The impact of first pregnancy and delivery on pelvic floor dysfunction

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DECLARATION

I declare that this thesis in candidature for the degree of Doctor of Philosophy has been composed entirely by myself. The work which is documented in this thesis was carried out by myself. All sources of information contained within which have not arisen from the results generated have been acknowledged.

Constantin Durnea

ABBREVIATIONS

ASC - anal sphincter complex

BMI - body mass index

CI – confidence intervals

COCP - combined oral contraceptive pill

CUMH - Cork University Maternity Hospital

DNPFD – Denovo postnatal onset PFD

EAS - external anal sphincter

ELCS - elective Caesarean Section

EMCS – emergency Caesarean Section

FD – faecal dysfunction

FI – faecal incontinence

FlI – flatus incontinence

FU – faecal urgency

ICS – International Continence Society

IOL – induction of labour

IUGA - International Urogynaecological Association

LAM – levator ani muscle

M [IQR] - the median score value and interquartile range

MOD – mode of delivery

MUI – mixed urinary incontinence

OAB – overactive bladder

OR – odds ratios

PFD - pelvic floor dysfunction

PIIINP - procollagen type III N-terminal propeptide

PINP - procollagen type I N-terminal propeptide

POP – pelvic organ prolapse

POP-Q – pelvic organ prolapse quantification

PPFD - Prepregnancy PFD persisting postnatally

RFs - risk factors

RR - relative risk

SD – sexual dysfunction

SUI – stress urinary incontinence

SVD - spontaneous vaginal delivery

UD – urinary dysfunction

UI – urinary incontinence

UU – urinary urgency

UUI – urgency urinary incontinence

VD – vaginal delivery

ABSTRACT

Background and Aims

Pelvic floor dysfunction (PFD) is a common problem among women, having a big impact on their quality of life and imposing a significant burden on society. The association between PFD and childbearing is commonly recognised, where the first delivery has been shown to have the greatest impact on the pelvic floor. However, the prevalence of various PFD symptoms in nulliparous women and associated risk factors are poorly described in the literature. Additionally, the role of prepregnancy pathology in postnatal PFD has not been investigated. This research aims to comprehensively investigate and describe PFD in young nulliparous women, and its correlation with postnatal pathology.

Structure and Methods

The 4P-Study (Prevalence and Predictors of Pelvic floor dysfunction in Primps) is a prospective study nested within the bigger SCOPE Ireland study (Screening for Pregnancy Endpoints). It was performed in Cork University Maternity Hospital (CUMH), having approximately 9000 deliveries per annum, with approximately 40% being primiparous women. This study consisted of two phases. Initially all recruited nulliparous women (N=1484) completed the validated Australian Pelvic Floor Questionnaire at 15 weeks' gestation, at the time of recruitment to the SCOPE study and repeatedly at one year postnatally (N=872). The questionnaire contained 4 sections with questions about urinary, faecal, prolapse and sexual dysfunction. In the second phase, which was performed at least one year postnatally, all women who did not have a second child and accepted the invitation (N=202), attended the clinical follow up including: pelvic organ prolapse quantification (POP-Q), 3D-Transperineal ultrasound scan (3D-TpUS) and collagen level assessment.

Results

A high prevalence of various types of PFD in nulliparous women was found. Urinary dysfunction (UD) was present in 61% of participants, faecal dysfunction (FD) in 41%, pelvic organ prolapse (POP) in 5% and sexual dysfunction (SD) in 41%. In 35% of affected participants, symptoms were associated with bothersomeness and at least 25% of all symptomatic women graded their PFD symptoms as severe. The majority of participants (58%) reported more than one type of PFD.

One year postnatally PFD had the following prevalence structure: UD- 73%, FD - 49%, POP - 14% and SD - 58%. More than half of total PFD were cases of prepregnancy PFD persisting postnatally. Multicompartment involvement was present in 71% of affected participants. Severe and bothersome symptoms were more common in participants with persistent PFD compared to Denovo pathology. Severity of prepregnancy PFD worsened in<15% cases postnatally.

POP had a high prevalence on POP-Q examination at one year postpartum: uterine prolapse-89%, cystocele-90%, rectocele-70%, up to 65% having grade two on POP-Q staging. The majority had multi-compartment involvement but 80% were asymptomatic. In the univariate analysis significant associations were found between POP and joint hypermobility, vertebral hernia, varicose veins, asthma and high collagen type III levels ($p<0.05$), confirming the role of congenital predisposition. In the multivariate analysis levator ani muscle (LAM) avulsion was only significant in selected cases ($p<0.05$). Caesarean Section (CS) was significantly protective against cystocele and rectocele, but not for uterine prolapse.

Clinically significant POP (POP-Q staging grade ≥ 2) had a high prevalence: uterine prolapse-63%, cystocele-42%, rectocele-23%. On 3D-TpUS ballooning of the LAM hiatus was detected in 33.2% and LAM avulsion in 29% of participants, with partial LAM avulsion in 22% and complete in 14%, bilateral avulsion being most prevalent. Postnatal POP symptoms were positively associated with similar prepregnancy symptoms (odds ratio (OR) 7.2, 95% confidence interval [CI] 1.19-44.33), LAM avulsion (OR 4.9 [1.44-16.97]), forceps delivery (OR 1.8 [0.96-3.25]) and negatively associated with CS (OR-0.2 [0.09-0.63]). LAM abnormality was associated with forceps delivery (OR 4.9 [1.44-16.97]) cystocele (OR 11.7[1.73-78.51]) and uterine prolapse (OR 6.8 [2.34-20.01]), whereas collagen levels did not play a role OR 1.01 [0.99-1.02].

Conclusion

PFD is very common in nulliparous women, with approximately one third having clinically significant symptoms. The majority of affected participants had more than one type of PFD.

It would seem that clinically significant changes to the pelvic floor occur in the majority of affected patients before the first pregnancy. However the first pregnancy and birth do not worsen prepregnancy PFD in the majority of cases. Childbearing appears to affect the preexisting symptoms of urgency and urge incontinence more than the symptom of stress urinary incontinence. CS seems to be more protective against postnatal deterioration of prepregnancy PFD compared to Denovo postnatal pathology. However, larger studies are needed to confirm these findings.

Mild to moderate POP has a very high prevalence in relatively young primiparous women. There is a significant association between POP, collagen levels, history of collagen disease and childbirth related pelvic floor trauma. These findings support a congenital contribution to the aetiology of POP, especially for uterine prolapse. However, pelvic trauma seems to be the risk factor with the greatest impact. CS is significantly protective against cystocele and rectocele only, with no effect on uterine prolapse.

LAM avulsion was present in one third of participants, being associated with POP and symptoms related to it. Congenital factors seem to play little role in the aetiology of levator muscle trauma, with forceps delivery being the main risk factor. Avoidance of difficult vaginal deliveries may prevent severe pelvic floor trauma.

This research could be a useful guide for power calculation and study design of future studies on PFD in nulliparous women and may provide a pre-pregnancy guide that could influence delivery options in “at risk” nulliparous women.

PUBLICATIONS AND PRESENTATIONS

PUBLICATIONS

1. Durnea CM, Khashan AS, Kenny LC, Tabirca SS, O'Reilly BA. **An insight into pelvic floor status in nulliparous women**. Int Urogynecol J 2014; 25:337-45.

2. Durnea CM, Khashan AS, Kenny LC, Tabirca SS, O'Reilly BA. **The role of prepregnancy pelvic floor dysfunction in postnatal pelvic morbidity in primiparous women** Int Urogynecol J 2014;25:1363-1374

3. Durnea CM, Khashan AS, Kenny LC, Durnea UA, Smyth MM, O'Reilly BA. **Prevalence, etiology and risk factors of pelvic organ prolapse in premenopausal primiparous women.** Int Urogynecol J 2014;25:1463-1470

4. Durnea CM, O'Reilly BA, Khashan AS, Kenny LC, Durnea UA, Smyth MM, Dietz HP. **The status of the pelvic floor in young primiparous women.** In print, accepted by "Ultrasound in Obstetrics and Gynaecology" DOI: 10.1002/uog.14711.

PRESENTATIONS WITH PUBLISHED ABSTRACTS

1. **Prevalence of pelvic floor dysfunction in primiparous women at 1 year after delivery** C. Durnea, V. Carlson, A. Khashan, L. C. Kenny, B. A. O'Reilly; Int Urogynecol J (2011) 22 (Suppl 1):S1–S195; International Urogynecology Association (IUGA) Annual meeting: Lisbon, Portugal, July 2011, **Oral presentation**

2. **Prevalence and predictors of pelvic floor dysfunction in primips-4p study** CM Durnea, AS Khashan, SS Tabirca, LC Kenny, BA O'Reilly Int Urogynecol J (2012) 23 (Suppl 2):S43–S244; International Urogynecology Association (IUGA) Annual meeting: Brisbane, Australia, September 2012, **Oral podium presentation**

3. **Pelvic organ prolapse in primiparous women one year post-partum**
   C Durnea, AS Khashan, LC Kenny, BA O'Reilly REPRODUCTIVE SCIENCES 20 (S 3), 336A-336A Society of Gynaecological Investigation (SGI): Orlando, Florida, USA, March 2013, **Poster presentation**

4. **Prepregnancy pelvic floor dysfunction and postnatal pathology**
   C Durnea, AS Khashan, S Tabirca, LC Kenny, BA O'Reilly REPRODUCTIVE SCIENCES 20 (S3), 336A-336A. Society of Gynaecological Investigation (SGI): Orlando, Florida, USA, March 2013, **Poster presentation**

5. **Risk factors for postnatal pelvic organ prolapse in primiparous women** C. M. Durnea, A. S. Khashan, L. C. Kenny, U. A. Durnea, M. M. Smith, B. A. O'Reilly Int Urogynecol J (2013) 24 (Suppl 1): S128 International Urogynecology Association (IUGA) Annual meeting: June 2013, Dublin, Ireland, **Oral presentation**

6. **How important is prepregnancy pelvic floor dysfunction in postnatal morbidity in primiparous women?** CM Durnea, AS Khashan, LC Kenny, BA O'Reilly Int Urogynecol J. 25 (4), 547-548; Joint annual scientific meeting BSUG/RCOG: RCOG, London, UK. October 2013. **Oral presentation**

PRESENTATIONS

1. **Initial data analysis of background pelvic floor function in nonpregnant population** Anu research medal conference: Killarney, Ireland, June 2010, **Oral presentation**

2. **Risk of pelvic floor dysfunction after first pregnancy and delivery**
   Irish Congress of Obstetrics, Gynaecology and Perinatal Medicine: Dublin, Ireland, November 2011, **Oral presentation**

3. **Childbirth and pelvic floor dysfunction, is there a causative or triggering correlation?** Registrar's prize - RCPI / JOGS meeting: Dublin, Ireland, February 2012, **Poster presentation**

4. **Pelvic floor dysfunction following first pregnancy and delivery** Anu Research Centre departmental meeting: Cork, Ireland May 2012, **Oral presentation**

5. **Prevalence and predictors of pelvic floor dysfunction in primips** Perinatal Ireland - Irish foetomaternal medicine society, Grant application: September 2012, **Oral presentation**

6. **Demographical and clinical estimation of magnitude, and causative factors leading to pelvic floor dysfunction following first vaginal delivery** Departmental meeting, Anu research centre, Cork, Ireland October 2012, **Oral presentation**

7. **The risk factors and contributors to postnatal pelvic floor dysfunction** Irish Congress of Obstetrics, Gynaecology and Perinatal Medicine: Druids Glen, Wicklow, Ireland, December 2012, **Oral presentation**

8. **An insight into the prevalence and aetiology of postnatal pelvic organ prolapse** Irish Congress of Obstetrics, Gynaecology and Perinatal Medicine: Druids Glen, Wicklow, Ireland, December 2012, **Oral presentation**

9. **The impact of first pregnancy and delivery on pelvic floor dysfunction** EUGA certification meeting of Cork urogynaecological centre: Cork, Ireland, May 2013, **Oral presentation**

10. **The role of research in clinical practice** Presentation for final year medical students: UCC, school of medicine, Cork, Ireland, October 2013, **Oral presentation**

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DEDICATIONS

- To my parents, who set up the fundamentals of everything in my formation as a school pupil, student, researcher and personality. Thanks to them I learnt what is meant by assiduity, perseverance and the basics of logical thinking - all much needed during the research process.

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“Research is the best way to satisfy your personal curiosity at the expense of funding bodies”

Lev Artsimovich

(Nuclear fusion and plasma physics physicist)

THESIS FORMAT AND CONTRIBUTIONS

Thesis background:

This study consisted of two phases. Initially the present project was commenced as an MD thesis, with the aim to investigate pelvic floor dysfunction (PFD) in nulliparous women before their first pregnancy and at 1 year postnatally. The project was called "The 4P-Study" (Prevalence and Predictors of Pelvic floor dysfunction in Primips). It was designed as an opportunistic prospective study, based on the cohort of participants enrolled in the parent SCOPE study (Screening for Pregnancy Endpoints). The SCOPE study is an international, prospective, multicentre cohort with the main aim of developing screening tests to predict preeclampsia, small for gestational age infants, and spontaneous preterm birth, which was performed on nulliparous women. There have been more than 50 publications based on the SCOPE project to date.

Initially the 4P-Study was conceptualised as a questionnaire-based study using the Australian Pelvic Floor Questionnaire, comprehensively covering all types of PFD. The participants had to complete the questionnaires in early pregnancy and at 1 year postnatally. However, at a later stage it was decided that the initial data were very interesting and novel and as a result this project was extended to include a second phase – the clinical follow up of recruited participants who completed both questionnaires. Accordingly, the MD thesis was upgraded by University College Cork (UCC) to a PhD thesis.

Thesis format:

This is a publication based thesis with eight chapters.

Chapter 1 Introduction: includes background information explaining the concept of pelvic floor dysfunction (PFD), focusing on its types and prevalence, burden to society,

causative factors and methods of investigation. This is followed by a review of the existing literature on female PFD and associated ultrasonographic and collagen changes, and concludes with the overall objectives and hypotheses for the present research project.

Chapter 2 Methods: provides a detailed description of the methods used and statistical analyses performed.

