusion criteria were women: 1) in the first trimester of pregnancy (<12 weeks), 2) singleton pregnancy, 3) who had a history of at least one miscarriage, 4) who planned attendance at the maternity hospital for routine antenatal care, 5) who were 18 years or older, 6) who had an adequate understanding of the English language. Exclusion criteria were: 1) a history of recurrent miscarriage (three or more consecutive miscarriages), 2) a threatened miscarriage i.e. vaginal bleeding during the first 3 months of pregnancy or 3) a history of other adverse pregnancy outcomes in previous pregnancies as it is known that these women are at higher risk of experiencing other complications (i.e. stillbirth, ectopic pregnancies, molar pregnancies, etc.).

The Early Pregnancy Assessment Unit (EPAU) is a specialised clinic dedicated to providing care to women in early pregnancy. The EPAU provides antenatal care in the first trimester to pregnant women who present with signs of threatened miscarriage, who have a history of miscarriage or recurrent miscarriage, who have a history of ectopic pregnancy and/or other risk factors early in pregnancy. The EPAU runs clinics from Monday to Friday. All pregnant women were recruited early in pregnancy while attending the EPAU for a reassurance scan (i.e. a scan that confirms viability early in pregnancy) from August 2017 to December 2017. Midwife sonographers identified potential women in accordance with the inclusion criteria. Once informed consent was obtained by the research nurse, the baseline questionnaire was administered at time one (T1). The baseline questionnaire was completed once and it included questions about past reproductive history and past medical complications. This information was collected for a second time from the medical

records in order to confirm the information provided by the participants. Participants were then asked to complete a survey in the second and third trimester of pregnancy (Supplementary Table 7.1.). For the first survey, women were given the option of bringing the survey home, and following completion, women were able to return the survey in the stamped addressed envelope provided. The second and third survey were completed using an online survey which was sent by email to the women. For women who did not have an email account, a hard copy of the main survey was sent by post. Women who were eligible, but declined participation were invited to provide anonymised baseline data for comparison including age and reason(s) for non-participation. Finally, pregnancy outcomes were collected during pregnancy (eg body mass index, blood pressure, early and late pregnancy loss) and after delivery (eg term or preterm delivery and birthweight; Supplementary Table 7.1.).

The survey was comprised of four sections including validated questions and psychometric scales (Table 1 - Supplementary Table 7.1). Section one collected demographic characteristics, these data were collected just once. Section two related to lifestyle behaviours such as smoking and alcohol consumption. Alcohol consumption behaviour was assessed using the AUDIT-C questionnaire[345]. Section three related to mental health and wellbeing. A summary of the Cronbach's alphas for each survey and the main characteristics are included in Supplementary Table 7.2.

7.4.1 Statistical analysis

Descriptive analysis for continuous variables and total scores were compared using means and standard deviations; for categorical variables frequencies were calculated and stratified by women status (eg completion of surveys, loss of follow-ups or

excluded from the study) and by time-point during pregnancy (i.e. first, second and third trimester of pregnancy). Mixed-effects regression models were used to estimate the mean at time one (T1) and the mean change from T1 to time two (T2) and T1 to time three (T3) for the psychometric scales. The advantage of using mixed-effects models instead of other non-parametric tests is that the mixed-effects models use all available data at each time-point rather than the data from individuals assessed at all times. Comparisons between women who had a live birth or had a miscarriage during our study were not possible as only two women among those who had pregnancy loss completed the first questionnaire. All the analysis were conducted using STATA statistical software v.24.

7.4.2 Ethical approval

Ethical approval

This study received ethical approval from the Clinical Research Ethics Committee of the Cork Teaching Hospital (ref: ECM 4 (p) 04/04/17)

7.5 Results

A total of 76 women were approached at the EPAU with 15 women excluded because they had a pregnancy of uncertain viability when approached (n=7), had a history of recurrent miscarriage (n= 4), had a history of neonatal death (n=1), were pregnant under methotrexate treatment (n=1), or refused participation (n=2). Three women were excluded after they consented to participate in the study: two had a pregnancy loss during the study period and one woman answered the first questionnaire after 20 weeks of gestation (Figure 7.1).

The median of weeks of gestation for women who responded the first survey was 9 weeks (IQR = 8-11 weeks), 21 weeks (IQR = 20-22 weeks) for women who responded the second survey, and 31.25 weeks (IQR = 30-32 weeks) for those who responded the third questionnaire. Responders were slightly older than non-responders (33.8 ± 4.2 vs 31.8± 5.3). Responders were more likely to have one previous live birth compared to non-responders (n=15; 42.9% vs n=8; 34.8% respectively). Responders were also more likely to have had two previous miscarriages compared to non-responders (n=8; 22.9% vs n=4; 18.2%). Half of the women who responded had private health insurance (n=16; 50.0%), compared to almost 43.5% of non-responders (n=10; Table 7.1). In the first questionnaire, the majority of women considered that their job was generally demanding or stressful (n=21; 60%; Table 7.3) and almost 69% (n=24) of women reported having a previous miscarriage in the last 12 months (Table 7.3).

Of the 58 eligible women, this study achieved a response rate of 60% (n=35) with 40% (n=23) of women choosing not to participate (Figure 7.1). Of the 23 women, six gave a reason for this, of whom all stated they did not have enough time to participate. Our retention rates for women who answered the second survey were 43% (n=15) and 51% (n=18) for the third survey respectively (Figure 7.1). A total of 34.3% (n=12) women answered all three surveys, 40% (n=14) only the first survey, 8.6% (n=3) the first and the second survey, and 17.1% (n=6) the first and the third survey (Figure 7.2). Outcome measures were recorded for 34 of the 35 women as health records of one woman could not be identified.

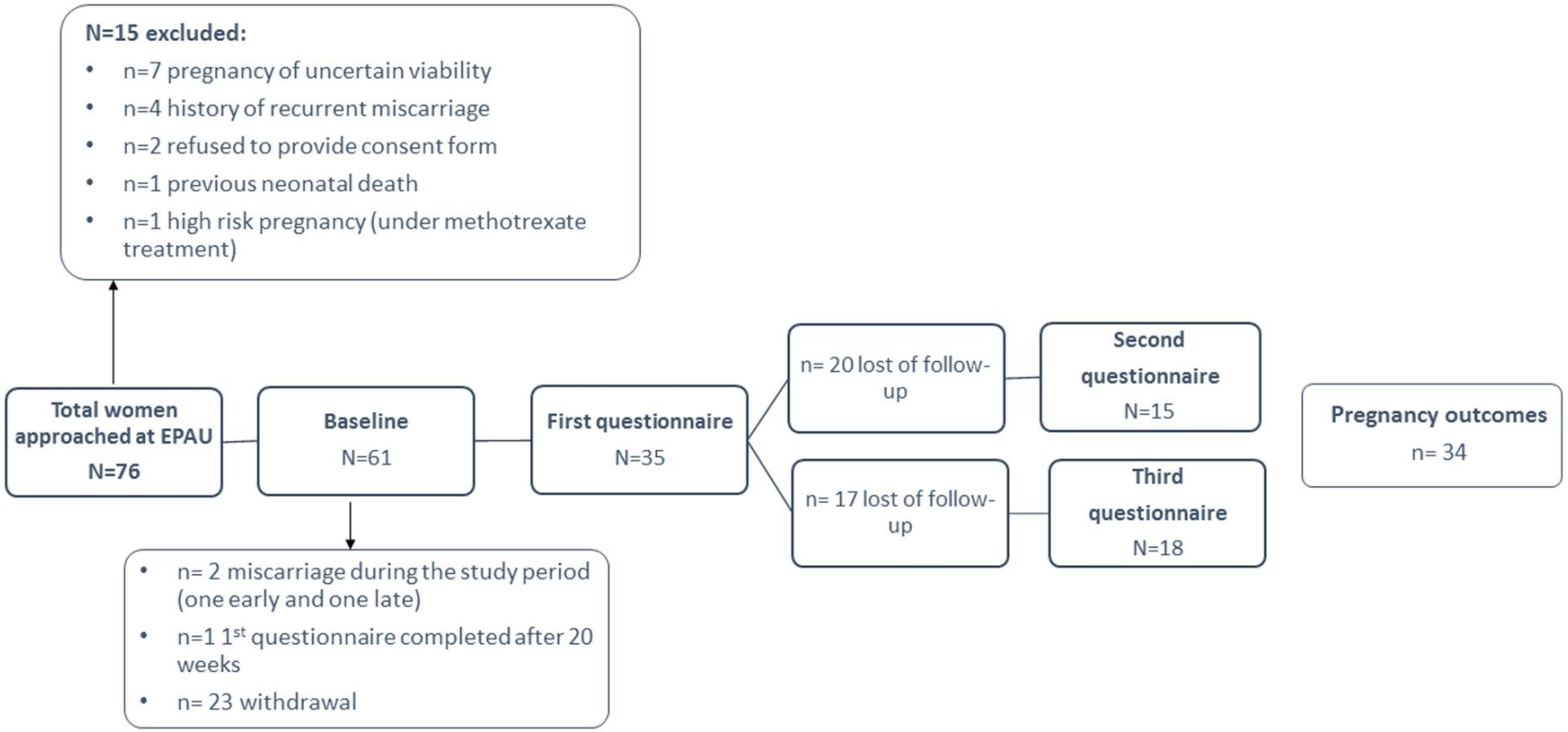


Figure 7.1. Flowchart of screening, recruitment and retention of participants in the feasibility study.

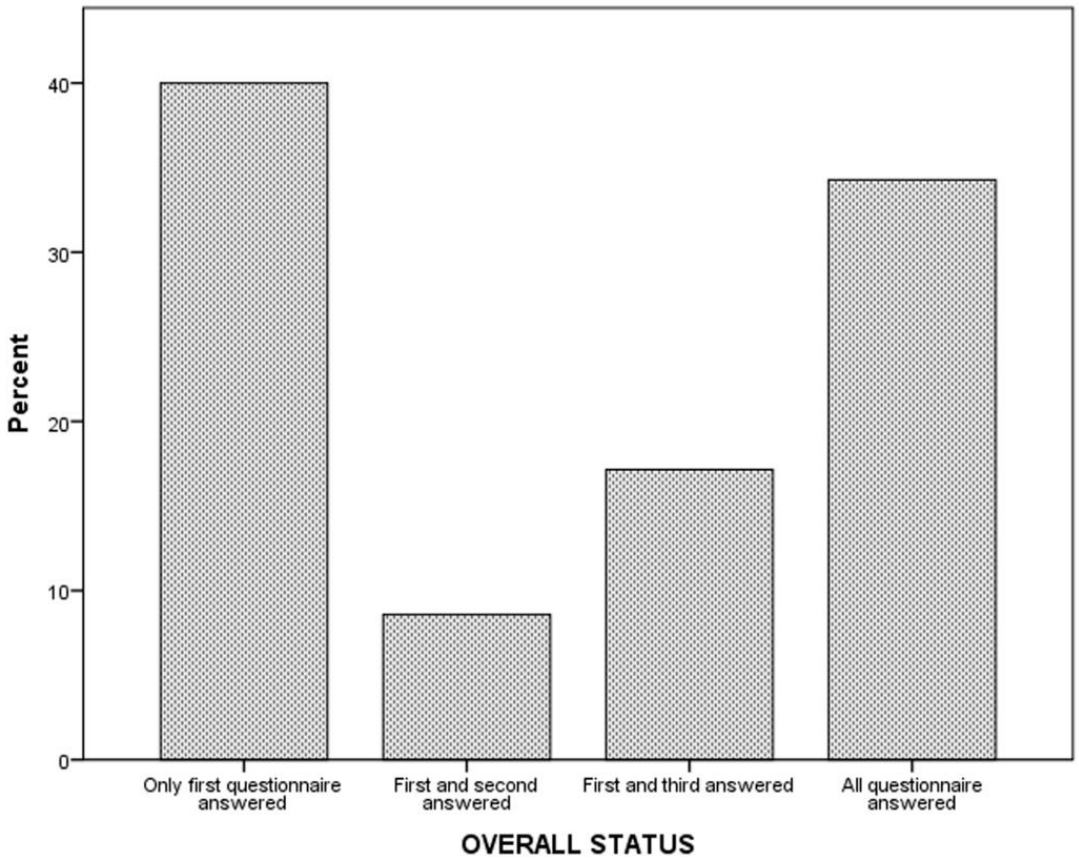


Figure 7.2. Number of questionnaires answered by participant.

The median of weeks of gestation for women who responded the first survey was 9 weeks (IQR = 8-11 weeks), 21 weeks (IQR = 20-22 weeks) for women who responded the second survey, and 31.25 weeks (IQR = 30-32 weeks) for those who responded the third questionnaire. Responders were slightly older than non-responders (33.8 SD 4.2 versus 31.8; SD 5.3; Table 7.1). Responders were more likely to have one previous live birth compared to non-responders (n=15; 42.9% versus n=8; 34.8% respectively; Table 7.1). Responders were also more likely to have had two previous miscarriages compared to non-responders (n=9, 25.7% versus n=4; 18.2%; Table 7.1). Half of the women who responded had private health insurance (n=16; 50.0%), compared to almost 43.5% of non-responders (n=10; Table 7.1). Sociodemographic characteristics are described in Table 7.2. In the first questionnaire, the majority of women considered

that their job was generally demanding or stressful (n=21; 60%; Table 7.3) and almost 69% (n=24) of women reported having a previous miscarriage in the last 12 months (Table 7.3).

Table 7.1. Differences in reproductive maternal characteristics at baseline between women who participate in the study and those who withdrawn.

	Total (n)	**Participate**	**Total (n)**	**Withdrawal**
Maternal age at this pregnancy, mean (SD; range)	35	33.8 (4.2; 25-43)	23	31.8 (5.3; 21-42)
Weeks of gestation at reassurance scan (self-reference), mean (SD; range)	33	8.2 (1.1; 6-11)	23	8.1 (1.1; 6-11)
Previous pregnancies, mean (SD; range)	35	2.1 (0.8; 1-3)	23	2.0 (0.8; 1-3)
Maternal age at first pregnancy, mean (SD; range)	33	29.2 (6.4; 16-40)	19	26.4 (6.4; 15-38)
Private insurance, n (%)	32	16 (50.0)	23	10 (43.5)
Intention to attend a private consultant during this pregnancy (Only for those women who had a private insurance), n (%)	17	6 (18.2)	10	1 (4.3)
Previous pregnancies	35		23	
Once, n (%)		11 (31.4)		7 (30.4)
Twice, n (%)		11 (31.4)		8 (34.8)
Three or more times, n (%)		13 (37.1)		8 (34.8)
Live births	35		23	
None, n (%)		13 (37.1)		8 (34.8)
One, n (%)		15 (42.9)		8 (34.8)
Two, n (%)		7 (20.0)		5 (21.7)
Three, n (%)		0 (0.0)		2 (8.7)
Previous miscarriages, n (%)	35	6 (17.1)	23	3 (13.0)
Number of previous miscarriages	35		22	
One		26 (74.3)		18 (81.8)
Two		9 (25.7)		4 (18.2)

Table 7.2. Socio-demographic and lifestyles characteristics at baseline (N=35)

Socio-demographic	**n (%)**
Irish (n=35)	27 (77.1)
Caucasian (n=34)	33 (97.1)
Current marital status(n=34)	
Married	26 (74.3)
Level of education(n=35)	
Primary/second level of education	3 (8.6)
Certificate/diploma	6 (17.1)
Degree	16 (45.7)
Postgraduate degree	9 (25.7)
Other	1 (2.9)
Employment status(n=35)	
Employed	31 (88.6)
Unemployed	1 (2.9)
Homemaker	2 (5.7)
Student	1 (2.9)
Financial status (n=33)	
Very good	14 (41.2)
Average	19 (55.9)
Below average	1 (2.9)
Smoked at least 100 cigarettes in your entire life: 5 packs or 100 cigarettes (n=34)	15 (44.1)
Currently smoker (n=15)	1 (6.7)
Last time smoking (n=14)	
- Since aware of pregnancy	1 (7.1)
- Before pregnancy	4 (28.6)
- More than 1 year ago	9 (64.3)
Alcohol consumption before getting pregnant (n=35)	
Monthly or less	14 (40.0)
2 to 4 times a month	14 (40.0)
2 to 3 times a week	7 (20.0)
Standard drinks containing alcohol in a typical day before getting pregnant (n=31)	
1 to 2 units	22 (70.0)
3 to 6 units	6 (19.3)
More than 6 units	3 (9.7)
Binge drinking (six or more drinks on one occasion) before getting pregnant (n=35)	
Never	11 (31.4)
Weekly	1 (2.9
Less than monthly	20 (57.1)
Monthly or more	4 (8.6)
Stopped drinking alcohol after being aware of pregnancy (n=25)	24 (96.0)
Missing (n=10)	

Table 7.3. Stressful life events

Stressful life events	n=35
Job generally demanding/stressful	
No, n (%)	9 (25.7)
Yes, more than 12 months ago, n (%)	5 (14.3)
Yes, in the last 12 months, n (%)	21 (60.0)
Loss of job/job insecurity	
No, n (%)	29 (82.9)
Yes, more than 12 months ago, n (%)	3 (8.6)
Yes, in the last 12 months, n (%)	3 (8.6)
Husband or partner lost their job/job insecurity	
No, n (%)	33 (94.3)
Yes, more than 12 months ago, n (%)	1 (2.9)
Yes, in the last 12 months, n (%)	1 (2.9)
Separation/divorce	
No, n (%)	32 (91.4)
Yes, more than 12 months ago, n (%)	2 (5.7)
Yes, in the last 12 months, n (%)	1 (2.9)
Serious financial problems	
No, n (%)	31 (88.6)
Yes, more than 12 months ago, n (%)	4(11.4)
Accident	
No, n (%)	35 (100)
Serious illness	
No, n (%)	35 (100)
Serious illness of someone else	
No, n (%)	25 (71.4)
Yes, more than 12 months ago, n (%)	3 (8.6)
Yes, in the last 12 months, n (%)	7 (20.0)
Death of someone close	
No, n (%)	28 (80.0)
Yes, more than 12 months ago, n (%)	3 (8.6)
Yes, in the last 12 months, n (%)	4 (11.4)
Death of child	
No, n (%)	35 (100)
Stillbirth	
No, n (%)	35 (100)
Miscarriage	
Yes, more than 12 months ago, n (%)	11 (31.4)
Yes, in the last 12 months, n (%)	24 (68.6)
Other stressful/traumatic event	
No, n (%)	28 (80.0)
Yes, more than 12 months ago, n (%)	2 (5.7)
Yes, in the last 12 months, n (%)	5 (14.3)

Table 7.4=Table 5 shows results from the multilevel linear mixed-effects regression models which estimated the mean at baseline (T1), and the mean change from baseline to each follow-up (T2 and T3). This study found an increased in mean changes for most of the scores for the psychometric scales (Table 5). Significant pre-post differences were found for state and trait anxiety (Table 7.4=Table 5). The mean change for most of the Pregnancy Experience Scale (PES) subcategories including uplifts and hassles (e.g daily positive and negative events that occurs in each person's life) increased in T2 and T3 compared to T1, except for intensity hassles (Table 7.4=Table 5). The mean change for depression during pregnancy was reduced in the T2 and T3 compared to T1, but the difference was not statistically significant. The percentage of women who reached scores of 10 or higher (eg indicating depression) decreased over the pregnancy (23% (n=7) for T1, in the 20% (n=3) for T2 and 17% (n=3) for T3 (Table 5). Mean changes for levels of stress according to the Revised Prenatal Distress Questionnaire (RPDQ) increased during pregnancy, but only the difference in the mean change for T3 was statistically significant compared to T1 (Table 7.4=Table 5).

Mean changes for physical functioning were reduced over the pregnancy (mean change and 95% CI: -19.0; -26.2 - -11.9 and -40.2; -48.7 - -31.7 for T2 and T3 compared to T1; Table 5). The mean change for the remaining subcategories for general health increased during the pregnancy, except for pain, which was reduced in T3 compared to T1 (Table 7.4=Table 5). Physical health limitation and emotional limitations were the two subcategories with the highest mean change for both T2 and T3 with statistically significant differences (mean change and 95% CI: -88.2; 70.3-106.0 and -40.2 for T2 and -48.7 - -31.7 T3; Table 7.4=Table 5). The mean changes

for the sleep quality dimensions slightly increased over pregnancy, except for sleep latency in T2, and day dysfunction due to sleepiness in T3. Significant pre-post differences were found for most of the sleep quality dimensions for T3, and for sleep latency in T2, with the exception of day dysfunction due to sleepiness which was not found to be significant in any time compared to T1(Table 7.4=Table 5).

All the women who participated in the study had a live birth (n=34; 100%; Table 6). Approximately 40% (n=14) of women had a normal weight (body mass index (BMI); 18.5 to 24.9 kg/m2) and 40% (n=14) were overweight (BMI 25.0 to 29.9 kg/m2) (Table 6). All women except one had a term baby, and 94% (n=32) of infants had a normal weight of 2500 grammes or higher [346] (Supplementary Table 7.3=Table 6).