The next four chapters were prepared for submission to peer reviewed journals and were all published. These papers investigated various aspects of PFD in nulliparous women and the impact of first pregnancy and delivery on postnatal PFD.

Chapter 3 (Paper 1): An insight into the pelvic floor status of nulliparous women

Chapter 4 (Paper 2): The role of prepregnancy PFD in the postnatal pelvic floor morbidity of primiparous women

Chapter 5 (Paper 3): Prevalence, aetiology and risk factors of pelvic organ prolapse in premenopausal primiparous women

Chapter 6 (Paper 4): The status of the pelvic floor in young primiparous women

Chapters 7 & 8: Discussion and conclusion of the overall thesis including directions for future research.

The publication-based format was chosen for the following reasons:

- Although the four papers were based on data from the SCOPE study, the final cohort for different papers varied and thus the inclusion/exclusion criteria were not the same for all five papers
- All papers focused on different aspects of PFD, such as questionnaire-based description of symptoms, objective clinical and ultrasound assessment or laboratory assessed collagen levels

Thesis contributions:

Constantin Durnea reviewed the existing literature under the supervision of Dr. Barry O'Reilly (Consultant urogynaecologist at Cork University Maternity Hospital [CUMH]); Professor Louise Kenny (Consultant Obstetrician and Gynaecologist at CUMH) and Dr. Ali Khashan (PhD) (senior lecturer at the Department of Epidemiology and Public Health, UCC). In addition, all four participated in the study design, data revision and preparation of manuscripts for publication including writing and revision for important intellectual content.

The initial statistical analysis was performed by Constantin Durnea under supervision and guidance of Dr. Ali Khashan. The initial analysis verification and complex multivariate analyses models were performed by Dr. Khashan.

The initial recruitment of participants and collection of initial prepregnancy completed Australian Pelvic Floor Questionnaire was performed by the SCOPE midwives during each booking visit. The postnatal questionnaires were prepared, mailed and collected

by Constantin Durnea. Letter preparation and mailing was partly performed by final year medical students Vanessa Karlson, Sabina Tabirca and Maeve Smyth, whose final year projects were based on the same dataset and were supervised in part by Constantin Durnea. The data from the questionnaires were added to the database, and analysed by Constantin Durnea. The participants' recruitment for the clinical follow up study, management of clinical appointments, and securing of required facilities and chaperone persons was carried out by Constantin Durnea.

The clinical follow up study including: clinical assessment of pelvic organ prolapse (POP) using the pelvic organ prolapse quantification (POP-Q) system, joint hypermobility assessment, transperineal ultrasound scan, blood sample collection for the collagen test and pre-ELISA processing of the sample were all performed by Constantin Durnea. To ensure an optimal quality of POP-Q assessment – a training workshop was attended in Lisbon, Portugal, at the International Urogynecology Annual (IUGA) meeting. Additionally, the POP-Q quality control was verified and assured by Dr. Barry O'Reilly.

The 2-D, 3-D and 4-D transperineal ultrasound scan image acquisition and analysis were performed by Constantin Durnea. To ensure an optimal quality of transperineal ultrasound scan image acquisition – a training workshop was attended at the same IUGA meeting, which was hosted by Professor H.P. Dietz, consultant urogynaecologist at Sydney Medical School Nepean, University of Sydney, Australia. Professor Dietz is a leading specialist in the area who developed and validated a number of transperineal scan methodologies. A repeated workshop, hosted by the same specialist, was attended at CUMH, Cork, Ireland. As part of the second workshop, training involved a one-to-one practical teaching session with multiple patients. Some images acquired within the

project were shared with Professor Dietz via Dropbox, in order to ensure an adequate quality control of image acquisition and analysis. Additionally, Professor Dietz co-authored the fourth article entitled “The status of the pelvic floor in young primiparous women”.

The ELISA test was performed by Constantin Durnea under direct supervision and guidance of Dr. Lynne Kelly (PhD), research bioscientist at UCC. Dr. Kelly has extensive experience in performing ELISA tests. All the work was done in the Anu Research Centre laboratory, where a large number of ELISA tests were performed within the parent SCOPE study. All dilutions and standard set up was done by Dr. Kelly.

Chapter 1

Introduction

1.1 Introduction – background

1.1.1 Pelvic floor dysfunction definition

Pelvic Floor Dysfunction (PFD) is defined as presence of symptoms of urinary incontinence (UI), faecal incontinence (FI), pelvic organ prolapse (POP), sensory or emptying abnormalities of the lower urinary tract, defaecation dysfunction, sexual dysfunction and chronic pain syndromes, which can present separately or coexist[1]. Vaginal delivery has been repeatedly mentioned as one of the main contributing factors[2-5].

1.1.2 Prevalence overview

In the general population, 1 in 3 women suffer from UI compared to 1 in 25 men, whereas this rate rises to 1 in 2 women after the age of 70. UI in women occurs regardless of childbearing, however in those who have been pregnant and have given birth this rate is much higher compared to those who were never pregnant[6]. Similarly, FI has a female to male ratio of 8:1 and is present in up to 10% of women who have given birth[7]. POP is an exclusively female problem and is seen in more than 40% of those aged between 50 and 75 years old[8]. The lifetime risk of undergoing an operation for prolapse is 11% and every 3rd woman will need at least one reoperation because of failed treatment[9].

1.1.3 Aetiology of PFD

There is a large body of original research demonstrating that vaginal delivery or even an attempt at it can cause urinary and faecal incontinence, as well as prolapse by damaging

pelvic muscles, nerves and supporting tissue. Risk factors associated with such damage have been defined and include forceps delivery, long duration of labour, and big babies (>4kg)[10-12]. On the other hand, it is much less clear whether such trauma is the cause or triggering factor leading to PFD and how important it is in the occurrence of pelvic floor morbidity later in life[13]. There is some evidence that postnatal PFD develops on the background of preexisting prepregnancy disease. Childbearing carries a risk ≤1% of contributing to persistent postnatal UI, with intrapartum risk factors having an uncertain role for long-term postnatal pelvic pathology[14].

There are different explanations of mechanisms and causative factors leading to PFD. One of the theories involves mechanical trauma during delivery and its effect on pelvic organ support, which has been extensively investigated using transperineal ultrasound scans[15-16]. Another hypothesis suggests that POP and incontinence can be explained by a congenital predisposition mediated via collagen abnormalities. Thus, intrinsic congenital pelvic weakness is the cause of PFD rather than childbearing trauma. Collagen is a large molecule, of which there are five major types. Collagen type I and III are most commonly found in ligaments, skin and bones, constituting the backbone of these structures. The former is offering strength to the structure, whereas the latter offers elasticity, depending on the predominant type of collagen in each tissue.

It has been demonstrated that patients with POP have a low level of general collagen in the pelvic fascial/ligamental tissue and a higher level of particularly collagen type III. This leads to imbalance between different types of collagen and specifically abnormal collagen I to III ratios[17-22]. Collagen abnormality seems to have a systemic clinical manifestation, about 50% of patients with recurrent pelvic prolapse having increased joint mobility[17, 19].

However the majority of the studies underpinning the above hypothesises fail to fully elucidate the real causative factors leading to PFD after childbirth as they are not linked to the patient's prepregnancy status, do not take into account risk factors present in labour and delivery and do not involve long term postnatal follow up to exclude those patients with transitory postnatal symptoms.

1.1.4 Diagnosis of PFD

PFD - Questionnaires

There are different tools to diagnose and assess the severity of PFD. The functional status and severity of symptoms are investigated using various PFD questionnaires. The validated questionnaires play a distinctive role, assuring that obtained data are reliable, quantifiable, and reproducible. There are questionnaires investigating severity of symptoms and the impact on Quality of Life (QoL), e.g. International Consultation on Incontinence Questionnaire (ICIQ)[23] investigating UI or Wexner Score[24] for FI. Other questionnaires are investigating symptoms only – such as the Urogenital Distress Inventory (UDI-6)[25] and The Female Sexual Function Index (FSFI)[26], or QoL only such as the Incontinence Impact Questionnaire (IIQ-7)[25] and the Faecal Incontinence Quality of Life Scale[27]. QoL questionnaires can be either disease specific, as described previously or generic e.g. SF-36 (The Short Form (36) Health Survey - a patient-reported survey of patient health). Questionnaires investigating PFD symptoms can be focused on a single type of dysfunction or specific combinations of them such as urinary dysfunction (UD), faecal dysfunction (FD), POP or SD. There are very few questionnaires assessing comprehensively all four types of PFD along with the grade of bothersomeness

experienced by patients such as the Australian Pelvic Floor Questionnaire[28] or the Epidemiology of Prolapse and Incontinence Questionnaire (EPIQ)[29].

POP - Classification systems

Quantification of POP is another aspect of PFD assessment. Different classifications have been proposed to measure the grade of POP. The most commonly used are the Baden-Walker, Shaw and the Pelvic Organ Prolapse Quantification (POP-Q) Systems. Each has different grading and landmarks. The most comprehensive and commonly accepted system nowadays is POP-Q[30]. It consists of eight landmark points and four identical grades of prolapse for each compartment. It requires a measurement ruler and a Sim's speculum. This is an objective way to quantify POP and has an excellent inter-observer reliability, with a kappa value of 0.88 for overall stage[31], 0.89 for the anterior and 0.86 for the posterior vaginal walls, 0.82 for the apex/cuff, and 0.72 for the cervix[32] .

PFD - Ultrasound changes

PFD is often associated with morphological changes in the pelvic anatomy. Initially Magnetic Resonance Imaging (MRI) showed promise as a sensitive tool for the detection of anatomical disruption in patients with PFD[33] however, it remains an expensive modality. In the recent decade there has been increasing interest in transvaginal[34] and transperineal ultrasound scans[35]. The 3D transperineal ultrasound scan (3D-TpUS) is the most versatile diagnostic tool in evaluation of PFD, being easily accessible and very cost-effective. It can visualise and quantify various types of POP[15], bladder neck mobility[13, 36-39], anal sphincter injury[40], levator ani muscle (LAM) trauma[13, 41] and identify LAM hiatal area abnormalities [13, 42-45].

PFD - Collagen abnormalities

One of the main modalities to assess the congenital predisposition to PFD is investigation of collagen abnormalities and collagen associated diseases. Different methodologies have been proposed to evaluate matrix metalloproteinase and collagen quantitative and qualitative changes. Initially, biopsies from sacrouterine ligaments or paraurethral tissue were taken with subsequent homogenisation and immunofluorescent analysis[17]. Later on equilibrium radioimmunoassay and ELISA test methodology were proposed to detect the concentration and correlation of different procollagen proteins in serum[46]. This investigation resembles the idea of detecting C-peptide in order to quantify insulin production.

1.1.5 Clinical manifestations of PFD

Urinary Dysfunction

Between 17% and 45% of adult women suffer from UI[6]. Although vaginal delivery plays a crucial role in the aetiology of UD, it is a recognised finding in nulliparous women as well as in primiparous women post CS[12,47]. Buchsbaum et al. reported that the rates of stress urinary incontinence (SUI) and urge urinary incontinence (UUI) were similar in nulliparous and multiparous postmenopausal women[48]. This is probably age related as well as a possible congenital predisposition. Additionally, Denovo UI is not a common postnatal finding without prior antenatal symptoms [49-51]. The role of obstetric factors seems to be transient and is of uncertain aetiologic significance three months postpartum[14].

Faecal Dysfunction

The reported prevalence of FI including flatus incontinence varies between 2-24%, whereas FI excluding flatus incontinence is 0.4-18 %[52]. The American NHANES study reported a prevalence of 8.3% of FI in non-institutionalized US adults, which consisted of 6.2% liquid stool, 1.6% solid stool and 3.1% mucus[53]. There is an obvious logical association between instrumental vaginal delivery and postnatal FI due to traumatic anal sphincter disruption. However, such a link is not so evident for other types of bowel dysfunction. It has been demonstrated, for instance, that 12% of young nulliparous women have signs of rectocele with disruption of septal integrity on 3D transperineal ultrasound scan. The authors concluded that the problem could be congenitally determined[54].

Pelvic organ prolapse

The Women's Health Initiative - one of the biggest studies investigating POP in the general population, reported the following rates of POP: uterine prolapse - 14.2%; cystocele - 34.3% and rectocele - 18.6%[8]. However, one of the biggest limitations of this study is the fact that it had not used the POP-Q classification system for assessment, which is considered the gold standard. On the other hand Swift et al. noticed that in some epidemiological studies POP grade I to II is detected in up to 90% of women on POP-Q assessment and questioned how clinically relevant this classification is[55]. POP is reasonably associated with parity and advanced age, because it is more common in these categories of women[8], where the main risk factors include vaginal delivery, high

infant birth weight and BMI[56]. However, it has been demonstrated that various types of POP can be present in women at all ages and parities[57].

Sexual dysfunction

SD is another aspect of PFD, which is becoming an important focus in the urogynaecological research field. The available data on SD have reported a prevalence of up to 50% of SD in women attending urogynaecological services. It has been shown that the major symptom is dyspareunia and sexual symptoms are associated with UD in 26-47% of the population studied[58]. Although SD is highly prevalent in women attending urogynaecological services, only a minority of urogynaecologists screen all patients for this type of dysfunction[59].

Information about the prevalence of SD in the general population is sparse, with the majority of studies focusing on impaired sexual function associated with various medical conditions (e.g. diabetes mellitus, neurologic diseases etc.). MacLennan et al. investigated various aspects of PFD in 1546 participants and reported a prevalence of dyspareunia of 3.9% and vaginal laxity of 5.2%[6]. Another study investigating SD in a relatively young sexually active population reported the following prevalences: SD - 37.6%, low desire - 23.6%, arousal disorder - 25.4%, lubrication disorder - 36.8%, orgasm disorder - 30.6% and dyspareunia - 21.8% in urban Chinese women[60]. The difference in prevalence of dyspareunia probably can be explained by use of different questionnaires and differences in participant's age groups. While the first study contained generic questions regarding PFD with answer options yes or no (no severity

grading was present), the latter used Female Sexual Function Index (FSFI) which is specifically designed to detect and score symptoms of SD.

1.1.6 The impact of PFD on quality of life and burden to society

PFD has an immense impact on a woman's psychological well-being and QoL. A series of studies have shown that feelings of helplessness, sadness, depression, general health anxiety, SD and even self-harm are more common in women with UI[61-62]. 75% of patients with UI are bothered by their symptoms, and 30% of this disturbance is reported to be moderate to severe. More than half of the patients reporting bothersome disturbance feel that the symptoms have a negative impact on their physical and social activity and self-confidence[63]. In addition to the QoL impairment, PFD is a burden to society. The total cost of overactive bladder (OAB) to the United Kingdom (UK) health care system was estimated at £750 million in 2000 and forecasted to approach the figure of £1 billion. by 2020[64]. The annual cost-of-illness estimated for UUI in Canada, Germany, Italy, Spain, Sweden, and the UK was €7 billion in 2005[65]. The life time medical cost for patients with SUI is 80% higher compared to those without incontinence[66]. Considering all these, there has been increased public and professional attention recently, focused on PFD following childbirth and these symptoms are sometimes being cited as indications for elective Caesarean section (CS).

1.2 Literature review

1.2.1 Literature review aims

The aim of the literature review is to assess how relevant pregnancy and delivery are in the aetiology of PFD. Childbearing may just trigger the development of PFD in someone

with a congenital predisposition. The best way to test this hypothesis is to compare prepregnancy and postnatal pelvic floor status in women embarking on their first pregnancy.

1.2.2 Literature review methods

Search strategy

The literature review search was performed using two electronic databases (MEDLINE from 1966 and The Cochrane Library from 1993). Three search strategies were used for each search. Initially the search was conducted using all studies which included any of the search terms, secondly followed by the 'OR' operator and finally the last step included the 'AND' operator following the principles of Boolean logic. The relevance of the studies was determined by screening the titles and abstracts. Additionally, reference lists of searched papers were screened for further relevant studies.

Search 1: *Studies investigating symptoms of PFD in nulliparous/primiparous women*

As described earlier, this project has had two phases: 1) the initial questionnaire-based epidemiological phase; 2) the objective assessment of participants. The literature review search also consisted of two stages. Initially, in 2010, a search was performed for epidemiological studies investigating symptoms of PFD in nulliparous/primiparous women and the impact of first pregnancy and delivery on them. The following search words and truncations were used: *nulliparous, nulliparas, nullip*, primiparous, primip*, pelvic floor dysfunction, PFD, urinary *, urinary dysfunction, urinary incontinence, urinary frequency, fecal* (Latin spelling) *dysfunction, faecal* (Greek spelling) *dysfunction, fecal frequency, faecal frequency, fecal incontinence, faecal incontinence, fecal urgency, faecal*

urgency, sexual dysfunction, dyspareunia, pelvic organ prolapse, POP, cystocele, rectocele, uterine prolapse, risk factors, RF, RFs, pre-pregnancy, pre-pregnancy, before pregnancy, antenatal, pregnancy, in pregnancy, during pregnancy, postnatally, post-natally, postnatal, 1 year, 12 months, prevalence, mode of delivery, MOD, instrumental delivery, forceps, vacuum, 3rd degree tear, third degree tear, 4th degree tear, fourth degree tear, perineal tear.

Search 2: *Studies investigating the role of collagen changes in the development of PFD and POP; prevalence and risk factors for POP and transperineal ultrasonographic methodology and changes after the index delivery (first birth)*

Another literature search using the same search strategies as previously was performed in 2012 after the extension of the initial project. The second literature review investigated the role of collagen changes in the development of PFD and POP, the prevalence and risk factors for POP and the transperineal ultrasonographic methodology and changes after first delivery. The following search words were used: *collagen, pro-collagen, procollagen, collagen type I, collagen type III, collagen type 1, collagen type 3,prolapse, pelvic organ prolapse, POP, cystocele, rectocele, uterine prolapse, transperineal scan, perineal scan, 2D transperineal scan, 2D perineal scan, 3D transperineal scan, 3D perineal scan, 4D transperineal scan, 4D perineal scan, labial scan, translabial scan, levator ani muscle avulsion, LAM avulsion, levator ani muscle trauma, LAM trauma, levator hiatus ballooning, levator hiatus distension.*

Eligibility Criteria

The following criteria were taken into account when the results of the different studies were compared: 1) whether the presented data reported specifically nulliparous and

primiparous women 2) whether potential confounders were adjusted for 3) whether a significant association was reported

1.2.3 Literature review results

1.2.3.1 Prepregnancy and postnatal PFD in nulliparous women

There is little research regarding PFD in nulliparous women with the majority of studies describing only the prevalence of particular symptoms. Although the postnatal aspect of PFD is slightly better elucidated, there are no studies to date linking prepregnancy and postnatal PFD in primiparous women. For this reason, in addition to reviewing studies on nulliparous /primiparous women, general data (unrelated to parity) on PFD were also analysed, in order to set up a reference point. The majority of studies focussed on a single type of PFD. However, occasionally studies investigated multiple dysfunctions[6], which pointed out that women with one type of dysfunction are highly likely to suffer simultaneously from multiple PFDs[67]. Studies investigating PFD symptoms in nulliparous and primiparous women are reviewed in Table A-1.1 (Appendix I).

1.2.3.2 Urinary dysfunction

The biggest study investigating UI in nulliparous women is the Swedish EPINCONT study (27,900 participants). It reported a prevalence of UI ranging from 8% to 32% and increasing with age[68]. The lowest prevalence of UI – 6.5% was reported by the NHANES study, investigating UD, FD and POP in different age and parity groups[69]. In contrast to a previous study investigating all UI, the latter recorded only moderate and severe UI. There is some evidence that UI in sexually active nulliparous users of the combined oral

contraceptive pill (COCP) can be higher (21.5%) compared to the background population (12.6%)[70]. There are transitory postnatal PFDs, which can persist up to 6 months postnatally or even longer[71]. That is why prevalence reported earlier in the postpartum period may appear higher. At 12 months after delivery a prevalence of 25.9% for SUI and 8.2% for UUI was reported in primiparous women[72-73]. CS was only partially protective against UI in primips, with up to 22.9% reporting UI at six months after the operation[74-75].

Several prospective studies investigating the correlation between prepregnancy prevalence of UI and antenatal UI have been identified. Brown et al. reported a 5-fold higher incidence of UI in the 3rd trimester of pregnancy than the prepregnancy prevalence[76]. Similarly there are prospective studies correlating Denovo UI during the first pregnancy and postnatal pathology[72, 77-78]. However, only one study was identified correlating prepregnancy and postnatal pathology in nulliparous women[79]. It demonstrated that prepregnancy UI is an independent risk factor for postnatal UI at 9 months postpartum. However, no studies have been found looking at the prepregnancy and postnatal correlation of PFD symptoms other than UI in primiparous women.

1.2.3.3 Faecal dysfunction

There are very few publications describing FD in nulliparous women. The reported prevalence of FI in nulliparous women in identified studies varied between 6.3% and 7.7%[69, 80]. The reported prevalence in primiparous women, ranged between 4.0% and 8.8%[69, 72-73, 81]. A single article reported the postnatal prevalence in primiparous women of flatal incontinence at 12%, liquid stool incontinence – 3.2% and solid stool incontinence – 1.1%[73]. FD seems to have a congenital predisposition. One study

investigated the association between parity and mode of delivery with symptoms of obstructed defaecation. It has been demonstrated, that the prevalence of rectocele, enterocele, intussusception and anismus leading to obstructed defaecation syndrome is not statistically different between nulliparous women, those post vaginal delivery and post CS[82]. There is a paucity of studies describing FD, particularly in young nulliparous women. No studies could be identified exploring the role of prepregnancy FD in postnatal morbidity.

1.2.3.4 Pelvic organ prolapse

The reported prevalence of prolapse in the general population is quite varied. For instance, the prevalence of cystocele has been reported to be between 34% and 90%[8, 55]. This is due to the use of different classification systems and grades of symptoms severity. For the same reason, H.P. Dietz proposed considering cystocele and rectocele grade I as part of the normal range[83]. This is confirmed by another study performed in young nulliparous women who were students of a US Military Academy, where asymptomatic prolapse stage I or II was diagnosed in 50% of participants, in the absence of any obvious risk factors[84]. The NHANES study reported a prevalence of 0.6% of moderate to severe prolapse in nulliparous women[69].

Congenital predisposition seems to play an important role in the aetiology of POP.

When compared nulliparous women with their parous sisters there was a high concordance in prolapse stage within sister pairs (74.3% to 91.1% by compartment), with vaginal delivery offering slightly higher risk[85]. An even higher degree of concordance of continence and pelvic support status was demonstrated on sets of parous/nulliparous identical twins, regardless of differences in mode of delivery[86].

Nevertheless, POP in nulliparous women remains an under investigated area, since there are no studies to date examining the prevalence of prolapse symptoms and their correlation with prolapse grade and postnatal pathology.

1.2.3.5 Sexual dysfunction

The reported combined prevalence for different symptoms of SD in the general population varies between 0.6-64%[87]. The same data for nulliparous women or after first delivery are not available. The most common symptom of SD is dyspareunia with a reported prevalence of 4.7%[88]. Bellelis et al. showed that dyspareunia is present in 55% of patients with endometriosis, which is more common in nulliparous women (55% of those affected)[89]. Coital incontinence has a reported prevalence of 2% in community based studies and 10-56% in clinical settings[87]. It has been demonstrated that it has a strong association with SUI and to a lesser extent with OAB[90]. About 80% of women having vaginal delivery reported vaginal laxity at 24 months postpartum. However when compared to CS, vaginal delivery did not have a statistically significant impact on SD[91]. In general, pregnancy and delivery does not seem to have a long term consequence on sexual function[92]. At 6 months postpartum 90% of women resumed having intercourse, of which 17% reported dyspareunia, with less than 5% describing it as severe and 61% of women reporting orgasm. Delivery mode and episiotomy were not associated with intercourse resumption or anorgasmia before pregnancy[93].

However, no studies specifically investigated SD in nulliparous women, and correlation of these symptoms with postnatal pathology. The majority of studies investigating the impact of childbearing on postnatal SD have been focussed on prenatal versus postnatal sexual satisfaction or comparison of SD following different modes of delivery[94].

1.2.3.6 Risk factors for PFD

Age, obesity, chronic bronchitis, multiparity and hereditary diseases suggestive of collagen disorders are common risk factors for UD, FD and POP[67]. Furthermore, women suffering from one type of dysfunction are likely to have other types in addition. UI after the first pregnancy was demonstrated to be related to antenatal SUI, prolonged labour in combination with operative vaginal birth [49, 77], use of oxytocin in labour and foetal weight > 4kg [10]. Other recognised risk factors are family history of similar conditions, multiple urinary tract infections[11]and depression[95].

Postnatal FI has been reported to be associated in primiparous women with a new onset of FI during pregnancy, positive family history and vaginal delivery[72-73]. In addition, CS does not seem to be completely protective against FI in primiparous women[72, 74]. Other reported risk factors associated with FI are age, menopause, obesity, parity, and associated SUI, whereas elective CS in one study seemed to be totally protective against FI[96]. Age seems to play a bigger role in the aetiology of FI than childbearing, whereas chronic diarrhoea appears to be a strong modifiable risk factor that may form the basis for prevention and treatment[53, 97].

The associated risk factors to POP are foetal birthweight, abdominal hernia surgery and chronic pulmonary disease, e.g. asthma. However, POP being associated with parity, was not associated with instrumental and preterm deliveries. Familial history of POP is present in approximately 30% of women with prolapse[98]. While vaginal delivery is considered to be a risk factor for POP, there is some evidence that it does not cause advanced prolapse beyond the hymen, for which the menopausal change is to be blamed[99].

Sexual function seems to be minimally impacted by childbearing. Sexual satisfaction does not appear to be associated with antenatal and intrapartum factors, with sexual dissatisfaction at 1 year postpartum being related only to sexual activity in early pregnancy[94]. Dyspareunia in the general population is associated with early sexual debut, primary level of education, and membership of minority ethnic communities[88]. Postnatal dyspareunia at 12 weeks postpartum was associated only with breast-feeding. Sexual function was described as similar to prepregnancy or improved after pregnancy[93]. Sexual function does not significantly differ at 12-18 months postnatally between women who had vaginal delivery without episiotomy, heavy perineal laceration, or secondary operative interventions and women having elective CS[92].

1.2.3.7 Transperineal ultrasound scan investigation of PFD

Despite the fact that TpUS is a relatively new methodology in the investigation of pelvic floor morphology and PFD, it is already well positioned among other imaging methods, having good correlation with the "gold standard" - MRI investigation[100]. There are many publications describing different methodologies investigating various aspects of pelvic floor anatomy. Many of them have been retested in order to confirm their intra and inter observer repeatability and reliability. The studies investigating PFD using TpUS are summarised and reviewed in Table A-1.2 (Appendix I). The 2D-TpUS has been successfully used for ultrasound quantification of POP. A bladder on transperineal scan to ≥10 mm and of the rectum to ≥15 mm below the symphysis pubis has been shown to be strongly associated with presence of symptoms[42]. 3D-TpUS can be reliably used for identification of LAM trauma. It has been demonstrated that a levator-urethral gap of >25mm on tomographic ultrasound imaging (TUI) mode correlates with LAM

avulsion[101] and abnormality specifically in three central slices can reliably distinguish a complete from a partial avulsion[102]. A distension of the levator hiatal area>25cm^2 is considered abnormal, being called "ballooning" and is associated with LAM avulsion[45]. The 3D- TpUS can be used for measurement of the subpubic arch angle, which may have an impact on vaginal delivery outcome**[103]**. The reliability of these scanning methods has been repeatedly retested and reconfirmed[104-105].

The prevalence of LAM avulsion is virtually non-existent in nulliparous women and has been reported in 12-36% of primiparous women[106]. There is evidence that levator defect after vaginal delivery is more than seven times higher than after CS, however, emergency CS is not completely protective[107]. LAM avulsion has been shown to be associated with bigger foetal head circumference, long second stage of labour and forceps delivery, whereas epidural anaesthesia seemed to be protective[41, 108]. Although there is evidence that sonographic pelvic structures mobility and functional status may normalise by six months postnatally[13], LAM trauma is considered to persist for life, with exceptional cases only being reported to heal[109].