Table 7.4. Psychological factors and general health

	Estimate T1 mean (95% CI)	**Change at T2 mean (95% CI)**	**Change at T3 mean (95% CI)**
PSS-10	14.4 (12.4-16.4)	+0.2 (-2.6; 3.0)	+0.1 (-2.5; 2.7)
STAIT			
- STATE anxiety	34.6 (30.9-38.3)	-14.7* (-18.7; -10.7)	-12.8* (-17.2; -8.4)
- TRAIT anxiety	31.9 (28.9-34.9)	-14.6 (-17.9; -11.3)	-9.5* (-12.9; -6.0)
EPDS	7.1 (4.8-9.4)	-0.2 (-2.5; 2.1)	-0.9 (-3.7; 1.7)
- Depression (10 or more), n (%)	7/30 (23.3)	3/15 (20.0)	3/18 (16.7)
PES	25.9 (23.2-28.6)	+6.4* (3.4; 9.4)	+8.0* (5.2; 10.8)
- Frequency uplifts	8.5 (7.8-9.2)	+3.2* (2.1; 4.2)	+3.4* (2.3; 4.4)
- Frequency hassles	6.7 (5.6-7.7	+1.7* (0.9; 2.6)	+1.9* (1.0; 2.8)
- Intensity uplifts	3.1 (2.8-3.3)	-0.3* (-0.7; -0.0)	-0.26* (-0.6; 0.1)
- Intensity hassles	4.5 (3.8-5.3)	+0.3 (-0. ; 1.1)	+0.03 (-0.7; 0.8)
RPDQ	7.6 (6.1-9.0)	+0.5 (-0.8; 1.7)	+1.3* (0.1; 2.5)
SF-36			
- Physical functioning	61.9 (54.0-69.8)	-19.0* (-26.2; -11.9)	-40.2* (-48.7; -31.7)
- Physical health limitation	69.3 (54.4-84.2)	+88.2* (70.3; 106.0)	+54.9* (36.6; 73.2)
- Emotional limitations	83.8 (71.9-95.7)	+60.0* (38.0; 81.9)	+50.2* (28.9; 71.5)
- Energy & fatigue	39.1(39.1-46.4)	+9.1* (1.5; 16.8)	+5.8 (-2.1; 13.7)
- Emotional wellbeing	74.8 (68.0-81.7)	+8.6 (-0.4; 17.6)	+1.0 (-8.4; 10.4)
- Social functioning	77.9 (69.5-86.2)	+13.3* (1.9; 4.7	+11.7* (0.8; 22.6)
- Pain	75.2 (68.2-82.2)	+0.5 (-8.9; 9.8)	-13.9* (-23.9; -4.0)
- General health	75.6 (70.6-80.5)	+0.1 (0.0; 0.7)	**
Sleep quality dimensions			
- Duration of sleep	0.7 (0.4-1.1)	+0.3 (-0.2; 0.7)	+0.5* (0.1; 0.9)
- Sleep disturbance	1.6 (1.4-1.8)	+0.1 (-0.2; 0.3)	+0.3* (0.1; 0.6)
- Sleep latency	1.1 (0.9-1.4)	-0.3* (-0.6; -0.008)	+0.1 (-0.3; 0.4)
- Day dysfunction due to sleepiness	1.1 (0.9-1.3)	+0.1 (-0.2; 0.4)	- 0.1 (-0.3; 0.2)
- Sleep efficiency	1.4 (1.1-1.7)	+0.1 (-0.4; 0.6)	+0.5* (0.1; 0.9)
- Sleep quality	1.2 (1.0-1.5)	+0.1 (-0.3; 0.4)	+0.5* (0.2; 0.9)
Total Sleep quality scores according to PSQI	0.7 (0.6-0.9)	-0.1 (-1.3; 1.2)	+1.6* (0.2; 2.9)
Good sleep quality (<=5), n (%)	18 (51.4)	5 (35.7)	4 (25.0)

Poor sleep quality (>5), n (%)	17 (48.6)	9 (64.3)	12 (75.0)

Note: *Missing data did not allow the calculation of the average; PSS-10: Perceived Stress Scale of 10 items; STAI: The State-Trait Anxiety Inventory; EPDS: Edinburgh Postnatal Depression Scale; PES: Pregnancy Experience Scale; RPDQ: Revised Prenatal Distress Questionnaire; PSQI: Pittsburgh Sleep Quality Index

7.6 Discussion

This feasibility prospective study provides preliminary data on mean changes on the psychological and general health outcomes during the three trimesters of a subsequent pregnancy for women who have a history of miscarriage. One of the main strengths of this study is that our preliminary quantitative data could be used to generate information for sample size calculations. Also, validated questionnaires were implemented and they were repeated three times during pregnancy. This study managed to obtain a response rate of 60% in the first questionnaire (eg hardcopy). However, our retention rates dropped when using an online questionnaire in the second and third trimester follow-up surveys (i.e. 43% and 51% respectively). This feasibility study found an increased in mean changes for most of the scores for the psychometric scales, except for state and trait anxiety, intensity uplifts and physical functioning. Significant pre-post differences were found for state and trait anxiety, and most of the PES and general health subcategories, except for intensity hassles and pain respectively. The mean changes for the sleep quality dimensions slightly increased over pregnancy, except for sleep latency and day dysfunction due to sleepiness.

Moreover, this study included other potential factors that might influence pregnancy such as general health assessment and quality of sleep. This study found that quality of sleep worsened over pregnancy and, we noted that a number of factors including stress and anxiety peaked in the second trimester and this is worth exploring further. Our preliminary findings may be helpful when planning and designing the collection of similar outcomes, but could potentially be compared to definitive evidence from large-scale cohort studies in the future. In addition, this study discusses potential

factors to recruit pregnant women in cohort studies, and it proposes alternatives to increase the response and retention rate for future study designs.

A motivated health workforce is essential for the screening and recruitment of potential participants in cohort studies[347]. Building a research community of recruiters and providing appropriate training have been pointed out as effective strategies to increase recruitment rates[348] However, there is limited evidence on health professionals' views and reasons to collaborate in research studies[349],[348]. Screening and recruitment of the potential participants were carried by the sonographers, midwives and by the research nurse at the interview. A list of inclusion and exclusion criteria were explained when provided to the ultrasound midwives who agreed to recruit for the study. However, this study found that a reasonable amount of women who chose to participate in our study had to be excluded from our study after confirming these women were ineligible. Therefore, it suggests that it is important to identify a team of midwives who are willing to collaborate as recruiters in advance of the study and to arrange several meetings with them over the course of the study, giving the team the opportunity to provide research updates and reminders[348] which should build a sense of a workforce and improve recruitment protocols.

Another potential factor that may have influenced our recruitment rate was that collaboration of ultrasound midwives was voluntary. Therefore, midwives gave their own working time and effort to screen potential participants without any incentive. This may have effected recruitment during busy times at the clinic, when potential participants might not be screened because they forgot to ask or because they were

aware of the length of time that it would take to explain the research[348]. Future, large-scale prospective studies should consider applying recruitment strategies such as providing incentives for recruiters. In addition, it might be important to have access to the participants' electronic health information in order to confirm past reproductive history or medical complications at the time of the screening.

Historically, pregnant women have been excluded from longitudinal research studies and clinical trials because of the potential risk of harming the fetus or the mother[350]. Although the need to include pregnant women in research studies is increasingly recognised, the ethical concerns and normative considerations are still being discussed[351],[352]. It is well-established that the underrepresentation of pregnant women in research studies impact the recruitment and retention rates[351]. In concordance with previous cohort designs that included pregnant women[353],[354],[355],[356], our study had a low recruitment and retention rate. Lack of time to commit was one reason why women declined to participate in cohort studies[353], and it was the main reason why women declined to participate in our study. This study initially hypothesised that using online questionnaires would have helped to facilitate commitment when participating in our study; however, our highest response rate was obtained at the interview stage (eg early in pregnancy), with a drop of retention rates when on-line questionnaires were provided. As pointed out by other studies, face-to-face interviews might be the best approach to collect information when including pregnant women in cohort studies[355]. In addition, it might be more efficient to approach women while they are attending the hospital or clinic appointments in order to follow-up over the course of the pregnancy. However, the low initial response rate indicates that other means of data collection may be needed to be considered in further longitudinal studies.

7.7 Conclusion

Pregnant women are traditionally excluded from research studies because of the potential harm for the mother and the fetus. This underrepresentation in clinical and longitudinal studies have limited the knowledge of recruitment and retention strategies among this target group. This feasibility study provides important information on potential factors to screen, recruit and retain pregnant women in cohort or longitudinal studies; as well as preliminary evidence about changes on psychological and general health factors over pregnancy among women with a history of miscarriage.

7.8 Implications for practice, policy and research

Implications for practice

- There is growing interest to obtain robust and high quality evidence about the potential effects of psychological wellbeing and lifestyle factors on subsequent pregnancies after miscarriage in order to be able to counsel clinical advice, generate clinical guidelines and provide appropriate interventions and care for this targeted group of women

Implications for policy

- There is a need to promote funding for cohort studies which aims to increase the limited evidence on psychological and lifestyle burden among women who experience pregnancy loss

Implications for research

- This feasibility study provides preliminary quantitative data on changes of psychological and general health scores over the three trimesters of pregnancy among women with a history of miscarriage
- The findings of this feasibility study could be helpful when designing cohort studies with similar outcomes, which will meet future pregnant women's needs
- There is a need to implement a study Within A Trial (SWAT) methodology in order to assess barriers and facilitators to recruit pregnant women who experience pregnancy loss and who participate in cohort studies

7.9 Supplementary Tables

Supplementary Table 7.1. Schedule of data collection during pregnancy and after delivery.

	Recruitment	***Trimester of pregnancy***			***Postnatal***
TIMEPOINT**	***0 (baseline)***	***T_1***	***T_2***	***T_3***	***T_5***
Weeks of gestation	***<12***	***12***	***20***	***30***	
RECRUITMENT:					
Eligibility screen	✓				
Informed consent	✓				
DATA COLLECTION:					
Baseline Questionnaire	✓				
Main Survey		✓	✓	✓	
Blood pressure from medical chart		✓	✓	✓	
Pregnancy Outcomes					✓

Supplementary Table 7.2. Questionnaires and psychometric scales

SECTIONS	SURVEYS
First: Baseline Characteristics	• Socio-demographic questionnaire
SECOND: Lifestyle behaviours	• Smoking behaviours • Alcohol consumption behaviour were assessed using the AUDIT-C questionnaire[345].
THIRD: Wellbeing and mental health questionnaires	• Levels of perceived stress using The Perceived Stress Scale (PSS-10) [284] and the Revised Prenatal Distress Questionnaire (RPDQ) [357]. • Levels of anxiety will be measured using The State-trait Anxiety Inventory (STAI) [358]. • Levels of depression The Edinburgh Postnatal Depression Scale (EPDS)[359]. • Stressful events during pregnancy were measured using Pregnancy Experience Scale[360].
FOUR: General health and quality of sleep	• General health was assessed using The 36-Item Short form Survey Instrument (SF-36) [361]. • The quality of sleep will be measured using The Pittsburgh Sleep Quality Index[362].

Supplementary Table 7.3. Cronbach's alpha and summary of main scores of questionnaires

Cronbach's alpha (items)	**Scores and meaning**	
Time1: 0.82 Time2: 0.85 Time3: 0.81	Levels of perceived stress were measured using The Perceived Stress Scale (PSS-10) [284]. PSS-10 is a 10 item scale. Each item is rated on a 5-point scale ranging from never (0) to almost always (4). Items 4, 5, 7 & 8 were reverse scored because there were positively worded items. The total ratings are summed with higher scores indicating more perceived stress.	
	Levels of anxiety were measured using The State-trait Anxiety Inventory (STAI) [358]. The STAI is a 40 items scale. Each item is rated on a 4-point Likert scale, ranging from 20 to 80 with higher scores positively correlated with higher levels of anxiety. A total of 20 items are focused in state anxiety (s-anxiety), which is defined as anxiety about an event, and 20 items are focused on trait anxiety (t-anxiety) or anxiety level as a personal characteristics).	
	S-Anxiety: Time1: 0.50 Time2:0.88 Time3:0.95	T-Anxiety: Time1:0.50 Time2:** Time3:0.93
Time1:0.76 Time2:0.97 Time3:0.97	Levels of depression were measured using The Edinburgh Postnatal Depression Scale (EPDS)[359]. The EPDS is a 10 items scale. The 7 negative items are scores from 0 "no, never" to 1 "yes, most of the time. Positive items are reversed. Maximum score is 30 and a higher scores means higher possibilities of having depression. A score of 10 or more is equal to depression.	
Time1: 0.81 Time2:0.80 Time3:0.80	Stressful events were measured using the Pregnancy Experience Scale (PES)[360]. The PES is a 20 items scale including 10 most frequent uplifts and 10 most frequent hassles. Each item is rated from 0 (not at all) to 3 (a great deal). Scoring yields 4 scores: the frequency of hassles and the frequency of uplifts were calculated by counting the number of items that are endorsed with values greater than 0; the intensity of hassles and the intensity of uplifts were calculated as the sum of scale scores (1-3) divided by hassles or uplifts frequency.	
Time1:0.82 Time2:0.84 Time3: 0.74	Levels of perceived stress specific for pregnancy were measured using the Revised Prenatal Distress Questionnaire (RPDQ) [357]. RPDQ is a 17 items scale with 3-point response category (i.e. n=0 not at all; n=1 somewhat; and n=2 very much). Responses are summed up to create a total score, ranging from 0 to 37.	
	General health was assessed using The 36-Item Short-form Survey Instrument (SF-36) [361]. The RAND SF-36 is a 36 items scale. Each item is rated between 1 and 6 and they are scores from 0 (maximum disability) to 100 (no disability). Subgroups of items create a total of 8 health concepts: Physical functioning, Physical health limitation, Emotional limitations, Energy & fatigue, Emotional wellbeing, Social functioning, Pain and General health. Total scores for each health	

	concept is calculated by summing up the scores for each item. The lower the score the more disability.	
	Physical functioning (10 items)	Time 1: .073 Time2:0.75 Time3:0.87
	Physical health limitation (4 items)	Time 1:0.93 Time2: ** Time3:0.83
	Emotional limitations (3 items)	Time 1: 0.99 Time2:** Time3:0.86
	Energy & fatigue (4 items)	Time 1: 0.72 Time2: 0.92 Time3:0.89
	Emotional wellbeing (5 items)	Time 1:0.79 Time2: 0.84 Time3:0.93
	Social functioning (2items)	Time 1: 0.70 Time2: 0.88 Time3:0.81
	Pain (2 items)	Time 1:0.67 Time2:0.50 Time3:0.87
	General health (5 items)	Time 1: 0.52 Time2: 0.58 Time3:0.64
Time1:0.77 Time2:0.78 Time3:0.76	Quality of sleep was measured using The Pittsburgh Sleep Quality Index (PSQI)[362]. The PSQI is a 13 items scale. The first 4 items are times of sleep measured in hh:mm, minutes or hours. They will be used to calculate the duration of sleep and the sleep efficiency. Items 5 through 10 are all 0 (never) to 3 (fairly often). Subgroups of items create 7 sleep groups: sleep disturbance, sleep latency, day dysfunction due to sleepiness, overall sleep quality according to the participant, need of medications to sleep, and total quality of sleep according to PSQI. Total scores of quality of sleep varied from 0 (better) to 21 (worse) Total scores range from 0 (better) to 3 (worse). Scores of 5 or less than 5 are associated with good sleep quality versus higher than 5 which are associated with poor sleep quality.	

Note: PSS-10: Perceived Stress Scale of 10 items; STAI: The State-Trait Anxiety Inventory; EPDS: Edinburgh Postnatal Depression Scale; PES: Pregnancy Experience Scale; RPDQ: Revised Prenatal Distress Questionnaire; PSQI: Pittsburgh Sleep Quality Index (PSQI). **Missing data did not allowed to calculate reliability at this time.

Supplementary Table 7.4. Outcomes at delivery **(N=34)***

	n (%)
Pregnancy outcome	
Live birth and singleton	n=34 (100)*
BMI (n=33)	
Underweight (<18.5 kg/m2)	1 (3.0)
Normal weight (18.5-24.9 kg/m2)	14 (42.4)
Pre-obesity (25.0-29.9 kg/m2)	14 (42.4)
Obesity (>30.0 kg/m2)	4 (12.1)
Preterm babies, n=32	
At term (>= 37 weeks)	32 (97.0)
Moderate to late preterm (32 to <37 weeks)	1 (3.0)
Blood Pressure (BP), n=34	
Systolic BP at 12 weeks, mean (SD)	117.2 (11.7)
Diastolic BP at 12 weeks, mean (SD)	72.1 (7.7)
Systolic BP at 20 weeks, mean (SD)**	121.2 (13.6)
Diastolic BP at 20 weeks, mean (SD)**	73.7 (9.5)
Systolic BP at 30 weeks, mean (SD)	118.3 (13.1)
Diastolic BP at 30 weeks, mean (SD)	71.9 (13.1)
Birth weight, n=34	
Normal weight at birth (>=2500 grammes)	32 (94.1)
Low birth weight (<2500 grammes)	2 (5.9)
Male weight, mean (range; SD)	3800.7 (2890-4780; 530)
Female weight, mean (range; SD)	3537.8 (2420-4860; 567.9)

Note: *One case was missing was missing for all the outcomes; ** Information for two cases missing

Chapter VIII

Psychological and support interventions to reduce levels of stress, anxiety or depression on women's subsequent pregnancy with a history of miscarriage: an empty systematic review.

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8.1 Abstract

Objective. The aim of this systematic review was to assess the effect of interventions to reduce stress in pregnant women with a history of miscarriage. **Design**. A systematic review of randomised controlled trials (RCTs). **Data source**. A total of 13 medical, psychological and social electronic databases were searched from January 1995 to April 2016 including PUBMED, CENTRAL, Web of Science and EMBASE. **Eligibility criteria**. This review focused on women in their subsequent pregnancy following miscarriage. All published RCTs which assessed the effect of non-medical interventions such as counselling or support interventions on psychological and mental health outcomes such as stress, anxiety or depression when compared to a control group were included. Stress, anxiety or depression had to be measured at least pre- and post-intervention. **Results.** This systematic review found no RCT which met our initial inclusion criteria. Of the 4140 titles screened, 17 RCTs were identified. All of them were excluded. One RCT, which implemented a caring-based intervention, included pregnant women in their subsequent pregnancy; however, miscarriage was analysed as a composite variable among other pregnancy losses such as stillbirth and neonatal death. Levels of perceived stress was measured by four RCTs. Different types of non-medical interventions, time of follow-up and small sample sizes were found. **Conclusion.** Cohort studies and RCTs in non-pregnant women suggest that support and psychological interventions may improve pregnant women's psychological well-being after miscarriage. This improvement may reduce adverse pregnancy-related outcomes in subsequent pregnancies. However, this review found no RCTs which met our criteria. There is a need for targeted RCTs that can provide reliable and conclusive results to determine effective interventions for this vulnerable group.

Keywords: systematic review, empty review, RCTs, miscarriage, pregnancy loss, stress, anxiety, depression, non-medical interventions.

8.2 Article summary

Strengths and limitations of this study.

- To our knowledge, this is the first attempt to systematically look at the psychological effect of non-pharmacological interventions on pregnant women with a history of miscarriage.
- This systematic review increases the awareness of the "evidence gap" in this vulnerable group.
- It also highlights the clinical importance of including pregnant women in randomised controlled trials and proposes reasons why different types of pregnancy loss should be investigated separately.
- However, this review was limited by the unexpected result and no further analysis were able to be completed.

8.3 Introduction

Recent studies have focused on the effect of women's psychological wellbeing during pregnancy and its effects on the mother and infant[185,363,364]. Women are highly reactive to stress in early pregnancy[150]. Approximately 25% of women report emotional distress during the antenatal period[365]. Given the importance of maternal psychological wellbeing for predicting outcomes, it is necessary to effectively examine appropriate interventions to reduce stress in pregnancy[366].Very recently, the UK National Institute for Clinical Excellence called for randomised controlled trials

(RCTs) to evaluate interventions aimed at tackling moderate to severe psychological disorders in the pregnant population[366].

Studies on stress during pregnancy have established that psychological stress might be associated with an increased risk of a number of adverse pregnancy outcomes, such as preterm labour and low birth weight[185,186,340,357]. Change in pregnancy-specific stress between the second and third trimester has been significantly associated with an increased likelihood of preterm deliveries[340,367,368] and with implications for fetal development[279,369]. These outcomes are among the leading causes of infant mortality and health problems which may persist not just into childhood but throughout their adult lives[357].

Miscarriage is one of the most common complications during early pregnancy[17,201]. It is estimated that miscarriage occurs in 20% of all clinically recognised pregnancies[4,5] and up to half of all pregnancies[370]. Experience of miscarriage may alter women's psychological and mental health and wellbeing[366,371]. Miscarriage has been associated with increased levels of distress[213,372], anxiety, and depression[212,373-379]. In some cases, the psychological symptoms of anxiety and depression can persist for up to 1 year after miscarriage[212,216-219]. In addition, it is increasingly recognised that the adverse psychological and mental health consequences of previous miscarriage continue not only after the loss, but also into subsequent pregnancies[199,224,373]. Some examples of the evidence found in the literature included higher levels of psychological distress[344,380-383], pregnancy-specific anxiety[299,381,384-386] and depressive symptoms[341,386].

However, few studies have evaluated the beneficial effect of psychological and supportive care in pregnant women who have had miscarriage and who are in their subsequent pregnancy. In a cohort study, Clifford et al. (1997) found that pregnant women who followed a specific antenatal counselling support plan had a significantly higher pregnancy success rate than those who did not participate[387]. Similar results were found in two other cohort studies carried out with women who experienced recurrent miscarriage[388,389], which is defined as three or more consecutive pregnancy losses[21]. These studies indicate the potential importance of providing support for women in a subsequent pregnancy following miscarriage[202,372].Therefore, the aim of this systematic review was to examine the literature to explore the effect of psychological and support interventions to reduce levels of stress among pregnant women who have a history of miscarriage.

8.4 Methods

The Cochrane Handbook for Systematic Reviews of Interventions[390], the Cochrane Consumers and Communication Review group for data synthesis and analysis[391] and The Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guideline[392] were adhered to for conducting and reporting this systematic review [Appendix 1]. This systematic review has not been registered in the international prospective register of systematic reviews (PROSPERO) database.

8.4.1 Eligibility criteria

Criteria for considering studies for this systematic review were:

Type of studies. All published randomized controlled trials (RCT), including cluster RCT, were systematically searched in this review. Controlled (non-randomized)

clinical trials, prospective and retrospective cohort studies, case-control or nested case control studies, cross-sectional studies, case series and case reports were excluded.

Types of participants. Women in a subsequent pregnancy with a history of miscarriage. Miscarriage was defined as a spontaneous loss of pregnancy from the time of conception until 24 weeks of gestation[15].

Types of interventions. All types of non-pharmacological interventions such as psychological, emotional, information or support group interventions, either alone or in combination with another control intervention; for example, standard care or other type of intervention.

Outcomes. Trials reporting quantitative outcome data were included. The primary outcome was levels of perceived stress which was defined as "the feelings or thoughts that an individual has about how much stress they are under at a given point in time or over a given time period"[393]. The secondary outcomes were: (1) levels of cortisol which was measured in saliva, urine, blood or hair; (2) levels of perceived anxiety which was defined as "the stable tendency to attend to, experience, and report negative emotions such as fears, worries, and anxiety across many situations"[393] and (3) levels of perceived depression which was defined as a "depressed or sad mood, diminished interest in activities which used to be pleasurable, weight gain or loss, psychomotor agitation or retardation, fatigue, inappropriate guilt, difficulties concentrating, as well as recurrent thoughts of death"[394]. Secondary outcomes had to also be measured pre- and post-intervention.

8.4.2 Information sources and search

A total of 13 medical, psychological and social electronic bibliographic databases were searched: PubMed, Cochrane Library, CENTRAL, EMBASE, Web of Science (Web of Knowledge), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Maternity & Infant Care Database, Science Direct, Elton B. Stephens Co (EBSCOhost), ProQuest Nursing and Allied Health Source, CLINICAL TRIALS, Journal Storage (JSTOR) and Clinical trials websites. The reference lists of potential studies were also screened to identify other relevant studies. Keywords and Medical Subject Headings (MeSH) were used to identify studies related to miscarriage and stress [Appendix 2]. The date of the last search was the 2nd of April of 2016. There were no restrictions by study design, setting, and country. All studies in English language were included. The literature search was limited by date (from January 1995 to April 2016).

8.4.3 Study selection

Search results were screened by two reviewers (ISLC, KM), first by titles and then by abstracts. Discrepancies were resolved with other reviewers (SM, KOD). Eligibility criteria of all potential studies were assessed using the "Data collection form for intervention reviews: RCTs only from April 2014" (by ISLC)[390] [Appendix 3]. Due to the variability in definitions of the condition, studies were included where the following terms appeared in their titles : *"miscarriage", "pregnancy loss", "perinatal loss", "spontaneous abortions", "early miscarriage"* and *"first trimester miscarriage".* They were excluded when the following terms appeared *"stillbirth", "recurrent miscarriage", "fetal death", "infertility", "subfertility", "VF",* "*perinatal death*", *"missed abortion", "induced abortion", "ectopic pregnancy", "pregnancy*

wastage, "oxidative stress", "antioxidants" and "Intimate partner violence". Recurrent miscarriage was excluded because of the differences in the aetiology, diagnosis and therapy between other types of losses[395,396]. No study was excluded for not identifying the outcome of interest in either title or abstract[397].

ENDNOTE X7 was the reference management software utilised to import, classify and analyse all citations in this systematic review. All citations from each database were automatically imported to ENDNOTE and then saved by electronic database and date of searching. Abstracts were also imported when they were available. Data collection was completed by one reviewer using data extraction forms and a second reviewer (SM) independently checked content. Definitions of the condition were obtained from abstracts or reading full reports of the studies. When miscarriage was analysed as a composite with other adverse pregnancy outcomes such as stillbirth or perinatal death, contact with the authors was made by email to try to obtain subsamples of the full datasets. Data extraction forms by the Cochrane Consumers and Communication Review Group[398] were used to describe main characteristics, methodology and main results (Appendix 4). A summary of the outcomes and the measurement of each outcome was assessed using the outcome matrix of the "Outcome Reporting Bias of Trial" (ORBIT)[397] (Appendix 5). Risk of bias was assessed using the "Assessment of Risk of Bias" by the Cochrane Bias Methods Group[399] (Appendix 6).

8.5 Results

A total of 4140 citations were identified through database searches and 8 were identified through other sources. After duplicates were removed, 3325 citations were identified during the screening process (see Figure 8.1).

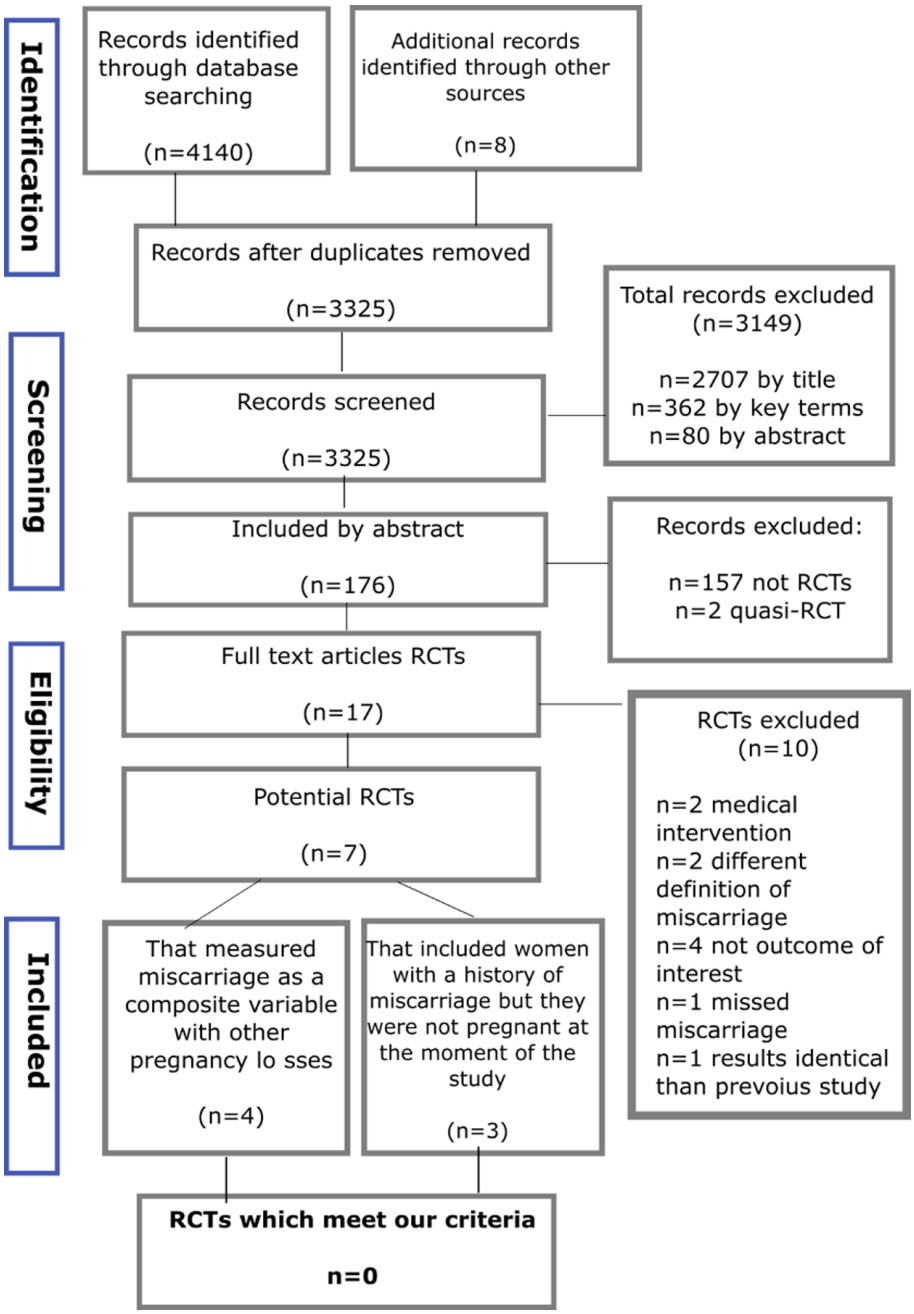


Figure 8.1. Flow diagram of the selection of the studies.

A total of 17 RCTs and 2 Clinical Controlled Trials (CCTs) were found in this review. This systematic review found no RCT which met all the inclusion criteria. Of the 17 RCTs, 10 were excluded for a variety of reasons including: no outcome of interest, medical intervention instead of non-medical interventions or pregnancy loss defined as a loss later than 24 weeks (See table 8.1).

Even though a number of studies (n=7) carried out non-pharmacological interventions to reduce levels of stress, anxiety or depression in women who have had miscarriage, those were excluded from the systematic review because women were not pregnant at the time of the study or because miscarriage was analysed as a composite variable including other types of perinatal loss such a stillbirth or neonatal death (See table 8.1). Furthermore, even though it was part of our initial objectives, this review did not find evidence of any RCTs that measured biomarkers of stress, such as cortisol, to assess the effect of psychological interventions in this population. As a consequence, no results were included in this systematic review.

Although none of the remaining RCTs met the full inclusion criteria (n=7) (See table 8.1), they have useful information for health professionals who are working in the area of pregnancy loss. In summary, only one RCT studied women while they were pregnant[400], but miscarriage was analysed as a composite variable with neonatal death. More than half of the RCTs identified were pilot or feasibility studies[400-403], and had a small sample size with low statistical power.

Table 8.1 List of all randomised controlled trials and clinical controlled trials (n=19) and reason for exclusion.

	Author, year	Pregnant* Yes	Pregnant* No	All RCTs and CCTs studies Reason for exclusion
CCTs (n=2)				
1.	Klein, 2012[96]		✓	Partially randomised patient design
2.	Sejourne, 2011[97]		✓	Quasi-randomised controlled trial
RCTs (n=10)				
1.	Adolfsson, 2006[98]		✓	No outcome of interest included
2.	Huffman, 2015[99]		✓	No outcome of interest included
3.	Lok IH, 2006[100]		✓	Results are identical than Kong, 2014
4.	Klinitzke, 2013[101]		✓	No outcome of interest included
5.	Kong, 2013[102]		✓	Medical intervention
6.	Lee, 2001[103]		✓	Medical intervention
7.	Neugebauer, 2007[104]		✓	Pregnancy loss later than 24 weeks
8.	Neugebauer, 2006[105]		✓	Pregnancy loss later than 24 weeks
9.	Nikcevic, 2007[106]		✓	Missed miscarriage
10.	Swanson, 1999[27]		✓	No outcome of interest included
RCTs (n=7)				
1.	**Côté-Arsenault, 2014[62]**	✓		**Pregnancy loss as a composite variable**
2.	**Johnson, 2016[63]**		✓	**Pregnancy loss as a composite variable**
3.	**Kersting, 2013[66]**		✓	**Pregnancy loss as a composite variable**
4.	**Kersting, 2011[65]**		✓	**Pregnancy loss as a composite variable**
5.	**Kong, 2014[107]**		✓	**Not pregnant at the time of the study**
6.	**Lee, 1996[64]**		✓	**Not pregnant at the time of the study**
7.	**Swanson, 2009[28]**		✓	**Not pregnant at the time of the study**

*Subsequent pregnancy after miscarriage. Not including pregnancy which resulted in miscarriage.

The most frequently measured outcomes were depression, anxiety, stress and grief (Appendix 5). Levels of perceived stress were measured by four RCTs[401-404]. Results

of the RCTs varied, with some suggesting a positive reduction in levels of stress and depression when women took part in psychological interventions compared to a control group (Appendix 4). Other studies found no change or did not reach statistically significant results on psychological outcomes (Appendix 4). Supporting files describing main characteristics, outcome matrix and risk of bias of those relevant seven RCTs can be found online (Appendix 4, 5 and 6). These supportive materials might help clinicians, researchers and decision-makers to increase the awareness of the available supportive interventions in the area of pregnancy loss, as well as the lack of evidence or methodological quality in these type of studies.

8.6 Discussion

The aim of this review was to systematically assess the effect of non-pharmacological interventions to reduce levels of stress in pregnant women who have had a miscarriage in their previous pregnancy. Unfortunately, no RCT met our inclusion criteria. The results of this review were unexpected given that firstly, several studies have previously reported the psychological impact on pregnant women with a history of miscarriage[385,405,406]; and secondly because relevant institutions and organisations in the area of clinical health practice have reported the need of good-quality, adequately powered randomised controlled trials (RCTs) to evaluate interventions aimed at tackling moderate to severe psychological disorders in the pregnant population[366,407].

8.6.1 Comparison with other studies

There is an agreement in the literature that women who miscarry may suffer from psychological morbidities after pregnancy loss and in a subsequent pregnancy[205,208,408]. However, there are important limitations when summarising this

evidence such as a lack of a comparison group within these studies or the overlapping of depression and anxiety symptoms and disorders[205]. Furthermore, levels of stress were not assessed in women following miscarriage or in subsequent pregnancy in any of the reviews identified[205,208,376].

According to the most recent Cochrane systematic review, which assessed the effectiveness of non-pharmacological interventions on women with a history of miscarriage, only six randomized controlled studies assessed the effect of psychological well-being interventions in women who experienced miscarriage[226]. None of them were carried out in women who were pregnant at the time of the study. These studies were also limited by a lack of power, unclear blinding or no blinding, heterogeneity between types of psychological follow-up and small sample size. Murphy et al. (2012) concluded that not enough evidence was achieved to state if psychological interventions were beneficial for women who miscarry[226].

8.6.2 Limitations of the study

As with other type of studies, this review is not free of limitations. Firstly, only one RCT included pregnant women despite previous pilot RCTs assessing non-pharmacological interventions to reduce levels of stress, anxiety and depression had included pregnant women as their target population[409-411]. Historically, pregnant women have been excluded from clinical research due to potential ethical considerations such as (1) they are classified as a vulnerable group, (2) the possible risk of harming the fetus or (3) the complicated physiology during pregnancy[412].

Several efforts have been made to encourage researchers and clinicians to challenge these limitations and to include pregnant women in clinical research[413]. The basic principles in ethical foundation for including pregnant women in clinical research are: (1) the need for evidence-based knowledge of effective treatments during pregnancy; (2) the uncertain risk of not treating or under treating a mother's condition; and (3) the ethical justification of the possible benefits of participating in research[413]. As Macklin (2010) stated "the next logical-and ethical-step is the enrolment and retention of pregnant women in clinical trials"[354].

Another limitation identified when undertaking this review was the different definitions of miscarriage found in the literature during the selection process. Definitions of miscarriage vary significantly between countries, professional bodies and clinical guidelines[12]. This variety of definitions made it difficult to compare and to evaluate the evidence between different countries in this field[12].

As important as the lack of an international concordance between definitions, this review found that some RCTs pooled together the results from miscarriage with other types of perinatal death such as stillbirth or neonatal death. One of the possible limitations is that, as per protocol (Appendix 7), interventions carried out among women with recurrent miscarriage and/or perinatal death, or as composite variables, were excluded in the screening process. It is reported that pregnancy loss and perinatal death have shown different psychological reactions to the loss[225,414,415]. Moreover, the impact that a specific intervention might have on psychological wellbeing may differ as women are managed differently in a subsequent pregnancy depending on the type of pregnancy loss they have experienced[10,11]. For instance, more resources are invested

in women with recurrent miscarriage[197], and supportive care is regularly offered to women with unexplained recurrent miscarriage[389,416,417]. Consequently, reporting composite results might mislead the evidence in this research area.

Studies also illustrate that there is no differences between gestational age at pregnancy loss and adverse psychological outcomes[344,418,419]. Hutti et al. (2015) found no statistically significant differences between type of loss and grief, anxiety, depression and PTSD among women in their subsequent healthy pregnancy[420]. In addition, greater grief intensity was associated with increased pregnancy-specific anxiety, depression symptoms and PTSD. As a result, alternative approaches suggest to evaluate psychological outcomes in subsequent healthy pregnancies after a loss such as adopting the theoretical framework of perinatal grief intensity[421,422].

8.6.3 Implications and conclusion

It is commonly perceived that empty reviews, that is, systematic reviews that find no studies eligible for inclusion, do not provide additional information that can be utilised by clinicians and other decision-makers[423]. However, some authors argue that empty reviews can be of critical importance (1) to raise awareness of the gaps in the evidence in a particular area of interest for either clinicians, researchers and decision-makers, (2) to know who is interested in the area and (3) to indicate the state of research evidence at a particular point in time[423,424]. In particular this review is clinically important because it might help encourage the development and implementation of well-designed clinical trials for assessing non-pharmacological interventions on pregnant women who have had a miscarriage.

In conclusion, it is accepted that miscarriage affects some women's psychological well-being, increasing their levels of stress after a single experience. It is also considered that previous miscarriage may be a factor in aggravating levels of stress in a subsequent pregnancy. There is a potential risk that women who have experienced miscarriage may be at risk for maternal stress during their subsequent pregnancy which in turn is associated with adverse pregnancy-related outcomes. To date few studies have assessed the effect of non-medical interventions in women after pregnancy loss. Moreover none of the RCTs, which were identified in this review, included pregnant women in their subsequent pregnancy after miscarriage. Therefore, there is a need for targeted, standardised, high-quality and appropriately powered RCTs that can provide reliable and conclusive results to determine effective psychological and support interventions for this vulnerable group.

8.7 Implications for practice, policy and research

Implications for practice

- There is a potential risk that women who have experienced miscarriage may be at risk for maternal stress during their subsequent pregnancy, which in turn is associated with adverse pregnancy-related outcomes.
- This review is clinically important because it might help encourage the development and implementation of well-designed clinical trials for assessing non-pharmacological interventions on pregnant women who have had a miscarriage

Implications for policy

- There is a need to promote funding for RCTs which aims to increase the limited evidence on psychological and lifestyle burden among women who experience pregnancy loss

Implications for research

- To date few RCTs have assessed the effect of non-medical interventions in women after pregnancy loss; moreover, none of the RCTs which were found in this review, included pregnant women in their subsequent pregnancy after the loss.
- There is a need for targeted, standardised, high-quality and powered RCTs that can provide reliable and conclusive results to determine effective psychological and support interventions for this vulnerable group

Chapter IX

Discussion

9.1 Discussion

Worldwide, women who get pregnant are at risk of experiencing one or several miscarriages during their reproductive life. Miscarriage is a global public health issue that not only affects women who experience miscarriage, but has also been proven to have an emotional impact on the women's partner and relatives. The estimated incidence and prevalence of miscarriage is higher now than what it was first estimated before the development and improvements of hormonal tests and fertility treatments. It is estimated that half of miscarriages are due to chromosomal abnormalities[62]. The high prevalence of chromosomal abnormalities that cause miscarriage and the lack of evidence on other underlying causes have prompted many to believe that miscarriage cannot be prevented. However with recent developments on the impact of miscarriage, understanding the causes of unexplained miscarriages has become a research priority. This is facilitating the establishment of new pathways of research that are focused on identifying causes, risk factors and potential treatments that will contribute to increasing a woman's chance of having a healthy baby at the end of pregnancy.