1.2.3.8 Collagen investigation of PFD

There are very few studies to date investigating collagen abnormalities particularly in nulliparous women with PFD. The majority of previous studies were targeting the general population irrespective of parity, mostly paying attention to the menopausal status and associated collagen related diseases. Studies investigating the role of collagen abnormality in development of PFD are summarised and reviewed in Table A-1.3 (Appendix I). The first comprehensive work in this area was done by Jackson who investigated vaginal-epithelial tissue in women with genitourinary prolapse[18]. He

demonstrated that POP is associated with a reduction in total collagen content due to increased collagenolytic activity, and collagen turnover accordingly, is up to four times higher in prolapse tissue. The next step was investigation of expression of various types of collagen in prolapsed tissue. It was demonstrated that expression of collagen type I in cardinal ligaments correlates with menopausal status, use of hormone replacement therapy (HRT) and age rather than with prolapse[110]. Conversely collagen type III expression was directly related to uterine prolapse, having increased levels in affected women. This was confirmed in a later study investigating uterosacral ligaments[111]. A significantly higher concentration of collagen type III in prolapsed tissue was explained by its abnormal quality, leading to a weaker collagen molecule and quicker breakdown. This explains a higher turnover of this type of collagen and higher expression in affected tissues[21] and is confirmed by increased levels of matrix metalloproteinases, an enzyme involved in collagen's triple helix degradation[112-113]. In contrast, a diminished turnover of collagen was reported by Keane et al.[20] and Edwal et al.[21] in women with UI and no POP.

Although it is recognised that collagen synthesis genes expression may be different in various tissues, there is evidence that various body hernias are associated with the same pattern of abnormal collagen I/III ratio as POP[114]. Furthermore, it was demonstrated that young women (<35 years old) with POP are more likely than older women to have an increased prevalence of congenital anomalies, as well as rheumatologic and neurologic diseases[115]. Additionally, patients with POP have a higher prevalence of varicose veins, joint hypermobility, rectal prolapse and they are more likely to have family members with POP as compared to women without POP. That is

why it was hypothesised that POP and other collagen-associated disorders may have a common collagen level based aetiology[116].

This hypothesis was explored by Knuuti et al.[46], who investigated the correlation among POP, benign joint hypermobility and blood serum concentration of PICP (procollagen type I carboxyterminal) and PIIINP (procollagen type III aminoterminal) – as markers of collagen synthesis. It was demonstrated that recurrent genital prolapse is more common in women with joint hypermobility as compared to normal mobility. Additionally, plain hypermobility was associated with higher levels of type I collagen, whereas a combination of recurrent prolapse and joint hypermobility were associated with type III collagen. Although there are no studies to date investigating the correlation between collagen assessment in blood serum and urogenital tissue biopsies, the results from the latter study showed the same pattern of collagen turnover as previous studies. This suggests that the described methodology could be used in future research of collagen abnormality in context of POP.

1.2.4 Literature review conclusion

1.2.4.1 PFD related symptoms

There is a good body of evidence demonstrating the prevalence and associated risk factors of the main PFD symptoms like urinary and faecal incontinence, POP and dyspareunia in general population. However, there is little evidence regarding PFD symptoms and risk factors in nulliparous women. The available data is very sparse and fragmentarily reflects the whole spectrum of PFD. The existing figures on urinary and faecal dysfunctions are mostly focussed around the symptoms of urinary and faecal incontinence and overactive bladder. Such symptoms as urinary and faecal frequency,

obstructed micturition and defaecation, nocturia, flatal incontinence have been investigated very occasionally or not at all. Similarly regarding the sexual dysfunction, symptoms like vaginal tightness or laxity, vaginal sensation during intercourse, differences between the prevalence of superficial and deep dyspareunia are understudied or have never been reported in the literature. Furthermore, many of these symptoms have not been investigated in nulliparous women and very little is currently known about the correlation of these symptoms before and after the first pregnancy.

1.2.4.2 Investigation of PFD using 3D - Transperineal scan

Transperineal ultrasound scan is currently playing an increasing role in the investigation of PFD. Various validated methodologies for scanning different pelvic structures with their reliability and repeatability confirmed have been established. Postnatal morphological pelvic floor changes in primiparous women such as POP, LAM avulsion and hiatal area ballooning, as well as their prevalence, have been repeatedly reported in the literature. Similarly, the associated anthropometric and intrapartum risk factors have been extensively investigated. However, little is known about the role of congenital factors and PFD changes present before the first childbearing as risk factors for postnatal anatomical abnormalities in the pelvic floor structures. Therefore, further research is required to address this gap in the literature to date.

1.2.4.3 Collagen investigation of PFD

In the general population there is a difference in collagen levels between women with prolapse and healthy women. Women with POP have a higher turnover of collagen type I and especially type III, due to abnormal collagen structure and quicker breakdown.

Clinically this is manifested by more fragile tissue, and a predisposition to prolapse formation. Collagen type III, demonstrates much more significant quantitative changes in prolapse and is a better marker of POP. Additionally, the change in collagen type I levels may be biased by age, menopausal status and use of HRT.

Collagen abnormality seems to be a systemic issue with simultaneous multiple manifestations in different parts of the body. Thus, blood serum investigation of collagen turnover appears to be a good alternative to homogenates of tissue biopsy. The association between collagen abnormality and PFD in nulliparous women is very poorly elucidated in the literature. Although parity and vaginal delivery are considered the main risk factors for development of POP, there is a body of evidence demonstrating that POP is not an extraordinary finding in nulliparous women. Further research is required in this area to elucidate the natural history of POP and elaborate if possible on preventive measures.

1.2.5 Directions for future research

We would recommend that future investigations should cover the following areas:

1.2.5.1 PFD related symptoms

The investigation of nulliparous women before their first pregnancy and after delivery would help to elucidate the real impact of childbearing on pelvic floor structures. The knowledge of the prevalence of Denovo and persistent PFD in primiparous women and the rates of worsening or improvement of persistent symptoms would help to develop strategies diminishing morbidity in this group. Additionally, this could help to outline the group of asymptomatic nulliparous women who are at risk of postnatal PFD and possibly propose some preventive measures.

1.2.5.2 Investigation of PFD using 3D - Transperineal scan

Future research ideally should include nulliparous cohorts of women before or in early pregnancy and repeatedly postnatally. This would allow a better elucidation of the real impact of first childbearing on PFD. Postnatal ultrasound findings should be correlated with presence of prepregnancy symptoms including prolapse changes or ultrasound anatomical abnormalities. Studies of collagen association may yield extra information explaining the natural history and development POP and LAM trauma.

1.2.5.3 Collagen investigation of PFD

Collagen changes seem to have a widespread manifestation. A systemic approach should be implemented in the investigation of patients with POP. Quantification of POP, using the POP-Q scoring system, should be correlated with complex exploration of family history of POP, presence of associated collagen related diseases, determination of collagen levels and presence of PFD symptoms. Especially this could add to the understanding of the natural history of POP, if performed in primiparous women and correlated with prepregnancy and intrapartum factors.

1.2.6 Objectives of the present study

There is a paucity of evidence on which to base counselling for individual patients about to embark on their first pregnancy with regard to potential PFD. It is unknown whether avoidance of potential childbearing related pelvic floor trauma is worth the risk, cost, and effort of elective CS. The goal of this study was to:

1) Quantify the background prevalence of PFD in nulliparous women and its correlation with potential risk factors.

2) Assess the postnatal prevalence of PFD at one year after first delivery and its correlation with prenatal pathology and mode of delivery.

3) Confirm postnatal POP related questionnaire findings by objective assessment of a cohort of participants at one year postnatally using POP-Q investigation and combining this data with information from the SCOPE study demographic data bank.

4) Assess the role of congenital predisposition in the development of PFD by investigating the collagen levels in a cohort of participants who participated in the objective assessment follow-up study. The goal of this sub-study is to test the hypothesis suggesting that high levels of collagen type III (conferring elasticity) is a putative cause of POP.

5) Investigate the postnatal prevalence of anatomical changes in pelvic floor anatomy after 1 year postnatally using 4D - TpUS. To correlate the presence of postnatal symptoms with structural anatomical changes and to delineate the difference between two groups of participants, with maximum and minimum PFD scores.

1.2.7 Hypothesis

The null hypothesis (H_0) for the present research was that:

1) The severity of Denovo postnatal PFD in primiparous women does not differ from persistent PFD with prepregnancy onset of symptoms.

2) Mode of delivery does not change the severity of persistent PFD postnatally.

3) Congenital predisposing factors play little role in the development of PFD as compared to intrapartum trauma.

4) Childbearing related PFD cannot be predicted before the first pregnancy

5) Elective CS does not prevent the development of PFD in the at risk group.

Chapter 2

Materials and Methods

2.1 Epidemiologic assessment of PFD in nulliparous and primiparous women

The epidemiologic assessment of PFD in nulliparous women prepregnancy and one year postnatally constitutes the backbone of the present thesis. This part of the project aimed to elucidate the real impact of the first childbearing on postnatal PFD. In the methodology section, in order to achieve the most comprehensive description of the methods used, each subheading begins with the rationale for the methodology followed by the performed measurements.

2.1.1 Assessment of background prepregnancy PFD in nulliparous women

The 4P-Study is a prospective study, nested within the Screening for Pregnancy Endpoints (SCOPE) Ireland study (www.scopestudy.net). The present study was reviewed and approved by The Clinical Research Ethics Committee of the Cork Teaching Hospitals (CREC), Ireland. It consisted of two parts: a questionnaire based survey followed by a detailed clinical, laboratory and imaging investigations in women approximately 12 months postpartum. We invited 2579 nulliparous women to participate in the SCOPE study, subsequently 1774 (69%) were recruited (Appendix II). This represents 17% of all nulliparous women who delivered in CUMH during the study period.

The validated Australian Pelvic Floor Questionnaire[28] was used to assess PFD prepregnancy and one year postnatally. We chose this particular questionnaire, because in contrast to others it covers all 4 compartments of PFD along with associated bothersome and condition specific quality of life problems. Unlike many other commonly used standardized questionnaires, it is a validated questionnaire, showing very good test–retest reliability (Kappa values ranged between 0.74 and 1.0 for

different sections) and good correlation with other questionnaires (Spearman's coefficient for different sections ranging between 0.63 and 0.92), as well as association with urodynamic findings[28]. The first, prepregnancy questionnaire was handed to all SCOPE participants, to be answered specifically on the day of recruitment, at 15 weeks' gestation and was returned completed by 1474 (83% of recruited to SCOPE) participants (Appendix II) . The prepregnancy questionnaires were completed between February 2008 and March 2011. All participants were specifically asked about prepregnancy symptoms, the questionnaire verbatim stating: "All these questions pertain to the period BEFORE you were pregnant", additionally they were verbally instructed to ignore any symptoms newly developed in pregnancy.

The questionnaire consists of 4 sections, including questions about all four types of PFD. Each section contains 10 – 15 questions (Appendix III). All answers are graded from 0 to 3, where zero means no symptom present and 3 - most frequent or severe symptom. Additionally, each section has a question about the grade of bothersomeness, due to symptoms, rated 0 to 3 (0 indicates no bother and 3 indicates severe bothersomeness). All questions from each section can be logically divided into primary symptoms, which are mandatory to diagnose a condition and secondary – giving extra information on severity of primary symptoms; for example, reduced fluid intake, pad usage, laxative use, grade of bother etc. The primary symptoms from the questionnaire were selected according to International Continence Society (ICS) definitions for various types for faecal or urinary dysfunction. Since we aimed to comprehensively investigate all possible types of dysfunctions, besides commonly described incontinence, we added symptoms related to overactive bladder in the urinary section; obstructed defaecation in the faecal dysfunction section – as a potential marker of congenital rectovaginal

septum defect and/or major rectocele[54]. It would be sensible to add "incomplete bowel emptying" question here, however there could be a potential for confusion, since this symptom is very prevalent and could be diet related. For the sexual section, we used dyspareunia, vaginal laxity and tightness – as primary symptoms. Regarding the prolapse, all questions included in this section can be regarded as primary symptoms for prolapse. These symptoms were selected as primary, because they were included in the pelvic floor distress inventory and repeatedly utilized in previous studies [6, 8]. The questionnaire additionally contains a total section score for "urinary", "faecal", "prolapse" and "sexual dysfunction". This score is meant to better characterise the severity of primary symptoms rather than representing a scale score [28] and it was calculated by adding all individual symptom scores in each section. In our analysis we considered clinically significant symptoms those with grade 2 or 3 severity from the questionnaire (meaning symptom present at least once weekly) or grade 1 with associated bother.

2.1.2 Assessment of PFD in primiparous women at one year postnatally

Postnatal questionnaires were completed at one year postnatal, in order to exclude postpartum short term transitory changes in the pelvic floor. These questionnaires were mailed by post with detailed instructions on how to complete them. Contact details were also provided in case further clarification was required. Each questionnaire was sent along with a pre-stamped envelope with a return address on it. In order to improve the response rate, a reminder letter was sent if the participant had not replied within 2 months. The postnatal questionnaire, similarly to prepregnancy one consisted of four sections, assessing all compartments of PFD, each section containing 10 – 15

questions (Appendices – III & IV). The only difference consisted in a remark on the top of the questionnaire asking if the participant is not pregnant at the time of completion. Here, all answers were graded similarly from 0 to 3, where zero means no symptom present and 3 most frequent or severe symptom. Additionally, each section had a question about the grade of bothersome, due to symptoms, rated 0 to 3 (0 indicates no bother and 3 indicates severe bother). In the postnatal questionnaire, again questions were divided into primary symptoms - mandatory to diagnose a condition and secondary symptoms – giving extra information on the severity of those primary symptoms e.g. reduced fluid intake, pad usage, laxative use, grade of bother etc. The selection criteria for primary symptoms were similar as in prepregnancy questionnaire. In our analysis of postnatal symptoms we considered clinically severe symptoms in those having grade 2 or 3 severity (meaning symptom present at least once weekly). The mode of delivery was classified into abdominal, including emergency and elective CS and vaginal, including spontaneous vaginal delivery (SVD), forceps and vacuum delivery. Main outcome measures were postnatal prevalence of various PFD symptoms, persistence rate of prepregnancy symptoms postnatally, the difference in severity of Denovo postnatal onset PFD (DNPFD) and prepregnancy PFD Persisting postnatally (PPFD), the rate and structure of multicompartmental PFD and the impact of mode of delivery on postnatal PFD.

2.2 Pelvic organ prolapse assessment

All 872 participants, who completed prepregnancy and postnatal Australian Pelvic Floor Questionnaire[28], were invited for pelvic organ prolapse (POP) assessment, which occurred between March and December 2012. We had a response rate of 60.8% (530), where the proposal for follow up was accepted by 46.8% (408). Those participants who

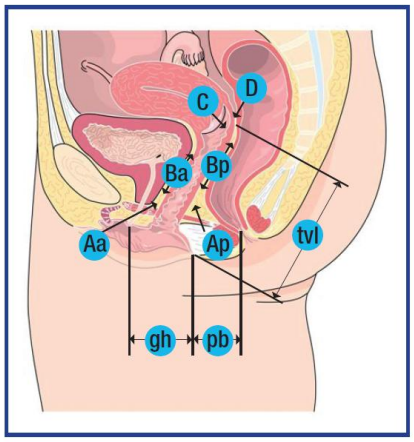
had more than one delivery, or were repeatedly pregnant at the time of follow up 23.6% (206), were excluded from the study (Appendix - II). Clinical follow up of 202 (23.2%) participants who met the inclusion criteria consisted of: pelvic organ prolapse quantification (POP-Q) assessment, joint hypermobility assessment - using Beighton hypermobility score, transperineal 2D/4D ultrasound scan for quantification of prolapse, a blood serum collection for procollagen quantification and lastly history taking on personal and family history of collagen related or other diseases shown previously to be associated with PFD and POP.

2.2.1 POP-Q assessment

The American Urogynecologic Society, the Society of Gynecologic Surgeons and the ICS approved a standardisation of terminology regarding female POP and PFD in 1996[30]. The pelvic organ prolapse quantification (POP-Q) classification, a part of this terminology standardisation process, is currently considered as gold standard in quantification of POP.

The POP-Q contains a set of standard points which are measured with a ruler. These points are located on the anterior and posterior vaginal wall and additionally include the most distal point of the uterine cervix. The line of hymenal insertion or the projection of hymenal remnants is considered as reference line, from which is measured the distance to all POP-Q points.

Figure 2.1: Explanation of the POP-Q points



The pelvic organ prolapse quantification (POP-Q) exam is used to quantify, describe, and stage pelvic support.

- There are 6 points measured at the vagina with respect to the hymen.
- Points above the hymen are negative numbers; points below the hymen are positive numbers.
- All measurements except tvl are measured at maximum valsalva.

Point	Description	Range of Values
Aa	Anterior vaginal wall 3 cm proximal to the hymen	-3 cm to +3 cm
Ba	Most distal position of the remaining upper anterior vaginal wall	-3 cm to +tvl
C	Most distal edge of cervix or vaginal cuff scar	
D	Posterior fornix (N/A if post-hysterectomy)	
Ap	Posterior vaginal wall 3 cm proximal to the hymen	-3 cm to +3 cm
Bp	Most distal position of the remaining upper posterior vaginal wall	-3 cm to + tvl
Genital hiatus (gh) – Measured from middle of external urethral meatus to posterior midline hymen **Perineal body (pb)** – Measured from posterior margin of gh to middle of anal opening **Total vaginal length (tvl)** – Depth of vagina when point D or C is reduced to normal position		

The coordinate of each POP-Q point was measured in centimetres, using a disposable measurement tape fitted on a disposable wooden spatula normally used for cervical screening. The measurement was done on maximal Valsalva manoeuvre held for at least 6 seconds in order to achieve maximal descend of the pelvic structures, as shown in previous studies[117].

Figure 2.2: POP-Q Staging criteria

POP-Q Staging Criteria	
Stage 0	Aa, Ap, Ba, Bp = -3 cm and C or D ≤ – (tvl – 2) cm
Stage I	Stage 0 criteria not met and leading edge < -1 cm
Stage II	Leading edge ≥ -1 cm but ≤ +1 cm
Stage III	Leading edge > +1 cm but < + (tvl – 2) cm
Stage IV	Leading edge ≥ + (tvl – 2) cm

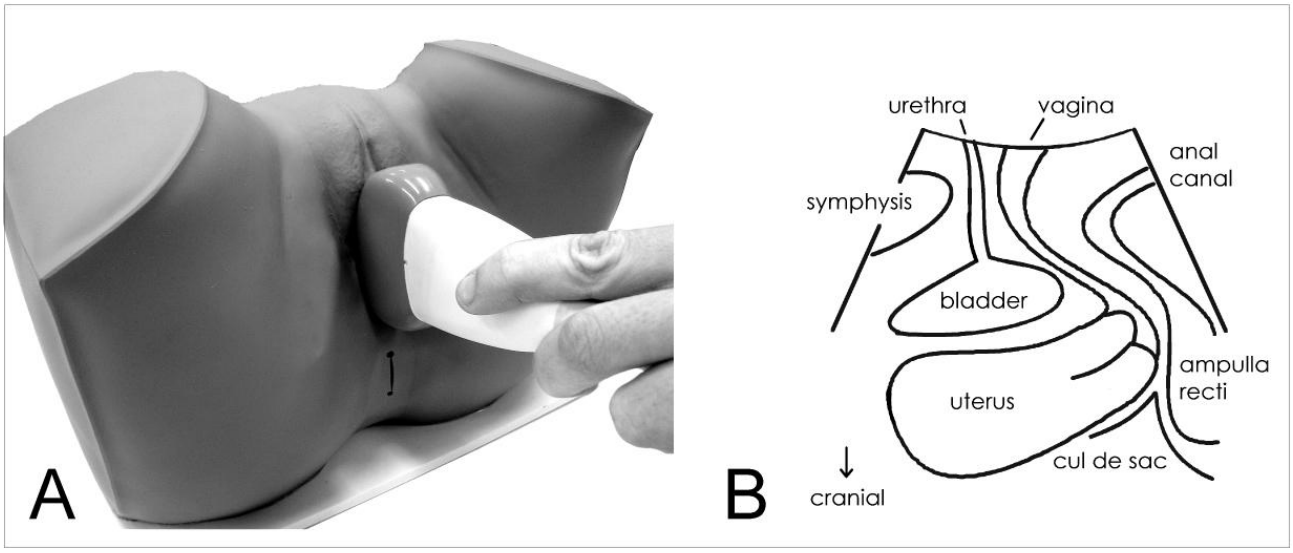
REFERENCE: Bump RC, Mattiasson A, Bo K, et al. The standardization of terminology of female pelvic organ prolapse and pelvic floor dysfunction. *Am J Obstet Gynecol.* 1996;175:13.

POP-Q assessment was performed before the transperineal ultrasound scan. The patient was placed in a semisupine position to facilitate both assessments. A disassembled disposable Cusco's speculum was used for visualisation of all target points on maximal Valsalva. The entire examination procedure was chaperoned by a female staff member, who also assisted with recording findings on a standard data sheet. In order to assess the impact of mode of delivery on POP, the POP-Q data were matched against demographic characteristics and mode of delivery as major confounders.

2.2.2 Prolapse quantification using 2D - Transperineal scan

The transperineal ultrasound scan makes use of a 3D 4-8 MHz probe used for obstetric practice. The probe is covered with a sterile cover and is applied to the interlabial / supraperineal area in sagittal plane. This methodology allows visualisation of the main pelvic structures such as pubic symphysis, bladder, urethra, uterus, vagina, rectum and anal canal in 2D mode (Figure 2.3).

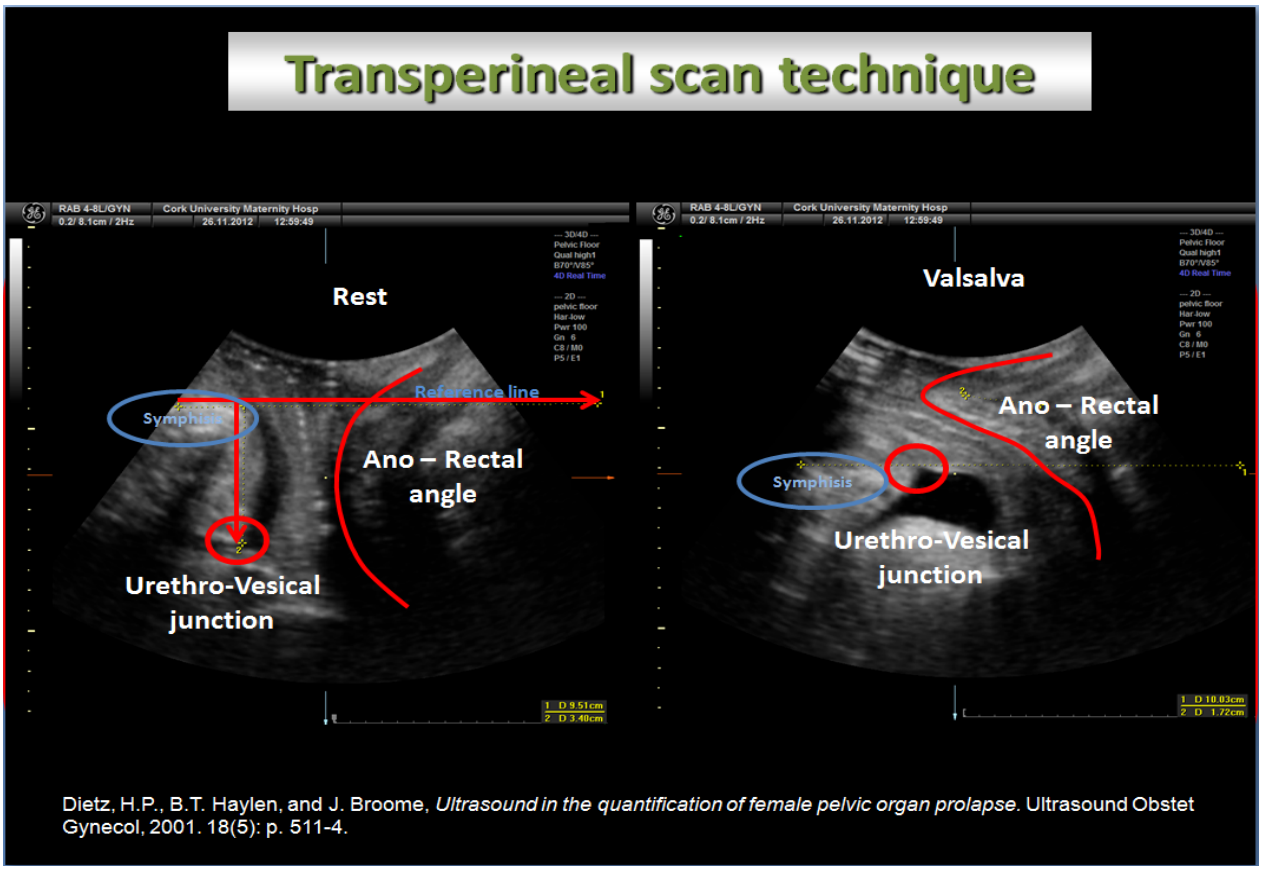
Figure 2.3: 2D - transperineal ultrasound scan



The POP can be quantified on a transperineal 2D ultrasound scan according to Dietz et al[42]. Two images were acquired – the first on rest and the second on maximal Valsalva, which was kept for not less than 6 seconds in order to achieve the best pelvic organ descend[117]. The inferior margin of the pubic bone was considered as a reference line. The distance from urethrovesical or anorectal junction was measured to the reference line (Figure 2.4).

Prolapse is classified into clinically significant and non-significant. For significant cystocele it was proposed a cut-off level of 10mm below the symphysis pubis (outside the pelvis) and for rectocele 15 mm. The authors did not propose a cut-off for uterine prolapse, probably because in a large number of cases the image of the uterine cervix can be occluded by the bowel loops and this measurement could be imprecise.

Figure 2.4: Prolapse quantification on transperineal ultrasound scan



2.2.3 Joint hypermobility assessment

Beighton joint hypermobility score is a system proposed to quantify joint hypermobility (Figure 2.5), mainly used in rheumatological and orthopaedic practice. It is considered that joint laxity is due to abnormal collagen levels in joint's capsular and ligamental connective tissue. It has been reported that POP is associated with joint hypermobility and various medical conditions linked with abnormal collagen[17, 116]. All these facts are indicative of a systemic manifestation of collagen abnormalities and suggest a role for congenital predisposition in the aetiology of POP[86, 118-119].