The objective of this thesis was to explore several dimensions of miscarriage following a biopsychosocial model, whereby this thesis investigated not only the biomedical dimension of miscarriage, but also explored psychological, behavioural and social dimensions of miscarriage in the Republic of Ireland[425]. A total number of six research projects were undertaken to investigate:

1. The incidence of hospitalisations for first-trimester miscarriages in Ireland and morbidity associated with blood transfusion and length of stay over two days using the Hospital In-Patient Enquiry (HIPE) database (Chapter 2)
2. The validity and reliability of the HIPE database and the register books to report diagnosis of miscarriage and the different classifications of miscarriage (e.g. missed, incomplete and complete miscarriage) using electronic health records (EHR) as a gold standard (Chapter 3)
3. The identification of potential modifiable risk factors affecting a cohort of pregnant women who attended an EPAU (Chapter 4)
4. The level of knowledge and awareness of causes, risk factors, and features of miscarriage among a sample of university students (Chapters 5 & 6)
5. The feasibility of measuring psychological and lifestyle factors in a prospective study among pregnant women with a history of first-trimester miscarriage (Chapter 7); and:
6. A systematic review of randomised controlled trials that assessed the effectiveness of non-pharmacological interventions to reduce stress, anxiety and depression among pregnant women who experience miscarriage (Chapter 8)

Some of these findings might be difficult to generalise to other countries because of the specific socio-demographic, cultural and health background of the Republic of Ireland (e.g. incidence rates, morbidities and risk factors). However, external validity may be inferred when interpreting the findings in relation to the lack of awareness of miscarriage among the educated population, or considering barriers and facilitators when designing

and carrying out prospective studies that include similar target populations and outcome measures. The need for designing and evaluating effective interventions to improve the mental wellbeing of pregnant women who have a history of miscarriage is required both nationally and internationally.

For the purpose of this thesis, the interpretation of the main findings, strengths and limitations, and implications for further research have been grouped into similar themes:

1) Incidence of inpatient admissions of miscarriage and data validation (Chapter 2 & Chapter 3)
2) Risk factors and interventions (Chapter 4, 7 & 8)
3) Awareness of miscarriage (Chapter 5 & Chapter 6)
4) Conclusions

9.2 Incidence of inpatient admissions of miscarriage and data validation (Chapter 2 & Chapter 3)

9.2.1 Main findings

Two studies were carried out to assess the incidence and data validation of inpatient admissions for miscarriage in the Republic of Ireland. The first study was a nationwide retrospective population-based study that estimated the rates of inpatient admissions for miscarriage and morbidity using the Hospital Inpatient Enquiry (HIPE) system from 2005 to 2016. The second study was designed to determine agreement of the diagnosis of miscarriage between electronic health records (EHR), the HIPE system and the hospital

register books at a tertiary maternity hospital in the Republic of Ireland from January to June 2017.

9.2.1.1 Prospective cohort study

The retrospective, secondary analysis using the HIPE national database has shown a 19% decrease in hospitalisation rates for first-trimester miscarriage over time, with a higher rate of complications in the Republic of Ireland. Advanced maternal age increased the risk of being admitted to the hospital compared to women aged 25 years or younger, and the younger women were more frequently treated publicly. This study did not find a relationship between advanced maternal age and risk of blood transfusion, yet rates of a prolonged stay at the hospital (e.g. over two days) decreased among women aged 30 years or older compared to women younger than 25 years. Interestingly, rates of blood transfusion and a prolonged stay at the hospital increased among women who were publicly managed compared to women who were treated under their private health insurance. Finally, when looking at the type of treatment, hospitalisations for miscarriage that was medically treated had fewer blood transfusions, but had a higher risk of a prolonged stay at the hospital compared to those who had an evacuation of retained products of conception (ERPC).

9.2.1.2 Concordance study

According to the findings obtained by the concordance study, the HIPE database, and the register books are reliable and valid sources for reporting hospitalisations for miscarriage at a national level. Statistically, a very good level of agreement for diagnosis of hospitalisations of miscarriage was found in this study; however, discrepancies were

found when classifying the different types of miscarriage between the three data sources. For instance, the HIPE database had a significantly lower percentage of hospitalisation for missed miscarriage compared to electronic health records (EHR). The number of ectopic and molar pregnancies was higher in the HIPE database compared to the EHR and the register books. In addition, a considerable number of missing admissions of miscarriage were found in the register books.

9.2.2 Strengths and Limitations

The findings of both retrospective studies are novel as, to the best of my knowledge no other studies have reported national trends of hospitalisations for miscarriage over a 12-year study period. In addition, there have been no reported studies that have validated national miscarriage data from the ROI or internationally. Moreover, the HIPE database was used to obtain data for both studies, which provided standardised data outcomes by using the ICD-10-AM diagnosis code across the 19 maternity hospitals in the ROI. One of the main strengths of the retrospective population-based study was the large sample size. It included over 50,000 hospitalisations of miscarriage, which reduced the uncertainty of the results by narrowing the margin of error and also provided a greater power to detect differences. Furthermore, the positive results obtained from the concordance study give validity and reliability to the diagnosis of miscarriage in Ireland, including the incidence rates reported in the population-based study.

Nevertheless, both studies have several limitations. Firstly, outpatient data were not available from the HIPE database, and only inpatient data were reported in the findings.

As a consequence, the overall burden of miscarriage is under-estimated at national level as an increasing number of women who miscarry are treated in outpatient departments. However, reliable rates for morbidities associated with hospitalisation for miscarriage are reported from this population-based study.

One of the main challenges that we found in both studies was the lack of standardised cut-offs to classify miscarriage by gestational weeks. For example, Clinical Guidelines in the Republic of Ireland define early miscarriage as the loss of the fetus within the first 12 completed weeks of pregnancy[426], whereas the restricted range of weeks of gestation available in HIPE only allowed us to define early miscarriage as a loss within 13 completed weeks of gestation (i.e. <5, 5-13, 14-19, 20-24 completed weeks of gestation). Although we initially explored incidence rates for both early and late miscarriage using HIPE data, we decided to exclude late miscarriages because the threshold to define stillbirth by the HIPE standards significantly differed from national Irish law[133]. The definition of stillbirth in accordance with the Irish Registration Act of 1994 defines stillbirth as an infant born with no signs of life from at least 24 weeks of gestation or with a birthweight of at least 500 grammes[133].

Similar challenges were encountered when comparing different types of miscarriage in the validation study between HIPE and Clinical Guidelines in the Republic of Ireland. We hypothesised that the differences found in the classification of miscarriage between the three data sources might have been influenced by the different cut-off points defining types of miscarriage in each data source. For example, according to Irish Clinical Guidelines, a miscarriage can be classified as a missed miscarriage, an incomplete

miscarriage or a complete miscarriage[15]. Missed miscarriages are usually identified by an ultrasound scan at an outpatient department (e.g. Early Pregnancy Assessment Units). Conservative, medical or surgical management using ERPC are normally offered to women who have a missed miscarriage. Information from women who opt for conservative or medical management is not recorded in HIPE as it is considered outpatient activity. However, some of these women might later opt for surgical management, and therefore they will be admitted to the hospital a few days after the treatment. During this period of time, some women will not experience any extra signs or symptoms before undertaking the ERPC and they are classified as having a missed miscarriage. However, other women will start bleeding or spotting, after confirming that the pregnancy is not viable and given that there are retained products of conception visible on ultrasound scanning, they are classified as having an incomplete miscarriage. Finally, a smaller number of women will bleed excessively for a day or a few days; when these women are admitted to the hospital and the ultrasound scan confirms that the uterus is empty, they are classified as having a complete miscarriage.

Hence, the differences in the type of classification of miscarriage might be influenced by the identification process and treatment of the miscarriage. For instance, although HIPE coders have access to both outpatient and inpatient information, they are only allowed to code information related to inpatient admission. The main definitions of miscarriage included in their standards are incomplete and complete miscarriages. Missed miscarriage is briefly defined as "the early fetal death with retention of dead fetus", and no further details are given to classify women who miscarry in this category. Interestingly, HIPE coders do identify and code molar pregnancies using a second diagnosis as they also have

access to post-discharge histological results. On the other hand, health professionals who record the diagnosis of miscarriage in the register books have information about the outpatient diagnosis (e.g. missed miscarriage), but the diagnosis will not generally be modified if post-discharge histological results confirm a molar pregnancy.

9.2.3 Implications for practice & future research

The retrospective population based study found a decrease in the rate of hospital admissions for miscarriage in the Republic of Ireland from 2005 to 2016. As discussed in the previous chapter, the modification of the cut-off values to identify miscarriage and the recommendation of performing a second ultrasound scan to confirm the diagnosis of miscarriage might have had an impact in the reduction of the incidence of hospitalisations during the study period. It is well known that advanced maternal age is a risk factor for adverse pregnancy outcomes. Therefore, it was not surprising that advanced maternal age was related to an increased number of hospitalisations due to miscarriage in this study. However, this study did not find differences in rates of blood transfusion according to maternal age, and interestingly, the rates of prolonged stay at the hospital were less common among older women compared to women aged 25 years or younger.

We speculated that the difference in rates of complications between public and private patients might be due to disparities in the quality of care received. Previous studies have found an association between higher risk of pregnancy loss and economic disparities [183,427]. A controversial but plausible factor that might have influenced this result is the delay in the time taken to provide care to public patients compared to private patients. In addition, women who are seen personally by a private consultant might be more closely

monitored than those who are assigned to a team of consultants who share-out ward duties. Moreover, public patients might be more likely to be reviewed by doctors in training and the speculated absence of senior clinical decision makers is one possible reason for disparities in care. We found no other study assessing the possible impact of health insurance coverage on the risk of complications among hospital admissions for miscarriage. In order to prevent disparities in the care provided among inpatient admissions for miscarriage this possible association should be investigated further.

Although the pathways of care for miscarriage have evolved in the recent decades, the optimal management is still in debate. For instance, this study found that medical and expectant management were less likely to require blood transfusion compared to women who were surgically managed. However, previous RCTs and systematic reviews have found that women who are expectantly managed are at higher risk of blood transfusion and a prolonged stay at the hospital compared to women who have surgical management [259,428]. The lack of outpatient data in the analysis might have influenced the association between expectant and medical management and reduced rates of blood transfusion, as we were not able to identify hospitalisations due to miscarriage that needed surgery because of a failed medical or conservative first-line of treatment. Morbidities associated with hospitalisation for miscarriage might differ from those women who are treated at outpatient settings or who participated in randomised controlled trials. However, there is a lack of clear and generalised evidence on morbidities affecting hospitalisations for miscarriage. More research is needed to explore the patterns of care and clinical indications at both outpatient and inpatient settings in order to improve protocols of management and the care provided.

Nationally, HIPE is used for estimating hospital activity and costs, and for assessing the efficiency of each participating hospital in the Republic of Ireland. It is well-recognised that type of treatments for miscarriage have a significantly different cost for health services. The MIST trial, conducted in the UK, was the largest economic evaluation of management of first-trimester miscarriage carried out as part of a randomised controlled trial for treatment of miscarriage[429]. According to this study, surgical management was the most expensive treatment compared to medical and conservative treatments[429]. The most cost-effective management for treating miscarriage was expectant management, even after taking into consideration unplanned interventions and unplanned admissions into consideration[429]. This was only applicable when expectant treatment was successful as first-line treatment, otherwise, medical management was more likely to be unsuccessful when used after a failed expectant management, as, the costs of unplanned interventions increased[429]. The discrepancy between types of classification of miscarriages in my study might have a negative clinical impact due to inaccurate data related to the numbers and type of miscarriages, and therefore, their associated cost. This misclassification might influence the decision process regarding the provision of funding for each hospital; these funding decisions therefore might not meet the needs of each hospital's activity.

Similarly, misclassifications of the type of miscarriage might mislead research evidence on recommendations for the most cost-effective type of treatment used to manage miscarriage. Cost-effectiveness is an important indicator when comparing different treatments, but it also should be interpreted according to other indicators when recommending types of managements[116,430]. For example, the NICE Clinical Guidelines

recommends medical management as the first-line of management for miscarriage based not only on the cost evaluation, but also on the outcomes for first-line treatment[428]. These findings are supported by a recent systematic and network meta-analysis review of randomised controlled trials assessing the effectiveness of different types of management for miscarriage, which found no differences in side effects and effectiveness between medical and surgical management[130].

Equally important, misclassifications of types of miscarriage might lead to inaccurate knowledge about women's preferences regarding type of management of miscarriage. This is essential since women's preferences should be taken into consideration whenever possible[130]. An exploration of preferences of type of management for first trimester miscarriage as part of the MIST trial found that reduction in pain levels and return to normal activities after management were the most cost valuable attributes [431]. Based on the results of the MIST study, women preferred surgical treatment over medical treatment and medical treatment over expectant treatment when several alternatives were offered[431]. Identifying the correct diagnosis of miscarriage is crucial in order to provide accurate evidence on the cost-effectiveness of management of miscarriage, but also to obtain women's preference about the type of management for the specific type of miscarriage.

In summary, findings obtained from the HIPE national database will be biased by reporting inaccurate types and numbers of miscarriage, and therefore, it might mislead the evidence to improve pathways of care according to the type of miscarriage. Ultimately, a national agreement should be achieved in order to facilitate accurate information about the type of miscarriages, but also to facilitate comparisons of the evidence on miscarriage

at national level. Therefore, there is a need to review, update and standardise definitions and type of miscarriage used not only in HIPE, but also in national health systems in the Republic of Ireland. There is a need to provide education and training to professionals who are working in the area of pregnancy loss, with the intention of increasing the entering of reliable data on miscarriage in the national health systems.

The concordance study found a considerable number of records missing in the register books compared to the EHR and HIPE. It is well-documented that doctors, midwives and nurses tend to experience high levels of burnout, work-related stress and dissatisfaction in the ROI and in Europe[277,278]. Retention problems and lack of staff in each shift increase staff's workload and may decrease the quality of care provided for patients[277,278]. The introduction of the EHR might have increased the workload of doctors, midwives and nurses in some maternity hospitals in Ireland. This duplication of information might result in subsequent human error as healthcare professionals have to enter the same clinical information into two different databases at the same time. Without the need for keeping paper-records, it might be time to evolve to only electronic records to decrease the amount of workload for health professionals in the maternity services and to enable access to the electronic health records for simple data analysis such as numbers of miscarriage. The introduction of the EHR in Ireland, through the development of the Maternal and Newborn Clinical Management System (MN_CMS), facilitates access to women's clinical information independently of the settings in which women who miscarry are treated. Therefore, researchers will be able to conduct high quality studies to produce more evidence on maternal outcomes at a national level. For example, some of the

limitations described in this chapter could be solved by using the EHR in future research (Figure 9.1).



Figure 9.1 Limitations of research studies in this chapter and potential solutions for future studies by using the National EHR in Ireland.

Nevertheless, the implementation of the EHR is relatively new, and some limitations were detected when using the EHR for the validity study. For example, the information related to the type of miscarriage for each hospitalisation was obtained from free text entered by the doctors who were in charge of the woman's care during her hospitalisation. This led to some difficulties when seeking the correct information whereby different doctors identified different types of miscarriage for the same women in the same hospitalisation period (e.g. incomplete versus missed miscarriage or incomplete versus complete miscarriage). In these cases, we had to look back to previous entries in order to verify the correct type of miscarriage (e.g. clinical status at the emergency department before the hospitalisation or previous clinical status in previous hospitalisations for the same miscarriage). Secondly, there is a classification for molar pregnancy in the EHR, but this might not be completed properly; therefore, every histopathological exam result had to be read in order to ascertain the correct miscarriage outcome. Finally, some theatre reports or important information of the woman was missing in the EHR, and therefore, it challenged the identification of miscarriage. This highlights the need for more efforts to be carried out to assure high-quality, accessibility, reliability and validity of the data related to miscarriage in the EHR.

9.2.4 Implications for data quality

The development and implementation of electronic health records (EHR) in Ireland mark the beginning of a new era of big data within the health and social care services. It is the keystone of the eHealth Strategy, which is the idea of developing a patient-centric longitudinal record for all clinical information at a national level[274]. The achievement of

a national EHR aims to involve better clinical decisions by having access to patient care information from multiple sources, and therefore, it will improve all aspects of patient care by standardising clinical pathways, practice and processes within and across organisations[274].

Moreover, having a national EHR will have a significant impact on how clinical audits and clinical research will be designed and managed. Some of the future visions for the national EHR are to populate other data sources such as HIPE system and the Central Statistics Office (CSO) in Ireland. In addition, the EHR will be able to provide accurate, reliable and complete information at each point of patients' care, but also to improve data quality, security and audit for access to patients' records[274]. For example, to date, there are 36 national pathways of care in the EHR. Each pathway of care contains the clinical information related to a unique maternal outcome (e.g. caesarean sections, the Robson 10-group classification system, induction of labour and blood transfusion). Each hospital has the potential to develop their own pathway of care, and the fields included in each pathway of care can be updated according to new evidence or care needs. The information from the pathways of care can be used to carry out clinical audits and reports at hospital level. For instance, there is a pregnancy loss pathway available in the EHR. This pathway allows easy access to a list of the number of cases who have been admitted for a pregnancy loss into the hospital (e.g first and second trimester miscarriage, ectopic pregnancy and stillbirths). Nevertheless, all these future visions and directions will be in vain if standardised high-quality data collection and data management plans are not established at a national level.

These are the most important implications for clinical practice and policy that are needed according to the evidence provided in chapters two and three:

1. The EHR should be the preferred database of choice to obtain information about pregnancy loss
2. It is important to standardise cut-off points of weeks of gestation for definitions of miscarriage (e.g. early and late miscarriage)
3. It is key to standardise the diagnosis of types of miscarriage (e.g. missed, incomplete, complete)
4. It is also essential to have better access to standardised data from antenatal clinics or early pregnancy clinics (outpatient departments)

Data entered in the EHR for miscarriage must be audited and improved in order to provide reliable and accurate information. For example:

1. It is essential to train healthcare professionals who are working in the maternity services and who are entering data in relation to miscarriage in order to optimise data quality in the EHR
2. There is a need to validate the diagnosis of miscarriage in the EHR
3. There is a need to audit data quality when entering estimations of blood loss during miscarriage, and to train healthcare professionals in the measurement of blood loss
4. It is imperative to develop and employ a standardised toolkit for measuring blood loss at a national level

In order to achieve the recommendations listed above, it is imperative to develop and implement a national audit and education programme for the optimisation of data in EHR related to miscarriage in the Republic of Ireland. The first three points are key to optimise the pregnancy loss pathway for national reports in Ireland. This will need the agreement of experts in the area of pregnancy loss at a national level. After the standardisation of cut-offs and types of miscarriage and the optimisation of the pregnancy loss pathway in the EHR, training courses should be designed and provided to the healthcare professionals involved in the obstetric care of women who miscarry[197,200]. For the improvement of measuring and entering data in relation to blood loss, the National Perinatal Epidemiology Centre (NPEC) has made similar recommendations in relation to estimating blood loss for major obstetric haemorrhage (MOH) since 2015[432]. Since then, NPEC has been involved in the development of a specific pro-forma to standardise the documentation of blood loss in MOH and postpartum haemorrhage (PPH). In addition, a quality improvement proposal for the management of PPH has been designed in collaboration with the National Women & Infants Health Programme (NWIHP), and the Health Service Executive (HSE) in the Republic of Ireland. Similar approaches and toolkits to the one developed by NPEC can be expanded for the improvement of data quality related to the measurement of blood loss for miscarriages in the Republic of Ireland.

In summary, assuring data quality should be prioritised when designing, planning and carrying out research studies or clinical audits. Lacking high-quality data will negatively impact on the reliability of the evidence provided, and it will misdirect the implementation of interventions, standards and resources.

9.3 Risk factors and interventions (Chapter 4, 7 & 8)

9.3.1 Main findings

Three studies were carried out among pregnant women with a history of miscarriage at CUMH. The first study was a prospective cohort study which included women who attended an Early Pregnancy Assessment Unit (EPAU) in 2012. The main objective of the prospective cohort study was to explore risk factors among women who attended an EPAU. The second study was a feasibility study examining barriers and facilitators for assessing behaviours and lifestyle and psychological factors over the course of the pregnancy among women who miscarried, and the third study was a systematic review that looked at RCTs, which assessed the effectiveness of non-pharmacological interventions among pregnant women with a history of miscarriage.

9.3.1.1 Prospective cohort study

Almost 50% of women who attended the EPAU had a subsequent miscarriage according to the findings of the prospective cohort study. In line with previous research, the prospective cohort study identified well-established risk factors for miscarriage such as advanced maternal age or high-risk pregnancies (e.g. threatened or recurrent miscarriage). Perceiving work as stressful or partners' job insecurity were also associated with a higher risk of early miscarriage. In contrast with previous literature, this study did not find an increased risk of miscarriage among women whose partners were at advanced age, nor with the women's general health behaviours and lifestyle factors (e.g. smoking or alcohol consumption). Similarly, this study did not find an association between working with a

computer screen and a higher risk of miscarriage; however, women who reported a stressful workplace were more likely to have a miscarriage in this study. High levels of perceived stress and stressful life events were not found to be associated with an increased risk of miscarriage in this study. After adjusting for confounding factors, only having balanced emotional wellbeing was associated with a decreased risk of miscarriage. Similar to balanced emotional wellbeing, nausea and vomiting was also associated with a decreased risk of miscarriage; however, this association was no longer significant after adjusting for confounders.

9.3.1.2 Feasibility

The second research project was a feasibility study, which explored barriers and facilitators for recruiting and retaining pregnant women in longitudinal studies. One of the interesting results was that response rates were higher in the first trimester of pregnancy compared to the second and third trimester. On the other hand, pregnant women were more likely to have a higher response rate when completing paper-based forms after a face-to-face interview compared to online forms. In addition, this feasibility study reports preliminary quantitative data on the total scores for validated psychological and general health questionnaires over the three trimesters of pregnancy among women with a history of miscarriage. Higher total scores for stress and anxiety were found in the first and the third trimester of pregnancy; whereas the lowest score for depression was found in the third trimester of pregnancy. Interestingly, prenatal distress and the quality of sleep worsened over the pregnancy.

9.3.1.3 Systematic review

The third study was a systematic review of randomised controlled trials (RCTs) that examined the effectiveness of non-pharmacological interventions to reduce levels of stress, anxiety or depression in pregnant women with a history of miscarriage. None of the 17 RCTs identified in the search met the inclusion criteria. The finding of this review was unexpected given that there is a vast amount of evidence that states the need of assessing non-pharmacological interventions to reduce levels of stress, anxiety and depression among women with a history of miscarriage[306,406] . One RCT included pregnant women at the time of the intervention[400], yet pregnancy loss was a composite variable including stillbirth and neonatal death as well as miscarriage. It was also interesting to find that most of the studies were designed to explore the effect of non-pharmacological interventions right after the loss, without including pregnant women in their subsequent pregnancy after miscarriage[226]. The psychological burden of miscarriage is known to reappear in subsequent pregnancies[205,341], and it should be taken into consideration when planning and designing RCTs in the area of pregnancy loss.

9.3.2 Strengths and Limitations

9.3.2.1 Prospective cohort study

One of the main strengths of the prospective cohort study was the large sample size included in the analysis (e.g. almost 300 women in the prospective cohort study). In addition, few studies have prospectively explored risk factors for miscarriage, which increased the internal validity and credibility of the findings and reduced the risk of recall bias. One limitation of the prospective cohort study was that I could not compare differences on psychological factors between responders and non-responders as there was no record kept of women who declined to participate in the study. Another limitation is

that this cohort study did not collect information about behaviours and lifestyle before the event of a miscarriage. Previous evidence shows that behaviours and lifestyle, perceived stress and daily stressors might have a negative impact on subsequent pregnancy outcome [150]. However, this study did not find an association between levels of stress, behaviour and lifestyle factors and women's general health and a higher risk of having a miscarriage. One hypothesis that could explain this discrepancy is that women who experience miscarriage might be more likely to improve their behaviours, lifestyle and general health after the event of a miscarriage and in their subsequent pregnancies[152].

Another limitation of the prospective cohort study was that although all the psychometric scales used in the study were validated, information related to their partner's behaviours and lifestyle or psychological wellbeing was not collected. Moreover, all outcome measures were self-reported and no biological predictors of stress (e.g. cortisol) were collected. Therefore, there is an increased likelihood of the findings being influenced by information bias.

9.3.2.2 Feasibility

The main reason for performing the feasibility study was to assess key elements for success to use in future larger-scale longitudinal studies. The main strengths of the feasibility study were that it assessed response and retention rates, it determined potential human and data management problems, and it explored staff willingness and centre capacity to carry out larger studies. Estimating the effect of time over the three trimesters of pregnancy was not one of the main objectives because of the potential bias with a small sample size. This study can be used to generate information for sample size calculation in

future studies. It could also be taken into consideration when designing and implementing large-scale cohort studies with comparable populations and research outcomes.

One limitation of the feasibility study was that retention rates were lower compared to the initial response rate. Selective attrition could have played an important role in this reduction. That means that women who were at higher risk of having higher scores in psychological measurement such as depression, stress or anxiety, were more likely to drop out of the study during the course of the pregnancy[433]. Another limitation was that no incentives were given to the midwife sonographers who collaborated in the recruitment and screening of potential participants for this feasibility study. Previous studies have reported a decrease in the willingness and commitment from the study personnel because of the lack of incentives or the lack of "feeling part" of the study[348]. Therefore, some eligible women might have not been approached during the screening process at busy times because the lack of dedicated time for the study by midwife sonographers.

9.3.2.3 Systematic review

No RCTs screened in the systematic review met the inclusion criteria; therefore, this review was what some authors call an "empty" systematic review. In "empty" systematic reviews, the research question defined at the beginning of the study design cannot be answered and conclusions cannot be drawn[424]. Therefore, most of the "empty" systematic reviews remain unreported because they are considered "negative" outputs[424]. However, it is becoming more accepted that empty reviews might highlight the state of the evidence at a particular point or research gaps in the research community[424]. It can be argued that the result of this empty review was obtained because of restrictive inclusion criteria. For

example, as per protocol (Appendix 7), RCTs had to include women with a history of miscarriage who were pregnant at the time of the intervention. This decision was reached because there was a Cochrane systematic review published already which assessed the effectiveness of non-pharmacological interventions to reduce anxiety, depression and grief among women with a history of miscarriage[226]. In addition, the Cochrane review focused mainly on the effect after the miscarriage, and it did not include women who were pregnant after the experience of a miscarriage[226].

Another limitation, which was already discussed in previous sections, was the lack of standardisation of the definitions of miscarriage and pregnancy loss worldwide[12]. The lack of an agreement of the definition of miscarriage challenged the identification of the RCTs in this review, and it will limit the comparison between studies in the future unless these definitions are internationally standardised. It could be argued that an additional limitation was that the systematic review excluded RCTs that reported pregnancy loss as a composite variable, that is, those RCTs that included miscarriage, stillbirth or neonatal death in one single pooled variable. However, it is still not certain if there is a difference between psychological burden and type or timing of pregnancy loss. Some studies have found no difference between weeks of gestation when the loss happens and psychological disorders after the loss or in subsequent pregnancy[344,420], whereas other studies have reported different psychological reactions depending on the type of loss[415,225]. Due to the conflicting evidence, this systematic review opted to focus exclusively on miscarriage. Given the different aetiology, this review excluded RCTs that included women with recurrent miscarriage. This decision was made predominantly because it is known that more resources and psychological support are provided for women who experience

recurrent miscarriage or women who had a late perinatal death[416,417]; therefore that might influence the resolution of parental bereavement after a pregnancy loss and modify the psychological burden[197]. Nevertheless, the main strength of this systematic review was that, to my knowledge, this was the first piece of work that systematically reviewed for RCTs that included non-pharmacological interventions to reduce the psychological burden among pregnant women with a history of miscarriage.

9.3.3 Implications for practice & future research

9.3.3.1 Prospective cohort study

Despite the high prevalence of miscarriage, approximately 50% of cases are attributable to chromosomal abnormalities[298]; meaning that a high number of women and their partners do not have a specific reason why their miscarriage occurred. This is the reason why identifying risk factors for miscarriage has become an important part of the research undertaken in the field of pregnancy loss. The majority of women who attend EPAUs usually present with a history of poor obstetric outcomes[289]. Having recurrent miscarriages or presenting with vaginal bleeding or abdominal pain are associated with a higher risk of miscarriage[290]. That could explain why almost 50% of women who attended the EPAU at the CUMH went on to have a subsequent miscarriage in the cohort study. Previous pregnancy loss is one of the most studied risk factors for miscarriage, whereas presenting with nausea or vomiting has been found to be a protective factor according to the literature[150,152]. However, neither of these factors were associated with miscarriage after adjusting for confounders in this prospective cohort study. That could mean that maternal age, body mass index, or high-risk presentation are stronger predictors for

miscarriage in the targeted population compared to women who do not have a history of poor obstetric outcomes.

As previously described, one of the most well-established risk factors for miscarriage is advanced maternal age[157]. Therefore, it is not surprising that age was a risk factor for miscarriage in the prospective cohort study. Some authors argue that age at first pregnancy is a modifiable factor that should be prevented[152]; however, several social and political challenges have been identified when encouraging women to reduce the age at first pregnancy. For example, it is well-established that the time of the first pregnancy is associated with educational attainment in medium and high-income countries[434]. The number of women who reach higher education has increased drastically in the last decades, and consequently, so has their economic independence and social status[434]. Women are becoming more career orientated and it sometimes can be difficult to combine work with the perspective of starting a family[435]. In her essay, Laurie Garrett recognised the important "obstacle" of childbirth when aspiring to develop a personal career between the age of 21 to 35[436]. Women who decide to start a family need to consider the required time off from work and the consequences associated with their career[436]. In addition, there has been a cultural shift towards individualisation and self-development in the Western world[435]. The Second Demographic Transition model (SDT) describes both the evolution of societies over time, but also individuals' value orientation of principal determinants such as fertility and family behaviours[435]. According to the SDT model, freedom of speech, psychological wellbeing and self-fulfilment are becoming the main priorities of individuals in Europe and in the Western countries, and therefore, individuals are less focussed on starting a family, having children or material properties[435].

In fact, there is a vast amount of evidence on the effect of family policies on fertility and childbearing behaviours[437]. A good example of a supportive policies towards family planning are to be found in the Nordic countries. In these countries, parental leave is paid for approximately one year following childbirth[438]. A study carried out in Sweden and Norway explored the relationship between fathers' and mothers' use of parental leave and continued childbearing[438]. It found a positive association between fathers' and mothers' use of parental leave and the higher likelihood of having another subsequent birth[438]. Supportive family planning might lead to the decision of having the first pregnancy at an early maternal age, and consequently, it might reduce the risk of miscarriage in that cohort. Nevertheless, family policies are very varied between countries, even among countries that are part of the European Union (EU)[437,439]. For example, it was not until 2010 when the EU established the minimum standards for family policies[440]. One of these recommendations included the Parental-Leave Directive in 2010, which gives men and women workers an individual right to parental leave of at least three months after the birth of a child[441]. Future research should investigate the minimum number of months of parental leave that should be recommended for promoting pregnancy at early maternal age and the effect on pregnancy and miscarriage rates at national or European level.

An example of the lack of supportive policies for women who miscarry at European level are the European Maternity Protection Act, 1994 which was implemented by the Council Directive 92/85/European Economy Community (EEC) and the Maternity Protection (Amendment) Act, 2004. According to this EU Act, women who experience a stillbirth, which is defined as the pregnancy loss after the 24th weeks of gestation, are entitled to a

basic period of 26 weeks and 16 weeks of additional maternity leave[442]. Therefore, women who had first or second trimester miscarriages do not qualify for maternity leave and must seek compassionate, annual or unpaid leave[442]. After experiencing a miscarriage, women should be offered time to grieve and time to heal in a rightful way. It is well-recognised that miscarriage has a psychological and emotional impact on women and their partners[215]. Further research should investigate if the provision of similar maternity leave would be beneficial for women who miscarry.

Another important factor that has been widely studied in recent years is the negative effects that prenatal mental health can have on the mother, the baby and the healthy development of a child[443,444]. A substantial body of evidence links prenatal health disorders with an increased risk of preterm birth, intrauterine growth restriction, neonatal death, and a negative impact on child development[443,444]. Yet, research has tended to focus on clinical mental disorders such as depression, anxiety and post-traumatic stress disorder, omitting other crucial psychological factors such as stress or grief. The Lancet's Perinatal Mental Health Series dedicated three papers to summarise the evidence in regards to non-psychotic and psychotic mental health disorders in the perinatal period and their negative impact on the fetus and the child[443,445]. The author draws attention to some of the most prevalent mental disorders during pregnancy such as depression, anxiety and they also consider bipolar disorder and psychotic disorders such as affective psychosis, and schizophrenia[444].

Although the effect of stress on human health, ageing and reproduction have been extensively investigated, the underlying psychological pathways are still unclear [446]. One

of the crucial barriers when researching stress is that it is not a monolithic concept but rather, a process that involves manifold social psychological and physiological aspects[446]. These main characteristics have influenced a lack of standardisation of definitions of stress, but also an absence of agreed "gold standard" measures in the research community[446]. For instance, stress can be objectively recorded using levels of cortisol in saliva or hair, but it can also be examined using a wide-ranging amount of self-reported psycho-metric scales. Some questionnaires are focused on "*stressors or stressor exposures*" such as life events (e.g. losing a job, getting divorced…); whereas others are used to measure the "*global subjective stress"* (e.g. perceived stress scales) or "*behavioural responses to specific stimuli"* (e.g. emotional responses, cognitive appraisals…) among others[446].

It is well-established that the experience of miscarriage has a psychological burden not only after the event but in subsequent pregnancies, for both parents and relatives[373,408]. However, only balanced emotional wellbeing was found to decrease the risk of miscarriage in this study population, and most of the psychological stress factors were not found to be associated with an increased risk of miscarriage in this cohort study. One potential explanation is that women who had a positive scan with a viable pregnancy had a reduction of stress and anxiety compared to women who had a history of miscarriage or who were experiencing bleeding or pain[387,447]. Another explanation may be driven by the fact that the limitations described above to measure stress are not exceptions when exploring levels of stress during pregnancy. The high heterogeneity between stress measurements impedes international comparisons between studies in this area of research.

Contradictory results might be due to differences in the study population, but they could also be affected by the lack of standardised stress measurements. Therefore, it is imperative to standardise definitions and measurement of stress in an attempt to obtain decisive evidence in the general population, but also during the perinatal period. Epel et al. (2018) has recently published an in-deep review of the stress measurement for the study of population science. This review included a list of a common language for stress and a more complex and precise stress model to be used when measuring and investigating stress[446]. In addition, they described the current literature of dimensions of "*stressor exposure characteristics*" and "*psychological and behavioural responses to specific stimuli or events"*[446].

The findings of the cohort study highlight the potential relationship between emotional wellbeing and the risk of miscarriage. There is a vast amount of evidence that links stress and miscarriage, even though several dimensions of stress were not associated with an increased risk of miscarriage in this study[190]. The advancement of applying biological predictors of stress (e.g. cortisol) for studying maternal stress during pregnancy and the prospect of applying the international standard for measuring stress might help to identify women who might be at higher risk of developing stress during pregnancy. It would also create the foundations of a well-recognised body of knowledge that stimulates the public acceptance of the effect of stress on miscarriage by trustworthy medical and health institutions[294]. Ideally, national screening plans will be established to evaluate women and partners' mental health during the perinatal period in order to provide better care and to improve mental health and pregnancy outcomes.

9.3.3.2 Feasibility

It is also crucial to take into consideration the underrepresentation of pregnant women in clinical research[354,412]. The main reasons why pregnant women have been systematically excluded from research studies or clinical trials are the risk of jeopardising the mother's health, and therefore, harming the fetus and the future child[412]. Several well-known health institutes have raised the need for performing research or clinical studies in this vulnerable group of the population[351,354]. According to the Perinatal Mental Health Series in The Lancet, the best way of improving the child and parental health is by prioritising and investigating the effectiveness of interventions[443]. Nevertheless, there is limited evidence on barriers and facilitators when carrying out health and clinical studies that include this targeted group[413].

In this thesis, a feasibility study was completed in order to investigate barriers and facilitators when recruiting, screening, and following up women with a history of miscarriage over the three trimesters of pregnancy. In keeping with the feasibility longitudinal study, previous evidence showed that face-to-face interviews might increase the engagement in longitudinal studies compared to online questionnaires when recruiting pregnant women[355]. Another important point to cover when planning cohort studies is ensuring a motivated workforce by building a research community and by providing incentives[332]. Training and multidisciplinary team meetings are essential for the coordination of large-scale longitudinal studies[355]. Nevertheless, there is little evidence in

the literature about the reasons why health professionals might be keen to collaborate or not in research studies[306,333].

Little is known about the fluctuations of psychological wellbeing, behaviours and lifestyle, or general health during the course of pregnancy among women with a history of miscarriage. This feasibility study reported preliminary data on variations of total scores for a wide range of validated psychological and health questionnaires. The small sample size of this feasibility study inhibits the formulation of further conclusions. The findings of this feasibility study should be interpreted with caution and no clinical implications should be extrapolated from them. This study found some distinctive results when examining psychological wellbeing during pregnancy. For example, total scores for perceived level of stress and anxiety were higher in the first and second trimester of pregnancy; and that total scores for depression worsened during pregnancy. Nevertheless, these findings suggest that psychological wellbeing varies during pregnancy among women who experienced a miscarriage. There is a need to plan and design large-scale cohort studies that look at the variety of psychological morbidity among this vulnerable group, but also the changes in social support, behaviours and lifestyle factors and general health.

9.3.3.3 Systematic review

Few interventional studies have assessed the effects of non-pharmacological interventions among women with a history of miscarriage[226], and even fewer still explore these same types of interventions among women who are in their subsequent pregnancy after miscarriage[297]. To our knowledge, there is only one previous Cochrane systematic review

which systematically searched for RTCs that aimed at investigating the effectiveness of non-pharmacological interventions to reduce levels of anxiety, depression and grief among women who miscarried[226]. Murphy et al. (2012) reported that not enough evidence was provided by the six RTCs to draw a robust conclusion of the effectiveness of these interventions[226]. Drawing conclusions from these types of RCTs might be challenging because of the complexity and the varied number of interventions designed to improve psychological wellbeing. In line with the findings published by Murphy et al. (2012), this systematic review found the following shortcomings in the design of the RCTs[226]:

- Lack of high-quality study designs and appropriately powered sample sizes
- Unclear blinding or no blinding
- High heterogeneity between types of non-pharmacological interventions (e.g. support groups, psychological or information interventions)
- High heterogeneity between the type of psychological outcome (e.g. depression, anxiety, grief and stress)
- Overlapping of signs and symptoms between the psychological disorders (e.g. depression and anxiety) and stress

Therefore, this "empty" systematic review indicates there is a gap in the knowledge of the effectiveness of non-pharmacological interventions that aim to improve psychological wellbeing among pregnant women who have a history of miscarriage. This thesis is clinically important because it might help to encourage the funding of well-designed and high-quality RCTs to assess the effectiveness of non-pharmacological interventions among this target population. Other RCTs have successfully proven the effectiveness of

non-pharmacological interventions in reducing postnatal depression with an improvement in children development even after 2 years post-partum[448]. Medical and health institutions and stakeholders should recognise the impact of psychological morbidity among women who miscarry and promote research in this area at an international level.

In summary, there is a need to carry out large-scale cohort studies that can measure the fluctuation of psychological, behaviours and lifestyle, and general health factors over the three trimesters of pregnancy and the potential negative impact in subsequent pregnancy outcomes. Furthermore, it is essential to design and carry out high-quality interventional studies, which investigate the changes in psychological status, behaviours and lifestyle factors, and general health during pregnancy. There is also a need to identify effective interventions that can improve the psychological wellbeing during pregnancy among women with a history of miscarriage.

9.4 Awareness of miscarriage (Chapter 5 & Chapter 6)

9.4.1 Main findings

A cross-sectional study was designed in order to explore students' understanding of miscarriage at University College Cork (UCC) between April and May of 2016. Chapter 5 described the results for students' understanding of rates, causes, and risk factors of miscarriage, whereas chapter 6 focused mainly on the results about students' knowledge of features for first and second trimester miscarriage, type of management and diagnostic tests available for women who miscarry.

In general, this cross-sectional study found a lack of knowledge of causes, risk factors, and features of miscarriage among university students at UCC. It was remarkable to find that only 20% of students correctly identified the prevalence of miscarriage in Ireland and that almost 30% of this sample believed that the prevalence of miscarriage was less common than 10%. Approximately 75% of the students knew that chromosomal abnormalities were a cause of miscarriage, yet only 43% recognised them as the leading cause. Less than 50% of the students were aware that being overweight is a risk factor for miscarriage. On the other hand, more than 80% of the students considered that stress was an established risk factor for miscarriage. University students were aware that heavy bleeding, cramping and pain were common features of miscarriage, yet approximately 70% did not know that miscarriage also occurs without any evident sign or symptom. University students were not aware that medical treatment is an alternative to surgery for managing miscarriage, and approximately 80% of the students reported that they had not received any information about miscarriage at school or university settings.

9.4.2 Strengths and Limitations

The main strength of this study was its sample size (i.e. more than 700 students included in the analysis), which represents one of the largest studies exploring knowledge and awareness of causes, risk factors, and features of miscarriage among university students in the literature. In addition, the sample was randomly selected which helped to increase the external validity of the findings. However, the nature of this study design involved some limitations. Firstly, a valid questionnaire to assess the study objectives was not available in the literature, neither were specific thresholds to classify some of the attributes (e.g. good and poor knowledge of miscarriage). Secondly, all the information

was obtained at one point in time from a single university, which implies that causation might not be inferred from the findings. Nevertheless, cross-sectional studies are the best approach for estimating prevalence, describing the population's characteristics and finding potential gaps of knowledge in the literature, which might help to design and implement future interventions[328].

Previous evidence has found that there is a lack of understanding of miscarriage among Irish adults aged 18-65 years in the Republic of Ireland[449]. Building on this work, it was important to study another population with more specific sociodemographic characteristics. University students represent a young and educated social stratum in a population. Identifying the gap of knowledge on miscarriage among this targeted group provides a better understanding of the needs of reproductive health information among the next generation of future families; and it helps to highlight the requirements for developing reproductive health education programmes in universities and in the community.