Figure 2.5: Thumb hypermobility

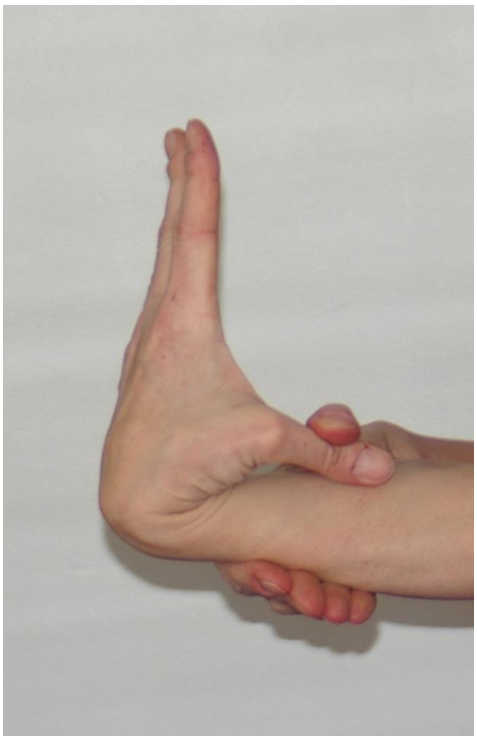
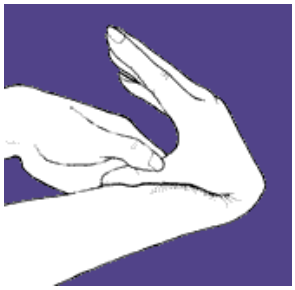


Figure 2.6: Beighton score assessment:

1. Score one point if you can bend and place you hands flat on the floor without bending you knees

2. Score one point for each knee that will bend backwards

3. Score one point for each elbow that will bend backwards



4. Score one point for each thumb that will bend backwards to touch the forearm

5. Score one point for each hand when you can bend the little finger back beyond 90°

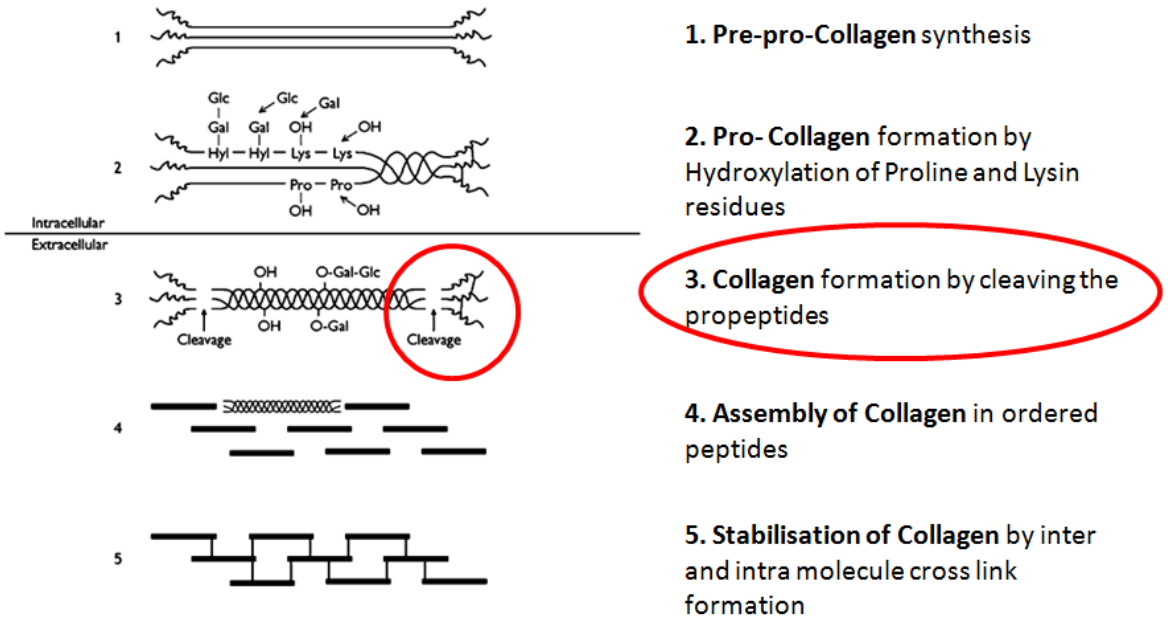
Table 2.1 Beighton joint hypermobility scoring

Test	Points
Able to put hands flat on the floor with knees straight	1
Able to bend left elbow backwards (hyperextend beyond 10°)	1
Able to bend right elbow backwards (hyperextend beyond 10°)	1
Able to bend your left thumb back on the front of your forearm	1
Able to bend your right thumb back on the front of your forearm	1
Able to bend you left little (fifth) finger back beyond 90°	1
Able to bend your right little (fifth) finger back beyond 90°	1
Able to bend your left knee backwards(hyperextend beyond 10°)	1
Able to bend you right knee backwards (hyperextend beyond 10°)	1

2.2.4 Collagen Investigation

The process of collagen synthesis consists of five steps. The first two are intracellular, occurring in the fibroblasts, the following three steps are extracellular[120]. When a procollagen molecule leaves the cell, during stage three, it is transformed from procollagen into tropocollagen by proteolytic cleavage of carboxy- and aminoterminals (Figure 2.7). These aminoterminals can be detected and quantified as markers of collagen synthesis in the blood serum or frozen tissue homogenates[121]. Procollagen N-Terminal Propeptides (PNP) and C-Terminal Propeptides (PCP) are collagen type specific and can be quantified by radioimmunoassay[46] or ELISA test[122].

Figure 2.7: Collagen synthesis mechanism



A blood sample was collected from 120 participants in plain 10 ml. vacutainers at the time of clinical follow up. Participants with highest and lowest value for point C (leading edge of cervix on POP-Q assessment) were selected from the cohort for procollagen

quantification. According to manufacturer's protocol, after collection the blood sample was kept in the fridge overnight at +4° C. On the following day the samples were centrifuged, in order to separate and store the blood serum. The serum samples were labelled and stored at minus 80°C for a maximum of 3 month as per manufacturer recommendation. When the required number of samples was achieved, serum procollagen quantification was performed in 96 participants by ELISA of procollagen type III (PIIINP), as a marker of collagen synthesis.

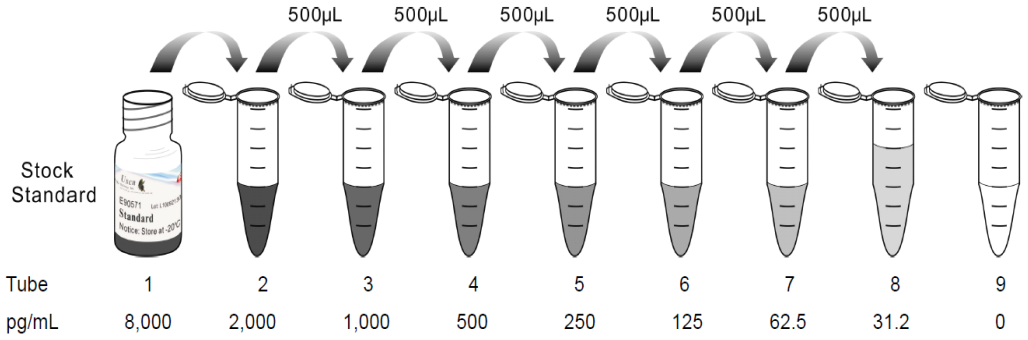
We utilized commercial ELISA tests manufactured by Uscn Life Science Inc. Wuhan. The Enzyme-linked Immunosorbent Assay Kit E90573Hu was used for quantification of procollagen type III N-Terminal Propeptide (PIIINP). Each plate contained 96 wells. All tests were performed in triplicates following the protocol below:

Figure 2.8: ELISA assay procedure summary

1. Prepare all reagents, samples and standards;
2. Add 100µL standard or sample to each well. Incubate 2 hours at 37°C;
3. Add 100µL prepared Detection Reagent A. Incubate 2 hours at 37°C;
4. Aspirate and wash 3 times;
5. Add 100µL prepared Detection Reagent B. Incubate 30 minutes at 37°C;
6. Aspirate and wash 5 times;
7. Add 90µL Substrate Solution. Incubate 10-15 minutes at 37°C;
8. Add 50µL Stop Solution. Read at 450nm immediately.

The initial samples were diluted according to the manufacturer instructions.
A dilution of 1:200 was used for the PIIINP test kit, as per manufacturer recommendation (Figure 2.9).

Figure 2.9: Sample dilution protocol



Following the addition of the Stop solution, the plate was read in a micro-titre plate spectrophotometer at a wavelength of 450ηm immediately. The average background value was subtracted from the mean of the triplicate test values for each sample. A standard curve was constructed using the mean optical density of the results from the standards against known concentrations. Sample values were interpolated from the curve and corrected for the dilution factor to determine the sample PIIINP concentrations.

To ensure reliability of all results obtained, the inter- and intra- assay coefficient of variation (CV) was calculated. The intra-assay CV was <13.6% and inter-assay was CV<19.2%. We acknowledge that these values do not reflect the best variation (ideally inter assay CV<15%), however this is within the robust limits of variation for clinical studies (CV<20%), where values up to 30% would be acceptable[123].

2.2.5 Association between personal and family history of medical conditions with collagen abnormalities association

Collagen abnormality appears to be a systemic issue. Although the genetic coding for collagen synthesis may have different expressions in various tissues, there is a body of

evidence indicating that collagen related problems seem to have a systemic manifestation. It has been demonstrated that POP is associated with joint hypermobility, abdominal, inguinal and vertebral hernias, varicose veins, mitral valve prolapse etc.[17, 46, 115-116].

In order to exclude a subjective impact on the POP-Q and transperineal scan assessment, the personal and family medical history was taken at the end of investigation. All participants completed a questionnaire containing questions regarding various medical conditions (Appendix VI), demonstrated in previous studies to correlate with POP and PFD. The majority of these diseases are considered to be associated with abnormal collagen or involve other mechanisms linking it to the PFD.

2.3 Assessment of postnatal PFD using 3D - Transperineal scan

The 3D scan consists of a set of 2D images acquired as separate slices and combined together. The 3rd spatial axis appears here, which is made up of a sequence of separate 2D slices. Thus, the final rendered 3D image can be considered a cube rather than a square, as in case of 2D scan. This cube can be rotated and examined from all sides. Additionally it can be "sliced" at different thicknesses and in different planes, and examined as a tomographic image.

The main goal of 3D scan in investigation of PFD is to visualise the anatomy of the puborectalis muscle, the medial most part of levator ani muscle (LAM) (Figure 2.10).

Figure 2.10: The axial view of a pelvic model

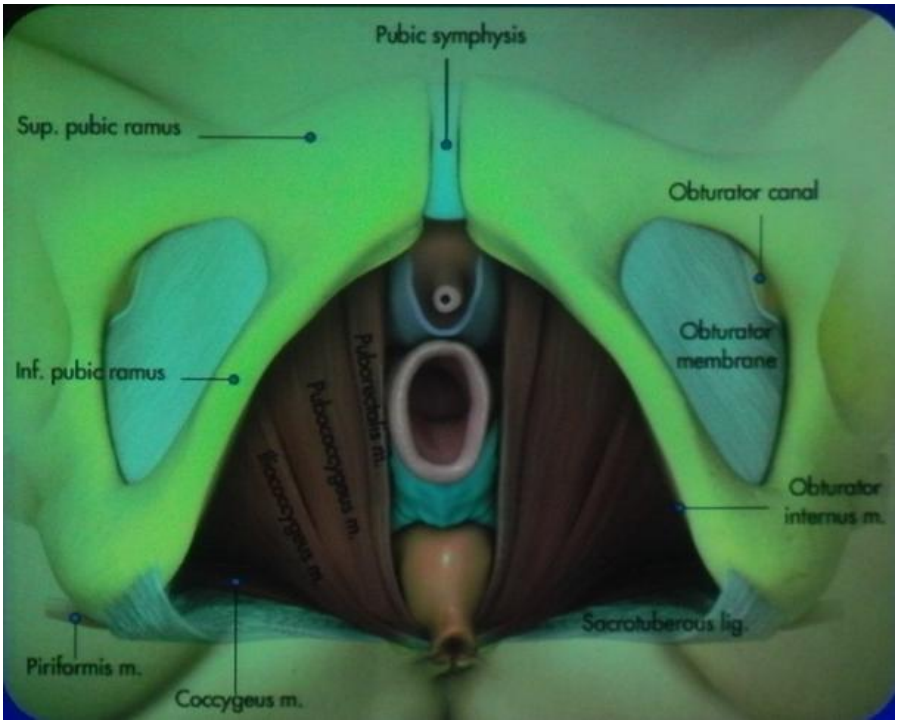
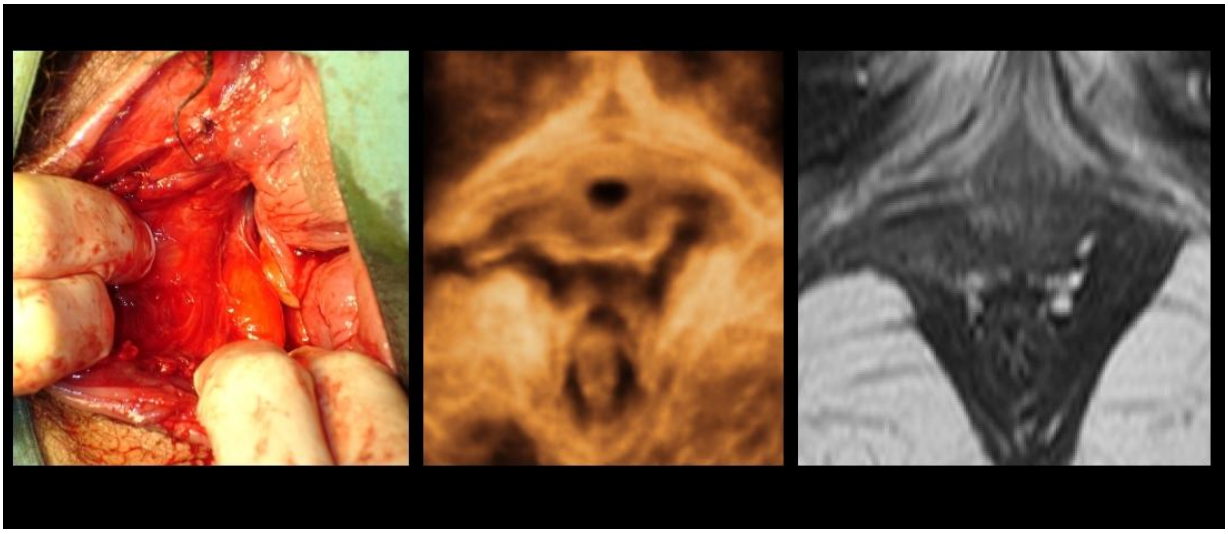


Figure 2.11 demonstrates an excellent correlation of clinical findings of puborectalis muscle avulsion with 3D ultrasound scan and MRI[124] .