9.4.3 Implications for practice & future research

Preconception healthcare is a relatively early health concept, which started in The United States of America (USA) in the early 80s[450]. Preconception healthcare is known for facilitating the empowerment of men and women and promoting well-informed pregnancy-related decisions[450]. A study carried out in the USA, found that although women were aware of the importance of preconception healthcare, their levels of knowledge of risk factors, which would impact their pregnancies, was limited[451]. It is accepted that the best stage for providing preconception health education for both genders

is during the adolescence or in early adulthood[452]. However, routine implementation of preconception health education in schools and community is almost non-existent[451].

Reasons why preconception healthcare education is not routinely offered in schools, universities and communities by policymakers in the Republic of Ireland, and all around the world, have not been investigated. It could be argued that there is not enough evidence that relates improvement of pregnancy outcomes with the promotion of preconception health education[451]. However, recent studies have obtained positive results regarding pregnancy outcomes after carrying out different pilot studies implementing preconception healthcare around specific issues that affect pregnancy such as diabetes, nutrition or lifestyle[453]. Early last year, the Lancet published a series of articles about preconception healthcare[454,455,456]. The authors recognised that preconception healthcare is a "neglected" topic all around the world; and therefore, they proposed "novel" preconception health care interventions which start from the beginning of pregnancy that can be applied at individual or population level[454].

The social taboos and the silence surrounding miscarriage contributes to misunderstandings and ambiguities in regards to the causes, risk factors and other features of miscarriage[457]. Therefore, previous evidence highlights the need for miscarriage education in a wide range of contexts such as the community, schools and universities[197]. Theological, psychological and social reasons why miscarriage is so poorly understood and investigated have been debated extensively. However, as it was expected, its implementation in the community is lacking all around the world. The figure of women and their biological processes such as pregnancy loss or menstruation have been often

considered as a negative or shameful period of life by several religions[458]. Couples who experience pregnancy loss might interpret their childlessness as divine punishment because of the absence of God's blessing[458]. Trying to answer the question of why they are not blessed with a child might trigger feelings of anger, disbelief and disappointment[458]. The lack of identification of the loss by the religious community might intensify a couples' grief, and jeopardise the resolution of this natural process. Bereavement support should take into consideration a couples' spiritual needs after a pregnancy loss in order to give voice and provide a safe and trusted place during the ongoing process of accepting the loss of a baby[458,459].

From a psychological and social point of view, several approaches have been discussed in the literature. Kluger-Bell, a therapist focused on reproductive crises, provides practical advice and coping techniques for those who have experienced a miscarriage in her book entitled "Unspeakable Losses". She also points out the silence and cultural taboos surrounding pregnancy loss[460]. Another word used to describe the process when experiencing a miscarriage was "liminality". Liminality is defined as "a member of society which is transitioning from one social role into another"[461]. In her essay, Reiheld established the liminality of miscarriage and discussed the identity disruption of miscarriage as well as the social debates in which it is involved (e.g. political and religious)[461]. She emphasised that miscarriage is not interpreted as a mere medical condition or event and that the loss of a pregnancy draws a line between "being or not being a parent"[461]. For example, a previous study confirmed that couples considered that revealing the miscarriage event makes people uncomfortable, increasing the taboo around the topic[462].

Added to the social taboo of miscarriage, several studies have reported that women who miscarry often feel guilt, shame or responsibility for their loss[207,317,371,463]. These feelings, in addition to the social taboo surrounding the issue of pregnancy loss, might prevent couples that experience miscarriage from sharing their experience with relatives or health professionals, and in some cases might increase the difficulty of seeking help. The social taboos among couples who experience miscarriage will contribute to a higher misunderstanding and poor knowledge of essential reproductive information that could impact on the prevention and promotion of healthy reproductive lifestyles[457]. Understanding the factors that influence the lack of awareness among the population and the widespread misconception of common knowledge about miscarriage are key challenges to tackle this issue.

To the best of my knowledge, the Republic of Ireland is one example of a country where preconception healthcare education is not routinely provided at schools, community or universities. Ireland could be used as a historical example to highlight some of the barriers and facilitators when implementing school-based programmes and the reasons why some programmes are delayed or are not generally accepted in the country[464]. Firstly, Ireland, like other predominantly Catholic countries, has a history of sexual repression and sexual taboo[464]. It is not surprising when education in the Republic of Ireland has historically been provided by Catholic schools where topics such as sexuality, sex or reproduction were taboo among the students and teachers. However, in recent years, Ireland has become an icon for liberal political and social changes. For example, Ireland was the first country to legalise same-sex marriage by popular vote in 2015, and it has recently

legalised abortion in some circumstances, also by popular vote. As it happens in countries with different political and religious approaches in their population, tensions have arisen between two polarising sides of debates when deciding political, social and educational issues in the country.

Although the friction between these two philosophical, political and educational approaches remains present in the country at the moment, considerable achievements have been made on implementing the school-based relationships and sexuality education (RSE) at a national level[464]. The point of no return in accepting the importance of the application of RSE in schools started when a study carried by the Royal College of Surgeons reported significantly high rates of unwanted pregnancies and abortion in the 1970s[464]. The first RSE support service in primary schools, however, was not established until 1996. Since then the number of schools that deliver RSE has increased in the Republic of Ireland. In fact, the most recent online survey carried out identified that 94% of primary schools in Ireland had an RSE policy in place in 2015[465]. There is contradictory evidence on the effectiveness of RSE in the literature[464,466-468]. However, the most recent synthesis of the evidence of RSE, which included five research studies in the UK, concluded that school-based sexual health programmes are linked with a reduction of sexual activity, the number of sexual partners and teenage pregnancies[467].

Using the application of school-based RSE in Ireland as an example, we could agree that implementing preconception healthcare education is possible if political and educational makers acknowledge the population's needs. In this regard, Universities are underused settings for improving preconception health awareness among the community, since they

are ideal settings to target young adults, both men and women, who are at reproductive age. Promoting preconception healthcare awareness in higher education settings might have an unmeasured impact on the population's health, and it might influence women's success rate of pregnancy outcomes. However, more research is needed to provide high-quality evidence of the implementation of preconception health care at universities, schools and the community and the potential impact on the population's long-term health outcomes.

9.5 Conclusion

In conclusion, the high prevalence of miscarriage characterises this reproductive event as a public health issue worldwide. It is well established that miscarriage can affect women's psychological, emotional, physiological and social wellbeing right after the event, but also in subsequent pregnancies.

This thesis presents a substantial body of knowledge that might help to fill the gap for some of the research questions about miscarriage. I have provided the main findings for each research question alongside some suggestions and recommendations for clinical practice and future research.

It is essential to design and implement high-quality study designs that provide robust and conclusive evidence on the overall burden of miscarriage, the morbidity associated with hospitalisation, and the risk factors that can prevent the event of subsequent miscarriage or poor pregnancy outcomes. It is imperative to obtain robust evidence on effective interventions to improve the psychological morbidity, specifically those at targeting

stress, anxiety, depression, and behaviours and lifestyle factors, in subsequent pregnancies after miscarriage.

An actual impact on reducing the prevalence and morbidity associated with miscarriage will only be achieved through the provision of adequate education and training about miscarriage for healthcare professionals: through the standardization of care before, during and after miscarriage but also in the next pregnancy. Furthermore, this evidence should be disseminated among the general population. The general population should be informed on essential reproductive health aspects of miscarriage, especially at early stages in their reproductive life, in order to give a better chance of making decisions on their reproductive behaviours and lifestyles. Finally, through the provision of reproductive health education, and social policies that aim to increase the social support for those who experience pregnancy loss, but also that promote the starting of a family at an early maternal age.

Therefore, the improvement of women and their partners' reproductive health requires the efforts of not only the healthcare professionals and researchers who work in the area of pregnancy loss, but the collaboration of public health advocates and policymakers.

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Appendices

Appendix 1. PRISMA 2009 Checklist.

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3-4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	No
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4-5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6 and supplementary file

Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6 and supplementary file
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6-7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	No
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Supplementary file
Summary measures/ of findings	13	State the principal summary measures (e.g., risk ratio, difference in means). Summary of main findings of individual studies	No relevant
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	No relevant

Section/topic	**#**	**Checklist item**	**Reported on page #**
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	No relevant
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	No relevant
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8-9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	10-11
Risk of bias within	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Supplementary

studies			file
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Supplementary file
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	No relevant
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	No relevant
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	No relevant
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	11-12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12-14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	14-15
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	No relevant

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097. For more information, visit: www.prisma-statement.org.

Appendix 2. Search strategy

Database and date		Key words	Hits
PUBMED: 20/01/2016	1	((((((((("first trimester miscarriage") OR "early pregnancy loss") OR "early miscarriage") OR "pregnancy loss")))) OR "miscarriage") OR miscarriag*)) OR (("Abortion, Spontaneous"[Mesh] OR "Abortion, Habitual"[Mesh]) OR "Embryo Loss"[Mesh])	39943
	2	Stress Disorders, Traumatic, Acute[Mesh] OR "Stress Disorders, Post-Traumatic"[Mesh] OR "Stress Disorders, Traumatic"[Mesh] OR "Stress, Psychological"[Mesh] OR "Stress, Physiological"[Mesh]	270750
	3	"first trimester miscarriage"[All Fields] OR "early pregnancy loss"[All Fields] OR "early miscarriage"[All Fields] OR "pregnancy loss"[All Fields] OR "miscarriage"[All Fields] OR (miscarriage[All Fields] OR miscarriage'[All Fields] OR miscarriaged[All Fields] OR miscarriages[All Fields]) OR (("Abortion, Spontaneous"[Mesh] OR "Abortion, Habitual"[Mesh]) OR "Embryo Loss"[Mesh]) AND ("Stress Disorders, Traumatic, Acute"[Mesh] OR "Stress Disorders, Post-Traumatic"[Mesh] OR "Stress Disorders, Traumatic"[Mesh] OR "Stress, Psychological"[Mesh] OR "Stress, Physiological"[Mesh]) AND (("1995/01/01"[PDAT] : "3000/12/31"[PDAT]) AND "humans"[MeSH Terms])	**283**
COCHRANE: 02/04/2016	1	MeSH descriptor: [Abortion, Spontaneous] explode all trees	739
	2	Miscarriage*	1210
	3	“early pregnancy loss”	80
	4	1 or 2 or 3	1685
	5	MeSH descriptor: [Stress, Psychological] explode all trees	4353
	6	MeSH descriptor: [Stress, Physiological] explode all trees	3372

	7	MeSH descriptor: [Hydrocortisone] explode all trees	4912
	8	Stress	30099
	9	Cortisol	7010
	10	5 or 6 or 7 or 8 or 9	36269
	11	4 and 10	**125**
CENTRAL (IN TRAILS): 02/04/2016	12	"miscarriage":ti,ab,kw and "stress" in Trials (Word variations have been searched)	**11**
	13	11	16
EMBASE: 20/01/2016	1	'miscarriage' or 'miscarriage' /exp OR miscarriage	32955
	2	spontaneous abortion'/exp OR miscarriag* OR 'pregnancy loss'	37884
	3	'stress'/exp OR 'hydrocortisone'/exp	317556
	4	2 AND 3	558
	5	2 and 3 and [1995-2016]/py	491
	6	2 and 3 and [1995-2016]/py and [humans]/lim	**457**
WEB OF SCIENCE/KNOWLEDGE: 23/01/2016	1	TOPIC: ("early miscarriage") OR TOPIC: ("first trimester miscarriage") OR TOPIC:("early pregnancy loss") OR TOPIC:("spontaneous abortion") OR TOPIC:("pregnancy loss"). Refined by: TOPIC: (("Stress" OR "Cortisol")). Timespan: 1995-2016.Search language=Auto	**679**
CINAHL: 02/04/2016	1	"early miscarriage" OR "first trimester miscarriage" OR "early pregnancy loss" OR (spontaneous abortion or miscarriage) OR (spontaneous abortion or miscarriage or abortion or misbirth). Limiters - Published Date: 19950101-20161231 (1995-2016); Human. Search modes - Boolean/Phrase	4329
	2	"stress" OR "stress management" OR "hydrocortisone" OR "cortisol" OR stress, psychological [mesh]. Limiters - Published Date: 19950101-20161231; Human. Search modes - Boolean/Phrase	58834
	3	("stress" OR "stress management" OR "hydrocortisone" OR "cortisol" OR stress, psychological [mesh]) AND (S28 AND S29)	**152**

MATERNITY AND INFANT CARE: 25/01/2016	1	(miscarriag* or "spontaneous abortion" or "first trimester miscarriage" or "pregnancy loss" or "early pregnancy loss" or "early miscarriage").mp. [mp=abstract, heading word, title]	4614
	2	limit 1 to yr="1995 - 2017"	3753
	3	("stress" or "cortisol" or "hydrocortisone" or "stress, psychologica").mp. [mp=abstract, heading word, title]	6006
	4	2 and 3	**112**
SCIENCE DIRECT: 25/01/2016	1	Search results: results found for pub-date > 1994 and ("first trimester miscarriage" OR "early miscarriage" OR "spontaneous abortion" OR "early pregnancy loss" OR "pregnancy loss") AND ("stress" OR "stress, Psychological" OR "cortisol" OR "hydrocortisone") AND LIMIT-TO(topics, "pregnancy") AND LIMIT-TO(topics, "woman").	**216**
EBSCOHOST: PSYCINFO: 25/01/2016	s7	"first trimester miscarriage" OR early miscarriage OR "early pregnancy loss" OR (pregnancy loss or miscarriage or spontaneous abortion). Limiters - Publication Year: 1995-2016; Population Group: Human. Search modes - Boolean/Phrase	20927
	S9	"stress" OR "stress management" OR "hydrocortisone" OR "cortisol" OR stress, psychological [mesh]. Limiters - Published Date: 19950101-20161231; Publication Year: 1995-2016; Population Group: Human. Search modes - Boolean/Phrase	810281
	S10	("stress" OR "stress management" OR "hydrocortisone" OR "cortisol" OR stress, psychological [mesh]) AND (S7 AND S9). Search modes - Boolean/Phrase	**671**
PROQUEST NURSING & ALLIED HEALTH SOURCE: 25/01/2016	1	("first trimester miscarriage" OR ("early miscarriage" OR "early pregnancy loss") OR ("spontaneous abortion" OR "pregnancy loss")) AND mesh.Exact("Abortion, Spontaneous")	228

	2	(stress OR (cortisol OR hydrocortisone)) AND mesh.Exact("Hydrocortisone" OR "Adaptation, Psychological; Social Support; Sociology, Medical; Stress, Psychological" OR "Stress, Psychological" OR "Stress" OR "Stress Disorders, Post-Traumatic" OR "Stress Disorders, Traumatic, Acute" OR "Stress Disorders, Traumatic")	10143
	3	1 and 2 = (("first trimester miscarriage" OR ("early miscarriage" OR "early pregnancy loss") OR ("spontaneous abortion" OR "pregnancy loss")) AND mesh.Exact("Abortion, Spontaneous" OR "Abortion, Spontaneous; Adult; Age of Onset; Aged; Case-Control Studies; Female; Humans; Incidence; Middle Aged; Parity; Risk Factors")) AND ("stress" AND mesh.Exact("Adaptation, Psychological; Social Support; Sociology, Medical; Stress, Psychological" OR "Stress, Psychological" OR "Stress" OR "Stress Disorders, Post-Traumatic" OR "Stress Disorders, Traumatic, Acute" OR "Stress Disorders, Traumatic"))	**2**
CLINICAL TRIALS SAGE JOURNALS: 27/01/2016	1	"early miscarriage" or "first trimester miscarriage" in all fields or "early pregnancy loss" or "pregnancy loss" inall fields or "spontaneous abortion" in all fields and "stress" or "cortisol" in all fields, from Jan 1995 through Jul 2016	**447**
JSTOR: 25/01/2016	1	("first trimester miscarriage" OR "early miscarriage" OR "early pregnancy loss" OR "spontaneous abortion") and ("stress" or "cortisol")	**917**
CLINICAL TRIALS WEBSITE*: 27/01/2016	1	spontaneous abortion; "pregnancy loss"; first trimester miscarriage, miscarrige and stress; ""first trimester miscarriage" OR "early miscarriage" OR "spontaneous abortion" OR "early pregnancy loss" OR "pregnancy loss") AND "stress"	**68**
A total of			**4140**
***Not included in Endnote, but in excel sheet.**			

Appendix 3. Eligibility criteria of full-text articles

	RCTs	Description of the inclusion criteria	Meet inclusion criteria?		
1	**STUDY ID**	**Adolfsson, A, 2006**	**Yes**	**No**	**Unclear**
	Study design	Prospective two-group randomized controlled trial.	1		
	Participants	All women who had experienced an early miscarriage.		0	
	Condition	Early miscarriage defined as a loss of a baby before 13 weeks of gestation.	1		
	Intervention	Structured conversation with one midwife for 1 hour focusing on the woman's experience of miscarriage and taking her through the process of Swanson's caring science theory.	1		
	Comparison	Regular visits with midwives during 30 minutes who asked about their general health and any complication.	1		
	Outcomes	Perinatal grief scale Swedish short version (PGS).		0	
	INCLUDED			No	
	Reason for exclusion	No pregnant women. No outcome of interest included.			
2	**STUDY ID**	**Côté-Arsenault, D, 2015**	**Yes**	**No**	**Unclear**
	Study design	Phase II: two-group randomised trial.	1		
	Participants	Pregnant women prior to 18 gestational weeks with at least one perinatal loss.	1		
	Condition	Women with a history of at least one spontaneous perinatal loss (miscarriage, stillbirth, or neonatal death).		0	
	Intervention	Caring-based nurse home visit intervention. Anxiety-reduction skills teaching in home visits.	1		
	Comparison	Pregnancy information booklets.	1		
	Outcomes	Self-report of threat appraisal of pregnancy (MTI); Pregnancy Anxiety Scale (PAS); Trait & State Anxiety (STAI), depression (CES/D); self-mastery; The maternal Antenatal Attachment scale (MAAS), Satisfaction with social support (SSQ-6).	1		
	INCLUDED			No	
	Reason for exclusion	Pregnancy loss as a composite variable.			
3	**STUDY ID**	**Huffman, C.S., 2015**	**Yes**	**No**	**Unclear**

	Study design	A randomized controlled trial.	1		
	Participants	Couples within three months after miscarriage.		0	
	Condition	Miscarriage defined as an unplanned, unexpected loss of pregnancy prior to 20 weeks gestation.	1		
	Intervention	Psychological well-being interventions.	1		
	Comparison	No treatment.	1		
	Outcomes	RIMS impact of miscarriage.		0	
	INCLUDED			No	
	Reason for exclusion	No pregnant women. No outcome of interest included.			
	STUDY ID	**Lok, IH 2006**	**Yes**	**No**	**Unclear**
	Study design	Randomized controlled trial. PhD thesis undertaken in The Chinese University of Hong Kong.	1		
	Participants	Women who had experienced a miscarriage.		0	
	Condition	Miscarriage defined as a loss of pregnancy up to 24 weeks' gestation (UK definition). WHO definition included up to 23 weeks' gestation.	1		
	Intervention	Group 1: "A one-hour psychological counselling immediately and 2 weeks after miscarriage".	1		
	Comparison	"Routine clinical care without specific psychological counselling".	1		
	Outcomes	General Health Questionnaire (GH1-12); Beck Depression Inventory (BDI).	1		
	INCLUDED			No	
	Reason for exclusion	No pregnant women. Results from chapter 5 in this PhD thesis are identical to Kong, 2014.			
5	**STUDY ID**	**Johnson, 2016**	**Yes**	**No**	**Unclear**
	Study design	Randomized controlled pilot trial.	1		
	Participants	Women who had experienced a perinatal loss in the last 2 weeks to 18 months.		0	
	Condition	Perinatal loss (miscarriage, stillbirth, or early neonatal death).		0	
	Intervention	Interpersonal psychotherapy (IPT) for major depression disorder (MDD).	1		
	Comparison	Coping with depression (CWD), a cognitive behavioural treatment which did not focus on perinatal loss nor social support.	1		
	Outcomes	Feasibility and acceptability; Time to MDD recovery (The longitudinal interval follow-up	1		

		examination); depressive symptoms (HRSD) and BDI; and social and interpersonal variable (Multidimensional Scale for Perceived Social Support and the Social adjustment Scale (SAS).			
	INCLUDED			No	
	Reason for exclusion	No pregnant women. Pregnancy loss as a composite variable			
6	**STUDY ID**	**Kersting, A, 2013**	**Yes**	**No**	**Unclear**
	Study design	Two-group randomized controlled trial.	1		
	Participants	Parent who had lost a child during pregnancy.		0	
	Condition	Miscarriage, termination of pregnancy due to fetal anomaly, or stillbirth. All participants were self-referral.		0	
	Intervention	Cognitive behavioural therapy for posttraumatic stress disorder PTSD.	1		
	Comparison	Waiting list condition.	1		
	Outcomes	Posttraumatic stress symptoms: Impact of Event Scale-Revised (IES-R); The inventory of complicated grief; the brief symptom inventory for assessing depression, anxiety and general mental health.	1		
	INCLUDED			No	
	Reason for exclusion	No pregnant women. Pregnancy loss as a composite variable.			
7	**STUDY ID**	**Kersting, A, 2011**	**Yes**	**No**	
	Study design	Two-group randomized controlled trial.	1		
	Participants	Mothers who had lost a child during pregnancy through.		0	
	Condition	Miscarriage, termination of pregnancy due to fetal anomaly, or stillbirth. All participants were self-referral.		0	
	Intervention	Cognitive behavioural therapy for PTSD.	1		
	Comparison	Waiting list condition.	1		
	Outcomes	Posttraumatic stress symptoms: Impact of Event Scale-Revised (IES-R); The inventory of complicated grief; the brief symptom inventory for assessing depression, anxiety and general mental health.	1		
	INCLUDED			No	
	Reason for exclusion	No pregnant women. Pregnancy loss as a composite variable			
8	**STUDY ID**	**Klinitzke, G, 2013**	**Yes**	**No**	**Unclear**

	Study design	Two-group randomized trial.	1		
	Participants	Partners who had lost their child during pregnancy.		0	
	Condition	The loss of a child during pregnancy by miscarriage, stillbirth, or medically indicated Abortion.		0	
	Intervention	5 weeks internet-based treatment program for writing therapy treatment program for writing therapy, which included the 3 phases "confrontation", "cognitive restructuring", and "social sharing".	1		
	Comparison	Waiting list condition.	1		
	Outcomes	General psychological distress (BSI); prolonged grief (ICG); Traumatic stress (IES-R); and social support (BSSS).	1		
	INCLUDED			No	
	Reason for exclusion	No pregnant women. No outcome of interest included.			
9	**STUDY ID**	**Kong G.W, 2014**	**Yes**	**No**	**Unclear**
	Study design	Two-group randomized trial.	1		
	Participants	Women who had been admitted with a diagnosis of miscarriage.		0	
	Condition	Miscarriage defined as a loss of baby occurring spontaneously before 24 weeks of gestation.	1		
	Intervention	Supportive counselling.	1		
	Comparison	Routine care.	1		
	Outcomes	General Health Questionnaire (GHQ-12) and Beck Depression Inventory (BDI).	1		
	INCLUDED			No	
	Reason for exclusion	No pregnant women.			
10	**STUDY ID**	**Kong, 2013**	**Yes**	**No**	**Unclear**
	Study design	A single randomised controlled trial.	1		
	Participants	Women presenting to the gynaecological unit for management of first-trimester miscarriage (missed or incomplete miscarriage) were invited to participate.		0	
	Condition	Missed miscarriage was confirmed by ultrasound examination with (i) intrauterine gestational sac with mean sac diameter of higher or equal 20 mm without fetal pole; (ii) presence		0	

		of fetal pole with no cardiac pulsation; and (iii) the gestational sac <20 mm with no interval growth or persistent absence of fetal cardiac pulsation on rescanning seven to 10 days later, or incomplete miscarriage which was supported by an opened endocervical os and ultrasonic findings of a mixed endometrial echogenicity.			
	Intervention	Surgical, medical and expectant management interventions.		0	
	Comparison			0	
	Outcomes	Chinese versions of 12-item General Health Questionnaire (GHQ-12); Beck Depression Inventory (BDI); Spielberger's State Anxiety Inventory (STAI); fatigue scale (FS); and Impact of Event Scale-Revised (IES-R).	1		
	INCLUDED			No	
	Reason for exclusion	Medical intervention. Pregnancy loss as a composite variable.			
11	**STUDY ID**	**Lee, C, 1996**	**Yes**	**No**	**Unclear**
	Study design	Two-group randomized controlled trial.	1		
	Participants	Women who had experienced a miscarriage and with a pregnancy of six to 19 weeks at the time of miscarriage, no previous miscarriages.		0	
	Condition	Miscarriage up to 19 week's gestation.	1		
	Intervention	Psychological debriefing for 1 hour by a female psychologist in their own home 2 weeks post-miscarriage.	1		
	Comparison	No intervention.	1		
	Outcomes	Hospital anxiety and depression scale (HADS); Impact of Events Scale (IES); Reaction to miscarriage questionnaire (RMQ); perceptions of care (POC).	1		
	INCLUDED			No	
	Reason for exclusion	No pregnant women.			
12	**STUDY ID**	**Lee, C, 2001**	**Yes**	**No**	**Unclear**
	Study design	Prospective, randomized controlled trial.	1		
	Participants	Women admitted to the gynaecologic unit with a clinical diagnosis of spontaneous abortion, a positive urinary pregnancy test, and transvaginal sonographic evidence of retained products of conception (POCs).		0	

	Condition				Unclear
	Intervention	Medical treatment protocol.		0	
	Comparison	Routine surgical evacuation of retained products of conception (ERPC).		0	
	Outcomes	The level of depression; general psychological; well-being; fatigue level; and social functioning.	1		
	INCLUDED			No	
	Reason for exclusion	No pregnant women. Medical intervention.			
13	**STUDY ID**	**Neugebauer, 2007**	**Yes**	**No**	**Unclear**
	Study design	An open pilot trial.		0	
	Participants	Participants were women seeking medical care for miscarriage at two New York City medical centers in low-income neighbourhoods.	1		
	Condition	Pregnancy loss up to 28 weeks of gestation (hereafter "miscarriage").		0	
	Intervention	Telephone-administered interpersonal counselling - a scaled-down. Variant of interpersonal psychotherapy (IPT).	1		
	Comparison	Treatment as usual (TAU).			Unclear
	Outcomes	The center for Epidemiologic Studies—Depression scale (CES-D).	1		
	INCLUDED			No	
	Reason for exclusion	No pregnant women. Miscarriage is defined within 28 weeks of gestation. Brief report. No full report.			
14	**STUDY ID**	**Neugebauer, 2006**	**Yes**	**No**	**Unclear**
	Study design	Pilot randomized controlled trial.	1		
	Participants	Participants were women seeking medical care for miscarriage from October 2001 to April 2002 in the emergency departments, the clinics, or the private practice setting in New York, serving predominantly low-income population.			Unclear
	Condition	Pregnancy loss up to 28 weeks of gestation (hereafter "miscarriage").		0	
	Intervention	Telephone-administered interpersonal counselling - a scaled-down variant of interpersonal psychotherapy (IPT).	1		
	Comparison	Treatment as usual (TAU).	1		
	Outcomes	Hamilton Rating Scale for Depression (HAM-D); Impaired functioning (Role Functioning	1		

		scale derived from 36 item Medical Outcomes Study questionnaire.			
	INCLUDED			No	
	Reason for exclusion	No pregnant women. Miscarriage is defined within 28 weeks of gestation.			
15	**STUDY ID**	**Nikcevic, A.V., 2007**	**Yes**	**No**	**Unclear**
	Study design	Two-groups randomized controlled trial.	1		
	Participants	Women attending for a routine scan at 10-14 weeks of gestation and found to have a missed miscarriage.		0	
	Condition	Missed miscarriage at 10 to 14 weeks' gestation.		0	
	Intervention	Psychological counselling.	1		
	Comparison	No psychological counselling.	1		
	Outcomes	Hospital Anxiety and Depression Scale (HADS) subscales anxiety and depression; Modified Texas Grief Inventory (TGI) subscales grief, self-blame and worry.	1		
	INCLUDED			No	
	Reason for exclusion	No pregnant women. Missed miscarriage.			
16	**STUDY ID**	**Swanson, K.M., 1999**	**Yes**	**No**	**Unclear**
	Study design	A Solomon-four-group randomized experimental design.	1		
	Participants	Women who miscarriage at 20 weeks or less, within 5 weeks of loss.		0	
	Condition	Miscarriage at 20 weeks or less.	1		
	Intervention	3 counselling session for 1 hour based on Swanson's Caring Theory and Meaning of Miscarriage Model at 1, 5 and 11 weeks after study entry.	1		
	Comparison	No intervention.	1		
	Outcomes	Rosenberg self-esteem scale; Profile of mood state (POMS) s; the impact of miscarriage scale (IMS).		0	
	INCLUDED			No	
	Reason for exclusion	No pregnant women. No outcome of interest included.			
17	**STUDY ID**	**Swanson, K, 2009**	**Yes**	**No**	**Unclear**
	Study design	Three couples-focused interventions and a control condition.			Unclear
	Participants	Couples of which the woman had experienced a miscarriage during the first year after miscarriage.		0	

	Condition	Miscarriage: unexpected or unplanned loss of pregnancy prior to 20 week's gestation.	1		
	Intervention	Nurse caring (NC): three counselling sessions for 1 hour: self-caring (SC): Three video and workbook modules: combined caring (CC): one counselling session for 1 hour, plus three SC modules.	1		
	Comparison	No treatment.	1		
	Outcomes	Depression (CES-D); Miscarriage Grief Inventory (adapted from the Texas Grief Inventory) subscales; pure grief (PG) and grief-related emotions (GRE).	1		
	INCLUDED			No	
	Reason for exclusion	No pregnant women.			
18	**STUDY ID**	**Klein, S, 2012**	**Yes**	**No**	**Unclear**
	Study design	External pilot of a modified "partially randomised patient preference" (PRPP) design that allows patients to opt for their preferred treatment allocation whilst retaining (to some extent) a conventional RCT design for those who are willing to accept random allocation.		0	
	Participants	Women who consecutively attended one of two EPAUs in Scotland and who have experienced the complete management of the index miscarriage before 24 weeks of gestation and their partners.		0	
	Condition	Miscarriage before 24 weeks of gestation.	1		
	Intervention	Web-based intervention (designed to promote mental wellbeing).	1		
	Comparison	Standard care.	1		
	Outcomes	Prevalence of anxiety and depression (HADS); The overall quality of life (SF-36).	1		
	INCLUDED			No	
	Reason for exclusion	No pregnant women. "Partially randomised patient preference" (PRPP) design.			
19	**STUDY ID**	**Sejourne, 2007**	**Yes**	**No**	**Unclear**
	Study design	Quasi-randomised controlled trial.		0	
	Participants	Women who had curettage or aspiration for a miscarriage.		0	
	Condition	Miscarriage defined as the expulsion of the maternal organism of an embryo or fetus of less	1		

	than 500 grams [1], which corresponds to approximately 20-22 weeks gestation.		
Intervention	All the women in Immediate intervention group (II) were asked to participate in a supportive intervention consisting of an interview with a psychologist and a telephone follow 15 days later. The average duration of interviews was 37 minutes (SD 14.38; 20 min - max 90).	1	
Comparison	All women of the Differed intervention (ID) group were asked to participate in research on the psychological experience of a miscarriage. A support service three months after their miscarriage was proposed.	1	
Outcomes	The Hospital Anxiety and Depression Scale (HADS); the Impact of Events Scale-Revised (IES-R); and the Texas Grief Inventory (TGI) at 3 and 10 weeks as well as 6 months.	1	
INCLUDED			No
Reason for exclusion	No pregnant women. Quasi-randomised controlled trial.		

Appendix 4. Main characteristics of excluded RCTs

Author, year	Design, country	Participants Sample size	Inclusion and exclusion criteria	Intervention and control group	Outcomes	Main results
Côté-Arsenault, 2014	Phase II: two-group randomised trial. Obstetrical healthcare provider sites in New York.	N=24 pregnant women prior to 18 gestational weeks with at least one spontaneous perinatal loss (miscarriage, stillbirth and neonatal death). Intervention (n=13); Control group (n=11).	**Inclusion criteria:** healthy, adult pregnant women, able to speak, read and write English, receiving prenatal care, 21 years of age or over and currently in their first or second trimester. **Exclusion criteria:** women with medical conditions or fetal diagnoses that precluded any chance of a healthy baby, multiple gestation beyond twins, or uncontrolled medical or mental illness.	**Intervention group:** 6 session of caring-based nurse home visit intervention based on Swanson's Theory of Caring, pregnancy diary, and anxiety-reduction skills teaching in home visits (HV). **Control group:** pregnancy information booklets on the same schedule as the intervention group home visits (HV).	**Emotional State**: PAS; STAI; CES-D and self-mastery. **Mother-baby relationship**: MAAS. **Social Network**: SSQ-6	No statistically significant differences were found between all outcomes means over the post baseline time period between groups. Only satisfaction scores had a significant interaction for post baseline time (p=0.0057), but not for further follow-ups.
Johnson, 2016	Randomized controlled pilot trial.	N=50 Women who had experienced a perinatal loss (including early and late fetal deaths, the death of a live-born neonate within the first	**Inclusion criteria:** between 18 and 50 years old; currently met all criteria for DSM-IV major depressive disorder as assessed by the Structure Clinical Interview for DSM-IV Axis I Disorders.	**Intervention group:** Interpersonal psychotherapy (IPT) for major depression disorder (MDD) adapted for perinatal loss. Both treatment consisted of a pre-group individual session, 12 group sessions, and a 1-	**Feasibility and acceptability**. **Time to MDD recovery**. Recovery is defined as eight consecutive weeks of a psychiatric status ratings	Participants who were allocated to the interpersonal therapy condition had a 35% higher incidence of MDD recovery at any given time during the study compared to those participants

		28 days, and termination due to medical indications) in the last 2 weeks to 18 months. Intervention (n=25); Control (n=25).	**Exclusion criteria:** women whose onset of current major depressive episode occurred prior to news of difficulties with the pregnancy or health risk to the infant; meeting criteria for lifetime schizophrenia, schizoaffective, or bipolar I disorder; current drug or alcohol dependence; current anorexia/bulimia; severe borderline personality disorder and any interpersonal psychotherapy (IPT) or cognitive behavioural treatment in the previous 12 weeks.	month individual booster session (a total of 14 sessions). Groups were slow-open, with group members able to enter the groups every 4 weeks. **Control group:** Coping with Depression (CWD), a cognitive behavioural treatment which did not focus on perinatal loss nor social support.	(PSRS) 1-2; Time to recovery is defined as the number of weeks between baseline and the beginning of the 8+ week series of PSR 1-2. **Time to PTSD recovery**. Also, post-traumatic stress disorder (PTSD) and non-study treatment received (medications or psychotherapy) using the same method. **Depressive symptoms.** **Social and interpersonal variables**. **Grief**.	in the control group with non-significant results (hazard ratio=1.35; 95% CI=0.60-3.02). The median time to recovery was 15 weeks for IPT and 22 weeks for the control group from baseline.

Kersting A, 2013	Two-group randomized controlled trial, Germany.	N=228 parents who had lost a child during pregnancy. Intervention (n=115); Control (n=113).	**Inclusion criteria:** having lost a child during pregnancy because of miscarriage, termination due to medical indications, or stillbirth; residence in a European German-speaking country; written and oral fluency in German; access to the Internet; age higher or equal 18 years old, and signed informed consent. **Exclusion criteria**: severely depressed mood or suicidal ideation; dissociative tendency; Risk of psychosis; current pregnancy; substance abuse and dependency; currently receiving treatment elsewhere.	**Intervention group:** an internet-based cognitive behavioural treatment program for complicated grief was specifically adapted to the needs of mothers after loss of a child during pregnancy. **Control group:** waiting list condition (WLC). Participants in this group were invited to begin the cognitive treatment after the post-test.	**Posttraumatic stress symptoms** using the IES-R. **Prolonged grief** using the ICG **General psychopathology and depression** using the BSI	Intervention group showed significantly reduced symptoms of posttraumatic stress, prolonged grief, depression and anxiety relative to the WLC control group. Significant improvement in all symptoms of posttraumatic stress disorder (PTSD) and prolonged grief was found from the post treatment evaluation to the 12-months follow-up.
Kersting A, 2011	Two-group randomized controlled trial, Germany.	N=83 parents who had lost a child during pregnancy. Intervention (n=48); Control (n=35).	**Inclusion criteria:** having lost a child during pregnancy because of miscarriage, termination due to medical indications, or stillbirth; residence in a European German-speaking country; written and oral fluency in German; access to the Internet; age higher or equal 18 years old, and signed informed consent.	**Intervention group:** an internet-based cognitive behavioural treatment program for complicated grief was specifically adapted to the needs of mothers after loss of a child during pregnancy. **Control group:** waiting list condition.	**Posttraumatic stress** reactions using the IES. **Grief** using the ICG. **General psychopathology and depression** using the BSI.	Participants in the treatment group showed significant improvements in posttraumatic stress, grief, depression and overall mental health, but not in anxiety or somatization. Medium to large effect sizes were observed, and the

			Exclusion criteria: severely depressed mood or suicidal ideation; dissociative tendency; Risk of psychosis; current pregnancy; substance abuse and dependency; currently receiving treatment elsewhere.	Participants in this group were invited to begin the cognitive treatment after the post-test.		improvement was maintained at 3 month follow-up.
Kong, G.W., 2014	Randomised controlled trial, Hong Kong.	N=280 patients diagnosed to have miscarriage were routinely managed as inpatients. Intervention (n=140); Control (n=140).	Inclusion criteria: Miscarriage defined as a loss of pregnancy up to 24 weeks' gestation. **Exclusion criteria:** patients who were unwilling to participate; with psychiatric disease requiring active treatment; who were non-Chinese; who were visitors to Hong Kong (e.g. tourists).	**Intervention group:** 1 hour counselling from a nurse counsellor after completion of baseline questionnaires in the hospital before discharge. They were followed up by the nurse two weeks later by telephone to reinforce the counselling. **Control group:** routine clinical care without specific psychological counselling.	**Proportion of women suffering psychological distress,** which was defined using the GHQ-12 for mental health. GHQ-12 score >=4 at 3 months after miscarriage. **Severity of depression** using the BDI. **Marital relationship adjustment** using the DAS scale.	No statistically significant differences were found in either the median scores or proportions of women at 6 weeks, 3 months or 6 months. By subgroup, women with high baseline GHQ-12 scores (>=4) had significant differences in the median scores of GHQ-12 between groups at 6 weeks and 3 months. Women with high baseline BDI scores (>12) had significant differences in the proportion scores of

						BDI between groups at 6 weeks. Both analysis were not intention-to-treat analysis.
Lee, 1996	Two-group randomised controlled study, Sheffield University Hospital NHS Trust, UK.	N=39 women who had experienced a miscarriage. Intervention (n=21); Control (n=18).	**Inclusion criteria:** pregnancy of six to 19 weeks at the time of miscarriage; aged 18 years or over; able to speak and read English fluently, had wanted the pregnancy to continue and were not under psychological or psychiatric care or taking psychoactive drugs at the time of miscarriage. **Exclusion:** women who had been intending to terminate the pregnancy because of the potential complexity of the emotional responses.	**Intervention:** One-hour-long session of psychological debriefing, by a female psychologist, in their own homes, at approximately two weeks post-miscarriage (phase 2). **Control group:** No intervention.	**Anxiety and depression** using The Hospital Anxiety and Depression Scale (HADS) **Stress using** The Impact of Events Scales (IES) **Reaction to Miscarriage Questionnaire** (RMQ). **Perceptions of Care** (POC)	The results failed to show significant difference between those women who were in an intervention group versus women in a control group in all of the outcomes (stress, depression and anxiety). Outcome scores at one week significantly predicted outcome at four months, suggesting that early assessment would be important in determining which women should be offered intervention.

Swanson, K, 2009	Randomised controlled trial, USA.	N=341 Couples of which the woman had experienced a miscarriage during the first year after miscarriage. Intervention: nurse caring (n=168 couples), self-caring (n=172 couples), combined caring (n=170 couples); Control (n= 172 couples).	**Inclusion criteria**: Couples were deemed eligible if both agreed to participate; they reported an unplanned, unexpected loss of pregnancy prior to 20 weeks gestation; they could speak and write in English and they were in a self-proclaimed committed relationship, geographically accessible, and within 3 months of loss. **Exclusion criteria:** unmarried people aged <19 were not eligible. Couples were excluded if only one member returned the baseline survey.	**Intervention group**: nurse caring (NC): three counselling sessions for 1 hour: self-caring (SC): Three video and workbook modules: combined caring (CC): one counselling session for 1 hour, plus three SC modules. **Control group:** No treatment.	**Depression** using the Center for Epidemiological Studies-Depression Scale (CES-D) **Grief** using the Miscarriage Grief Inventory (MGI) with two subscales: **PG** subscale focused on thinking about the miscarriage and crying inwardly and outwardly about the lost baby. **GRE** subscale focused on feelings that indicate distance (numbness, avoiding thinking about it) and distress (guilty, angry, unfair).	Nurse caring showed the broadest positive impact on couples' resolution of grief and depression. However, grief resolution was accelerated by self-caring for women and combined caring for men.