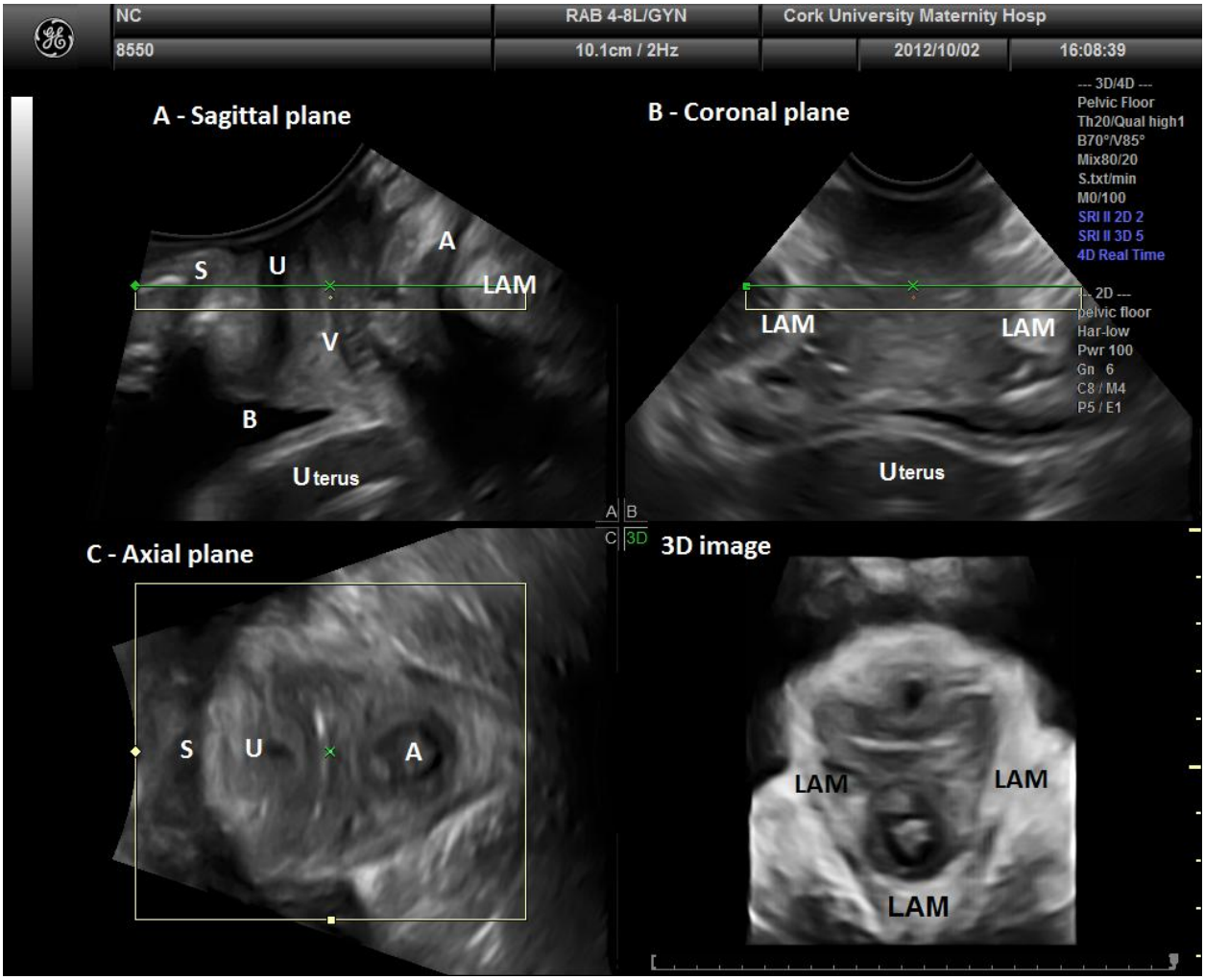
Figure 2.11: Correlation among clinical findings, 3D-USS and MRI investigation



As described previously, the transperineal ultrasound scan makes use of a 3D 4-8 MHz probe intended for obstetric practice. The probe is covered with a sterile cover and is applied to the interlabial / supraperineal area in sagittal plane. This methodology

allows visualisation of the main pelvic structures such as pubic symphysis, bladder, urethra, uterus, vagina, rectum, anus and puborectalis muscles. The images can be seen simultaneously in 2D Sagittal / Coronal / Axial planes and as 3D rendered image (Figure 2.12). The initial image is acquired in render mode then rotated and focussed at level of minimal hiatal dimension (the green line) (Figure 2.12)

Figure 2.12: Transperineal image acquired in 3D "Render" mode



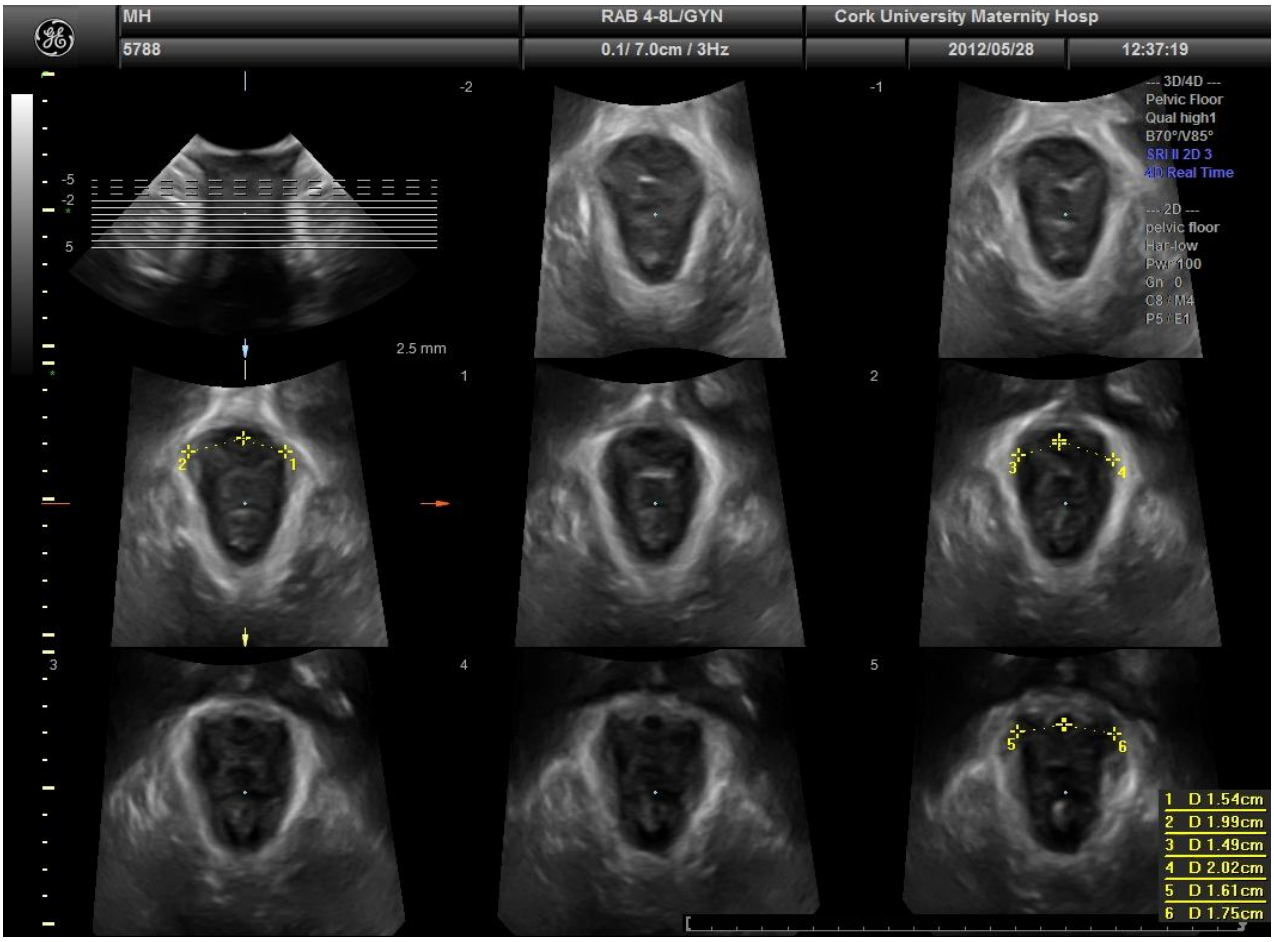
The following structures can be observed on the picture:

S – symphysis pubis U – urethra B – bladder V - vagina

A – anus LAM – levator anal muscle (puborectalis part)

The image is switched then to the Tomographic Ultrasound Investigation (TUI) mode (Figure 2.13). TUI mode is a sequence of 2D images sliced from the acquired 3D image in render mode.

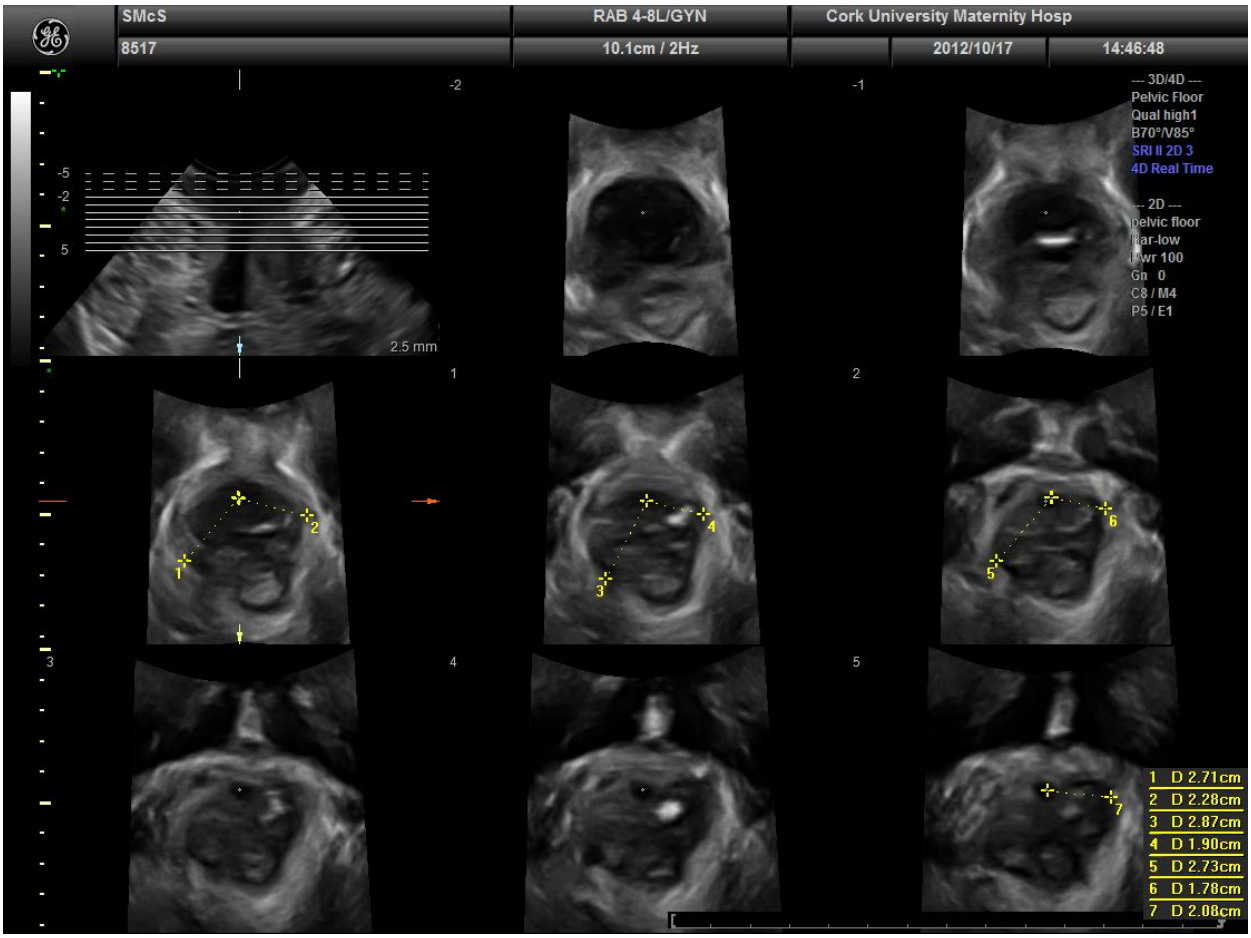
Figure 2.13: Tomographic Ultrasound Investigation mode



A slice thickness of 2.5 mm is used to investigate LAM trauma. The reference slice (first slice in the second row with a red arrow on it) demonstrates the morphology of LAM at the level of minimal hiatal dimension. The ultrasound criterion, confirming that the reference slice is chosen correctly, consists in symphyseal junction opening status in middle 3 slices. There should be an open / closing / closed sequence. Two slices on top of it demonstrate the LAM status at 2.5 and 5 mm. below or caudad to the reference plan (the USS image is inversed anatomically), whereas the remaining five at 2.5 – 7.5 mm

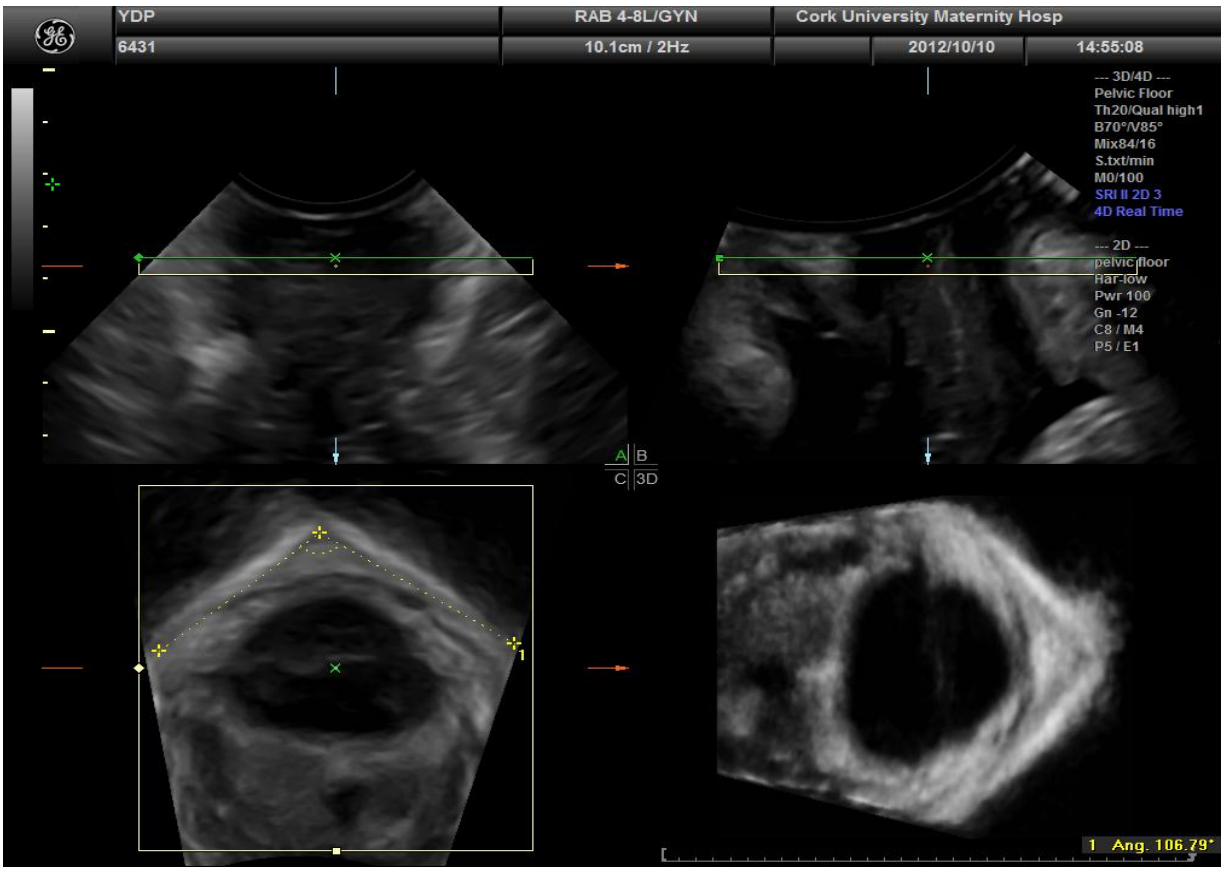
cephalad or above it. A complete avulsion is considered to be present if trauma is present in all 3 middle slices. Any other combination not including middle 3 slices are considered partial avulsions[102]. The levator–urethral gap measurement has been shown to be an objective criterion in detecting LAM avulsion with a cut-off of >25 mm[101] (Figure 2.14).