Appendix 5. Outcome matrix of excluded RCTs

Type of intervention Author, year	Review Primary outcomes		Review Covariates		Trial variables					Data collection times (follow-ups)
	Stress	cortisol	Anxiety	Depression	Grief	General Health	Social Support	Impact of miscarriage	Others	
Six one-hour counselling nurse vs information booklets										
Côté-Arsenault, D., 2014	×	×	✓	✓	×	×	✓	×	Antenatal attachment; pregnancy; Self Mastery	At baseline (first or second trimester in pregnancy), at time 2 = 22 to 24 weeks gestation and time 3 = 32 to 34 weeks gestation.
Measurement			PAS & STAI	CES-D			SSQ-6		MAAS; MTI	
14 sessions Interpersonal psychotherapy (IPT) vs Coping with Depression (CWD)										
Johnson, 2016	✓	×	×	✓	✓	×	✓	×	Distress*	At baseline, at "treatment week 4" (average 7 weeks after baseline) and "treatment week 8" (average 11 weeks after baseline); immediately following treatment (an average of 18 weeks after baseline); and also at 3 and 6 months after the end of the treatment.
Measurement	LIFE			HRSD & BDI	PBG S & ICG		SAS		PTSD	
One one-hour counselling vs no counselling										
Kong, G.W., 2014	×	×	×	✓	×	✓	×	×		At baseline (diagnosis of miscarriage at hospital), and at 6 weeks, 3 and 6 months after miscarriage.
Measurement				BDI		GHQ-12				
Lee, C., 1996	✓	×	✓	✓	×	×	×	✓	Perception of care	At baseline (approximately 2 weeks

Measurement	IES		HADS	HADS				RMQ	POC	after miscarriage) and 4 months post miscarriage.
Internet-based intervention vs waiting list										
Kersting, A., 2013	✓	×	✓	✓	✓	×	×	×	Mental health	At baseline (pre-treatment time); at 5 weeks after intervention (time 2 or post treatment time); at 3 months follow-up (time 3) and at 12 months follow-up (time 4).
Measurement	IES-R		BSI for anxiety	BSI for depression	BSI for grief				BSI for general mental health	
Kersting, A., 2011	✓	×	✓	✓	✓	×	×	×	Mental health	At baseline (pre-treatment time); at 5 weeks after intervention (time 2 or post treatment time) and at 3 months follow-up (time 3).
Measurement	IES-R		BSI for anxiety	BSI for depression	BSI for complicated grief				BSI for general mental health	
Three one-hour counselling vs no counselling										
Swanson, K., 2009	×	×	×	✓	✓	×	×	×		At 1 month (baseline), 3, 5 and 13 months after miscarriage.
Measurement				CES-D	PG & GRE					
Total of Studies	**4**	**0**	**4**	**7**	**4**	**2**	**3**	**1**		

✓Indicates full reporting of results for treatment comparison of interest; × Indicates no reporting; ✹ Indicates partial reporting (i.e. only the p-value is given for the comparison). BDI (Beck Depression Inventory); BDI-II (Beck Depression Inventory-II); BSI (brief symptom inventory); BSSS (Berlin Social Support Scales); CES-D (The Centre for Epidemiologic Studies Depression Scale); DAS (Dyadic Adjustment Scale); GRE (grief-related emotions); GHQ-12 (General Health Questionnaire); HADS (Hospital Anxiety and Depression Scale); HRSD (Hamilton Rating Scale for Depression);); ICG (Inventory of Complicated Grief); IES (Impact of Event Scale); IES-R Impact of Event Scale-Revised; LIFE (The Longitudinal Interval Follow-up Examination) MAAS (The Maternal Antenatal Attachment Scale); MTI (Moneyharm Threat Index); PAS (Pregnancy Anxiety Scale); PG (pure grief); PBGS (Perinatal Bereavement Grief Scale); RMQ (Reaction to miscarriage questionnaire); POC (Perceptions of care); SAS (Social Adjustment Scale); STAI (State & Trait Anxiety Scale).*Distress was measure by The Longitudinal Interval Follow-up Examination (LIFE) tracking post-traumatic stress disorder (PTSD); However, no specific measured was used during the study.

Appendix 6. Risk of bias of excluded studies

	Meet inclusion criteria?			
Côté-Arsenault, D, 2015	**Low**	**High**	**Unclear**	**Support for judgement**
Random sequence generation			x	It is not stated in the paper.
Allocation concealment			x	It stated that "random assignment to group, intervention or control was made with equal probability", but it did not describe it.
Blinding of participants and personnel			x	There is not a statement of participants being blinded.
Blinding of outcome assessment	x			"A research assistant blind o group assignment, picked up completed questionnaires from all women".
Incomplete outcome data	x			95.8% of enrolled woman (n=23) completed the study; 100% retention in the control and 92% in the intervention group.
Selective outcome reporting?			x	All the pre-selected outcomes seemed to be addressed. Protocol was not accessed.
Other bias				
Notes				
Johnson, 2016	**Low**	**High**	**Unclear**	**Support for judgement**
Random sequence generation	x			"Randomization occurred in a 1:1 ratio and was stratified by type of loss (miscarriage, stillbirth, early neonatal death) and whether or not a participant was receiving other mental health (pharmacotherapy or psychotherapy) treatment. It was generated by an individual not affiliated with the study.
Allocation concealment	x			"Group assignment placed in sequentially numbered opaque envelopes that were sealed until the principal investigator verified that each individual was eligible for the study".
Blinding of participants and personnel			x	Participants not stated as blinded.
Blinding of outcome assessment			x	Clinicians and outcomes assessors not stated as blinded.
Incomplete outcome data	x			Of the 25 women randomised to the intervention group, 7 dropped out of treatment and 3 were lost to follow-up; Of the 25 women in the control group, 11 dropped out of treatment and 2 were lost to follow-up. 90% of participants provided at least some follow-up data.
Selective outcome reporting?			x	Protocol is not mentioned. However, all the pre-selected outcomes seemed to be addressed.
Other bias				
Notes				
Kersting, A, 2013	**Low**	**High**	**Unclear**	**Support for judgement**
Random sequence generation	x			Randomisation using a true random number service (http://www.random.org). Randomisation was performed by the study coordinator and was not stratified by any participant characteristics.

Allocation concealment			x	It is not stated who or how they allocated participants.
Blinding of participants and personnel			x	It is not stated.
Blinding of outcome assessment			x	It is not mentioned.
Incomplete outcome data	x			A total of 115 participants were randomized. Of these, 16 dropped out during treatment. A total of 99 participants (86.1%) in the TG completed the intervention and posttreatment assessment. Of the 113 participants randomized to the WLC, 13 dropped out during the waiting list with a competition rate of 88.5%
Selective outcome reporting?			x	Protocol is not mentioned. However, all the pre-selected outcomes seemed to be addressed.
Other bias				
Notes				

Kersting, A, 2011	**Low**	**High**	**Unclear**	**Support for judgement**
Random sequence generation	x			Randomization was done using a random number table retrieved from (http://ts.nist.gov).
Allocation concealment			x	It is not stated who or how they allocated participants.
Blinding of participants and personnel			x	It is not stated.
Blinding of outcome assessment			x	It is not mentioned.
Incomplete outcome data	x			A total of 78 participants were randomized. A total of 59 (76%) completed the intervention and posttreatment assessment. The response rates in the control group (WLC, 79%; n=26) and the intervention group (TG, 72%; n=33).
Selective outcome reporting?			x	Protocol is not mentioned. However, all the pre-selected outcomes seemed to be addressed.
Other bias				
Notes				

Kong G.W, 2014	**Low**	**High**	**Unclear**	**Support for judgement**
Random sequence generation	x			"Computer-generated random number using block sized between two and ten to ensure approximately equal group sizes".
Allocation concealment	x			"The results of group allocation from randomisation were sealed in a set of opaque and sequentially numbered envelopes, and released by a research nurse after randomisation".
Blinding of participants and personnel			x	It is not specified.
Blinding of outcome assessment			x	It is not specified.
Incomplete outcome data	x			A total of 368 women fulfilling the recruitment criteria. Of these, 88 (23.9%) declined.

Selective outcome reporting?			x	Protocol is not mentioned. However, all the pre-selected outcomes seemed to be addressed.
Other bias				
Notes				

Lee, C, 1996	**Low**	**High**	**Unclear**	**Support for judgement**
Random sequence generation	x			"Women were randomly allocated to Group 1 or Group 2".
Allocation concealment			x	Not stated.
Blinding of participants and personnel			x	Participants not stated as blinded.
Blinding of outcome assessment			x	Clinicians and outcomes assessors not stated as blinded.
Incomplete outcome data		x		7 women did not return questionnaire and were excluded from the study. 14 indicated that they did not wish to have a follow-up appointment and were excluded from the data analysis.
Selective outcome reporting?	x			Reports all pre-specified outcomes but we were not able to access the trial protocol.
Other bias	x			There was no statement indicating that the study was stopped early.
Notes				

Swanson, K, 2009	**Low**	**High**	**Unclear**	**Support for judgement**
Random sequence generation	x			"Card-pulling protocol".
Allocation concealment	x			"It involved two team members: one who shuffled the cards, vigorously shook the box, and lifted the box above the card puller's eye level, and the other who reached up and blindly pulled a card out of the box". "After a card was drawn, both members recorded results".
Blinding of participants and personnel				Participants not stated as blinded.
Blinding of outcome assessment			x	Clinicians and outcomes assessors not stated as blinded.
Incomplete outcome data	x			A total of 341 couples were randomized. 46 participants dropped the study, 20 women and 26 men. Nurse Caring: 1 lost of 168; self-caring: 25 lost of 172; combined caring: 11 lost of 170; and no treatment: 9 lost of 172.
Selective outcome reporting?	x			Protocol was not accessed. However, all the pre-selected outcomes seemed to be addressed.
Other bias				
Notes				

Appendix 7. Protocol of the systematic review

Review title: "No-medical interventions for reducing stress levels in the subsequent pregnancy of women after miscarriage: a systematic review of randomized controlled trials"

Anticipated or actual start date: 14/01/2016

Anticipated completion date: 30/08/2016

Stage of review at the time of this submission: "Formal screening of search results against eligibility criteria". Started.

Named contact: Ms Indra San Lazaro Campillo. indra.campillo@ucc.ie. Department of Obstetrics & Gynaecology Cork University Maternity Hospital. 5th floor - Postgraduate Study Room, 5S - 30. Wilton, Cork City, Cork, N/A. The Republic of Ireland. Phone number: +353861047766.

Organizational affiliation of the review: None

Review team member's and their organisational affiliations: Dr Keelin O'Donoghue, Senior Lecturer and Consultant Obstetrician and Gynaecologist, Cork University Maternity Hospital, University College Cork, Ireland; Dr Sarah Meaney, Research Officer, National Perinatal Epidemiology Centre, University College Cork, Ireland; Indra San Lazaro Campillo, PhD Candidate, Department of Obstetrics and Gynaecology, University College Cork, Ireland. Karen McNamara, PhD Candidate, Pregnancy Loss Research Group, Department of Obstetrics and Gynaecology, University College Cork, Ireland and Cork University Maternity Hospital, Cork, Ireland,

Funding sources/sponsors: None.

Conflicts of interest: The authors declare that they have no known conflicts of interests.

Collaborators: Dr Paul Corcoran, Senior Lecturer in Perinatal Epidemiology, National Perinatal Epidemiology Centre in the Department of Obstetrics and Gynaecology and with the Department of Epidemiology and Public Health, University College Cork, Ireland. Members of HRB Clinical Research Facility Cork.

Review question: Do non-pharmacological interventions reduce the level of perceived stress in pregnant women who have a history of first-trimester miscarriage in comparison to non-intervention or standard care?

PICO question:

1. Participants: Pregnant women who have a history of early miscarriage
2. Intervention: Non-medical/pharmacological interventions: behavioural interventions, psychological interventions, information or support groups.
3. Control group: Standard care or non-intervention or other non-pharmacological intervention.
4. Outcome: Level of stress measured by questionnaires or cortisol levels

Objective: To assess the effectiveness of non-pharmacological interventions to reduce the level of stress in pregnant women who have a history of early miscarriage.

Search strategy. We will search the following psychological and social electronic bibliographic databases: PubMed, Cochrane Library, CENTRAL, EMBASE, CINAHL,

Maternity & Infant Care Database, ProQuest Nursing and Allied Health Source, Web of Science (Web of Knowledge), Science Direct, JSTOR, CLINICAL TRIALS. Databases include in EBSCOhost: Academic Search Complete, eBook Collection (EBSCOhost), General Science Full Text (H.W. Wilson), Library, Information Science & Technology Abstracts, PsycARTICLES, Psychology and Behavioral Sciences Collection, PsycINFO, Social Sciences Full Text, SocINDEX with Full Text, UK & Ireland Reference Centre. We will also include clinical trials registration websites such as clinicaltrials.gov, EU clinical trials registration and International clinical trials registry platform for ongoing or recently completed trials.

We will use Medical subject headings (MeSH) or major topics when these are available and it will be adapted to each requirement of the electronic databases. The search strategy will include terms relating to the condition and with the intervention such as: “Spontaneous Abortion”; “Embryo Loss”; “Stress, Physiological”; “Stress Disorders, Traumatic”; “Stress Disorders, Traumatic, Acute”; “Stress Disorders, Post-Traumatic”. MeSH terms which are related with stress: “Stress, Psychological”; “Stress, Physiological”; “Stress Disorders, Traumatic”; “Stress Disorders, Traumatic, Acute”; “Stress Disorders, Post-Traumatic” and MeSH terms which are related with cortisol: “Hydrocortisone”.

There will be no restrictions by study design or language restrictions. The literature search will be limited to human. Studies published between January 1995 and the date the searches are run will be sought. Quantitative studies will be included in the search strategy. We will also scan the references lists of included studies or relevant reviews identified through the search. A final search will be run before the final analysis.

URL to search strategy: This is an example of the research strategy done in PubMed: ("first trimester miscarriage") OR "early pregnancy loss" OR "early miscarriage" OR "pregnancy loss" OR "miscarriage" OR miscarriag* OR (("Abortion, Spontaneous"[Mesh] OR "Abortion, Habitual"[Mesh]) OR "Embryo Loss"[Mesh]) AND ("Stress Disorders, Traumatic, Acute"[Mesh] OR "Stress Disorders, Post-Traumatic"[Mesh] OR "Stress Disorders, Traumatic"[Mesh] OR "Stress, Psychological"[Mesh] OR "Stress, Physiological"[Mesh]) AND (("1995/01/01"[PDat] : "3000/12/31"[PDat]) AND Humans[Mesh]).

When MeSH or major topics are not available in the electronic database we will use the following terms: “early miscarriage” OR “first-trimester miscarriage” OR “spontaneous abortion” OR “pregnancy loss”, “stress” OR “psychological stress” and “cortisol”.

Participants/population: Our study population are pregnant women who have a history of early miscarriage. We will consider trials that define miscarriage as a loss within the first 12 completed weeks of pregnancy[1]. Even though our study will be focused on early miscarriage, we will include studies which include the word miscarriage, spontaneous abortion or pregnancy loss in their titles. This decision was made due to the different definitions of miscarriage internationally[2]. However, we will only include trials that define miscarriage as a spontaneous loss of pregnancy before the fetus reaches viability, which is considered from the time of conception until 24 weeks of gestation[3]. When miscarriage was analysed as a composite with other adverse pregnancy outcomes such as stillbirth or perinatal death, contact with the authors was made by email to try to obtain subsamples of the full datasets.

Intervention: This systematic review will include randomised controlled trials that assess the effectiveness of non-medical interventions such as behavioural, psychological, information or support groups. We will consider trials if they compare the experimental interventions with no intervention groups, usual care or other non-medical intervention groups.

Comparator/control: usual care or non-intervention.

Types of study to be included initially: All published randomised controlled trials (RCTs), including cluster RCTs will be considered in our systematic review. We will exclude controlled (non-randomised) clinical trials, prospective and retrospective cohort studies, case-control or nested case-control studies, cross-sectional studies, case series and case reports.

Context: There will be no restrictions by type of settings or country

Primary outcome: Level of stress is the primary outcome of this review. We will consider trials that measure both perceived level of stress (e.g. validated questionnaires) and/or physiological measures of stress (e.g. biomarkers of stress such as cortisol in saliva, blood, urine or hair).

Definition of primary outcome: Perceived stress is defined as the feelings or thoughts that an individual has about how much stress they are under at a given point in time or over a given time period[4]. Levels of cortisol will be included when they are measured in saliva, urine, blood or hair.

Types of endpoints for primary outcome: Levels of perceived stress should be measured before and after the intervention using psychometric scales such as the Perceived Stress

Scale[5]. Cortisol levels should be measured before and after the intervention using saliva, urine, blood and/or hair.

Secondary outcome: Secondary outcomes will include other mental health disorders such as anxiety and depression. Trials that only consider anxiety and depression, but do not include levels of stress will be excluded from the search. Two main secondary outcomes will be included in this review. The first one is the level of anxiety. Trait anxiety is defined as "the stable tendency to attend to, experience, and report negative emotions such as fears, worries, and anxiety across many situations. This is part of the personality dimension of neuroticism versus emotional stability. Trait anxiety also manifests by repeated concerns about and reporting of body symptoms[6].

The second outcome is depression. Depression is characterized by "depressed or sad mood, diminished interest in activities which used to be pleasurable, weight gain or loss, psychomotor agitation or retardation, fatigue, inappropriate guilt, difficulties concentrating, as well as recurrent thoughts of death. Depression is more than a "bad day"; diagnostic criteria established by the American Psychiatric Association dictate that five or more of the above symptoms must be present for a continuous period of at least two weeks[7].

Types of endpoints for secondary outcomes: levels of anxiety should be measured before and after the intervention in both groups using similar psychometric scales to The State-Trait Anxiety Inventory (STAI)[8]. Levels of depression should be measured before and after the intervention in both groups using similar psychometric scales to the Beck Depression Inventory (BDI)[9].

Data extraction: We will use ENDNOTE X7 as a reference management software to import, classify and manage all the citations. All the citations will be automatically imported to ENDNOTE according to electronics databases. Citations will be imported at the time they are being reviewed. When definitions of miscarriage are not clear in the titles or abstracts, full-texts will be uploaded and read. Duplications of the citations will be managed with ENDNOTE X7.

Two reviewers will screen for potentially eligible records independently. All records will be screened by title first and by abstract second. For those abstracts that meet the inclusion criteria, full-texts will be read and reviewed. In case of discrepancies between the reviewers, a third reviewer will be asked to evaluate. If the methodology or outcome is uncertain in the full-text, reviewers will contact the authors of the original studies to obtain more information about the study. A maximum of three attempts to contact the authors will be made.

We will use the "Data collection form for intervention reviews: RCTs only from April 2014" for collecting, reporting and analysing information about the studies[10]. We will complete the form for all the potential studies included by the search strategy and we will assess the eligibility criteria for each one. In summary, we will collect data for all potential studies related to characteristics of the study, general information and study eligibility, methods, characteristics of trial participants, characteristics per intervention group: intervention and/or comparison group, characteristic of outcome measure and other characteristics.

Risk of bias assessment: We will assess the risk of bias for each study using the "Assessment of Risk of Bias" by the Cochrane Bias Methods Group[10]. There are six domains to be considered: selection bias, performance bias, detection bias, attrition bias, reporting bias and other bias. Definition of each bias and their judgements are included in Appendix 5 of the handbook[10]. The criteria for judging the risk of bias in the "Risk of Bias" assessment tool is included in Appendix 6[10]. In summary, we will assess the below risk of bias: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), other bias (bias due to problems not covered in the previous bias).

Strategy for data synthesis: Number of participants in each group and the number of missing data will be reported for all the studies that meet the inclusion criteria. If data are appropriate for synthesis, we will classify them by type of data measured in each outcome (e.g. dichotomous or continuous). For dichotomous variables, we will obtain descriptive and association findings (e.g. odds ratio, risk difference, confidence intervals (CI) and/or significant values (p-values). For continuous outcomes we will obtain mean, standard deviation (SD) and/or another type of variance outcome specified (e.g. standard error, SE). Review Manager 5 (RevMan 5), the software used for preparing and maintaining Cochrane Reviews will be used for creating forest plots[11, 10].

A narrative synthesis will be also completed to describe the comparison group, outcome and subgroup if any, as described in the paper. We will also include time points; reasons for post-intervention or change from baseline; reasons for missing participates or moved

from other groups; and statistical methods used and appropriateness of these methods (e.g. adjustment for correlation).

We will use the "The Grading of Recommendations Assessment, Development and Evaluation (GRADE) to assess the quality of evidence, the strength of recommendations and the evidence summaries in this systematic review[12].

Finally, we will use "Outcome Reporting Bias in Trials (ORBIT)" and "Selective Outcome Reporting (SOR)" to assess possible publication and outcome reporting bias[13].

Individual patient data (IPD) will not be considered in this review. Main limitations of including IPD are described by Riley, R.D., et al (2010). These limitations include "substantial time and costs to contact study authors, obtain their individual participant data, input and clean the provided individual participant data, resolve any data issues through dialogue with the data providers, and generate a consistent data format across studies"[14].

Analysis of subgroups or subsets: If data are available, we will analyse the type of miscarriage according to the weeks of gestation. Two groups will be made, the first one including women who had a first-trimester miscarriage, (e.g. loss before 12 completed weeks of gestation), and second-trimester miscarriage (e.g. loss between 13 weeks of gestation and before 24 completed weeks of gestation).

Reporting of findings. The Preferred Reporting Items for Systematic Review and Meta-Analysis will be used for reporting the methodology and findings of this systematic review[15].

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