Figure 2.14: Complete right sided LAM avulsion (the image is anatomically reversed)



Additionally we measured the angle of the subpubic arch (Figure 2.15). The image acquired in render mode was rotated in plane A (sagittal) until the highest length of symphysis pubis rami was obtained in plane C (axial). This image was rotated 90 degrees to the right, in order to obtain a normal anatomical position, and the subpubic arch angle was measured[103]

Figure 2.15: Subpubic arch angle measurement



2.4 Statistical analysis

All statistical analyses were performed using Stata Software 10.0. and IBM SPSS Statistics 19.0. All statistical tests were two-sided and a p-value of less than 0.05 was considered statistically significant.

2.4.1 Study 1 – "Prepregnancy PFD"

Descriptive statistics were used to analyse the Median score value and Interquartile Range (M [IQR]) for each primary symptom of the questionnaire. Non-parametric Spearman correlation test was used to measure the relationship between the score in each section of the questionnaire and the reported associated bothersome score in that section.

2.4.2 Study 2 – "Postnatal PFD"

Descriptive statistics were used to analyse the median score value and interquartile range (M [IQR]) for the primary symptoms in each section of the questionnaire. Log-linear binomial regression was used to estimate the relative risk (RRs) of having Denovo or worsening postnatal symptoms in relation to mode of delivery. RRs were adjusted for maternal age, body mass index (BMI), education, smoking and marital status. When convergence was not achieved, a recognized problem with this model, log-linear Poisson regression with "robust" estimation variance was used[125]

2.4.3 Study 3 – "Prolapse and collagen abnormalities"

POP-Q assessment statistical analysis

Log-linear binomial regression was used to estimate the RRs of developing various types of POP in relation to mode of delivery. RRs were adjusted for maternal age, body mass index (BMI), education, smoking and marital status. When convergence was not achieved, a recognized problem with this model, log-linear Poisson regression with "robust" estimation variance was used[125].

2D-Transperineal scan statistical analysis

Descriptive statistics and cross-tabulation was used to assess the number of symptomatic participants among those diagnosed with significant POP on transperineal scan.

Beighton hypermobility score statistical analysis

The correlation between Beighton hypermobility score and POP was tested with Kruskal-Wallis test and Spearman rank correlation as appropriate. We investigated the correlation between the hypermobility score and the presence of various types of prolapse in isolation as well as in combination.

Collagen investigation statistical analysis

The association between various POP types and procollagen type III levels was assessed using Student's t-test.

Medical history association with POP statistical analysis

The association between POP and various medical conditions was analysed using chi-square test.

2.4.4 Study 4 – " Postnatal pelvic floor anatomy change on 3D TpUS""

To investigate the effect of potential risk factors on PFD, stepwise ordinal logistic regression was used to calculate the Odds Ratio (OR) and 95% Confidence Interval (95% CI). In ordinal logistic regression, the outcome measure was ordinal with more than two categories. RRs with borderline statistical significance ($p<0.1$) were used for multivariate logistic regression. Main outcome measures were, rectocele, uterine prolapse, LAM trauma, and LAM hiatal ballooning. The examined risk factors were subpubic arch angle, collagen type 3 levels, personal / family history of collagen related diseases, induction of labour, mode of delivery, Oxytocin augmentation, duration of labour, foetal head circumference and birthweight.

Chapter 3

Study 1

An insight into the pelvic floor status in nulliparous women

This paper was published in International Urogynecology Journal

Durnea CM, Khashan AS, Kenny LC, Tabirca SS, O'Reilly BA. An insight into pelvic floor status in nulliparous women. Int Urogynecol J 2014; 25:337-45.

3.1 Abstract

Introduction: Few studies have comprehensively investigated the prevalence of various types of pelvic floor Dysfunction (PFD) in women before their first pregnancy. However, no previous studies have investigated in detail all four compartments of PFD and the correlation between them.

Methods: This was a cross-sectional study nested within a parent prospective study Screening for Pregnancy Endpoints (SCOPE) performed in a tertiary referral teaching hospital with approximately 9,000 deliveries per annum. Nulliparous women completed the validated Australian Pelvic Floor Questionnaire at 15 weeks' gestation, at the time of recruitment to the SCOPE study. The questionnaire contained four sections, with questions about urinary, faecal, prolapse and sexual dysfunction in the prepregnancy period.

Results: A total of 1,484 participants completed the prenatal questionnaire. Urinary dysfunction was present in 61 % of participants, faecal in 41%, prolapse in 5% and sexual in 41 %; in 37 %, dysfunction was perceived as bothersome. At least one clinically significant symptom, defined as severity grade 2 or 3, or grade 1 associated with being bothersome, was reported by 58.2% of participants. More than one type of PFD was present in 57.6% of cases. The severity score of each symptom within a PFD section was associated with total section score.

Conclusions: We confirmed a high rate of PFD in nulliparous women. Clinically significant symptoms and associated bother were very common among symptomatic participants. The majority of affected women had more than one type of PFD. Postnatal

follow-up is needed in order to elucidate the role of pre-pregnancy symptoms in the aetiology of postnatal pelvic floor pathology.

3.2 Introduction

Pelvic floor dysfunction (PFD) has been defined as presence of symptoms of urinary (UI) or faecal (FI) incontinence, pelvic organ prolapse (POP), sensory or emptying abnormalities of the lower urinary tract, defaecation dysfunction, sexual dysfunction (SD) and chronic pain syndromes, which can present separately or coexist[1]. Many theories have been advanced to explain the association between morbidity of pelvic structures and different risk factors. Obesity, childbearing, advancing age and menopause are major recognized predisposing factors[126]. In the last few decades, various epidemiological and clinical studies have repeatedly shown that pregnancy and vaginal delivery are among the main risk factors for PFD[6, 11-12, 57]. However, UI is a recognised finding in nulliparous women, as well as in primiparous women post-Caesarean section (CS)[12]. There is an increasing body evidence showing that PFD cannot be explained by childbearing alone, as thought previously, and is probably linked to preexisting pelvic morbidity or intrinsic weakness[36, 127]. The major change in pelvic floor status seems to occur after the first pregnancy and delivery[8, 128]. It is recognised that CS reduces the risk of PFD[79, 129], although it does not offer total protection against it[12, 130]. Furthermore, Denovo urinary incontinence is not a common postnatal finding without prior antenatal symptoms[49-50]. Moreover, pregnancy and delivery carries a risk of <1% of initiating persistent postnatal stress urinary incontinence (SUI). The role of obstetric factors seems to be transient and is of uncertain aetiologic significance after 3 months postpartum[14]. For this reason, it remains unclear as to whether childbearing-

related risk factors are causative or just triggering events on a background of prepregnancy, preexisting PFD.

Despite the fact that there are many large epidemiologic studies, such as the Epidemiology of Incontinence in the County of Nord-Trondelag (EPINCONT) and National Health and Nutrition Examination Survey (NHANES), none have focussed on detailed prepregnancy pelvic floor status, particularly in premenopausal, nulliparous women. In addition, the majority of them investigated various types of incontinence or POP, which are only a limited part of the entire spectrum of PFD. There is a paucity of information on problems such as urinary frequency and urgency, SD or correlation between different components of PFD specifically in premenopausal, nulliparous women.

In the Prevalence and Predictors of Pelvic Floor Dysfunction in Primips (4P-study) reported here, we aimed to fill this gap in knowledge and test the hypothesis that PFD is not a condition caused by childbearing alone but could be a clinical manifestation of background preexisting pathology or congenital predisposition. As an initial step, we intended to comprehensively describe the PFD status in premenopausal nulliparous women by assessing the prevalence of all four types of PFD: urinary, faecal, prolapse and SD. In addition, we aimed to assess the correlation among the four types of PFD, along with associated bothersome symptoms, in women before their first pregnancy.

3.3 Materials and Methods

The 4P is a cross-sectional study nested within the larger parent Screening for Pregnancy Endpoints (SCOPE) Ireland study (www.scopestudy.net). SCOPE is an international, prospective, multicentre cohort study with the main aim of developing

screening tests to predict preeclampsia, small for gestational age infants and spontaneous preterm birth. The SCOPE database contains detailed information regarding family history of various medical conditions, personal medical history, antenatal and intrapartum outcomes, mode of delivery, foetal and maternal outcomes, postpartum period and associated complications. Inclusion criteria required the participants to be nulliparous in their first ongoing pregnancy and having a singleton foetus with a gestational age <15 weeks. Exclusion criteria consisted of preexisting risk factors for pregnancy complications, such as diabetes, hypertension, three or more terminations or miscarriages and previous cervical knife cone biopsy. SCOPE Ireland was performed in a tertiary maternity hospital with approximately 9,000 deliveries a year, where 40–42% were nulliparous women.

The study reported here was reviewed and approved by the Clinical Research Ethics Committee of the Cork Teaching Hospitals (CREC), Ireland, and consists of two parts: a questionnaire-based survey, followed by detailed clinical, laboratory and imaging investigations in women approximately 12 months postdelivery. We invited 2,579 nulliparous women to participate in the SCOPE study; subsequently, 1,774 (69%) were recruited (Appendix II). This represents 17% of all nulliparous women who delivered in the maternity hospital during the study period.

The validated Australian Pelvic Floor Questionnaire[28] was used to assess PFD prepregnancy and 1-year postnatally. We chose this particular questionnaire because it covers all four types of PFD plus investigates associated bother and condition-specific quality of life (QoL) problems. It is a validated questionnaire showing a very good correlation with other questionnaires and an association with urodynamic findings[28]. The first prepregnancy questionnaire was handed to all SCOPE participants to be

answered specifically on the day of recruitment and at 15 weeks' gestation and was returned completed by 1,474 (83% of recruited to SCOPE) participants (Appendix II). The prepregnancy questionnaires were completed between February 2008 and March 2011. All participants were specifically asked about prepregnancy symptoms, with the questionnaire stating (verbatim): "All these questions pertain to the period BEFORE you were pregnant". Additionally, patients were verbally instructed to ignore any symptoms newly developed during pregnancy. The second questionnaire was completed 1 year following delivery in order to characterise the long-term consequences of pregnancy on the pelvic floor; collection and processing of postnatal questionnaires continues.

The questionnaire consists of four sections, including questions about all four types of PFD. Each section contains 10–15 questions (Appendix III). All answers are graded from 0 to 3, where zero means no symptom present and 3 means the most frequent or severe symptom. Additionally, each section has a question about the grade of bother due to symptoms, rated 0–3 (0 indicates no bother and 3 indicates severe disturbance). Not each separate question from the questionnaire has an individual clinical value when assessing PFD. All questions from each section can be logically divided into primary symptoms, which are mandatory to diagnose a condition, and secondary symptoms, giving extra information on severity of primary symptoms, such as reduced fluid intake, pad usage, laxative use, bother etc. (Table 3.1). For analysis, primary symptoms from the questionnaire were selected according to International Continence Society (ICS) definitions for various types for faecal (FD) or urinary (UD) dysfunction.

As we aimed to comprehensively investigate all possible types of symptoms and dysfunctions besides incontinence symptoms commonly described in other studies, we investigated more questions from the questionnaire related to symptoms of overactive

bladder in the urinary section and obstructed defaecation in the FD section. For the sexual section, we used dyspareunia and vaginal laxity and tightness as primary symptoms. Regarding the prolapse, all questions included in that section can be regarded as primary symptoms for prolapse. These symptoms were selected as primary because they were included in the Pelvic Floor Distress Inventory and repeatedly utilized in previous studies[6, 8]. The questionnaire additionally contains a total section score for UD, FD, POP and SD. This score is meant to better characterise the severity of primary symptoms rather than represent a scale score[28]; it was calculated by adding all individual symptom scores in each section. In our analysis, we considered clinically significant symptoms as those with grade 2 or 3 severity from the questionnaire (meaning symptom present at least once weekly), or grade 1 severity with associated bother due to presence of symptoms (Table 3.1).

3.3.1 Statistical analysis

All statistical analyses were performed using Stata Software 10.0. Descriptive statistics were used to analyse the median score value and interquartile range (IQR) for each primary symptom listed in the questionnaire. Nonparametric Spearman correlation test was used to measure the relationship between the score in each section and the reported bother score due to symptoms in that section. All statistical tests were two sided, and a p value <0.05 was considered statistically significant.

3.4 Results

Mean participant's age was 30 years, mean body mass index (BMI) 24.9 kg/m2, 88% had >12 years of education and 27% were smokers. The characteristics of 4P study participants were similar to those from SCOPE (Table 3.2).

The response rate for prepregnancy questionnaires was 83% from all SCOPE participants; <1% of answers were missed at the time of completion. The prevalence of all questionnaire symptoms is presented in Table 3.3.

Overall, 19% (276) of all participants were asymptomatic for primary symptoms in all questionnaire sections, whereas 81% (1,208) reported at least one symptom and 58% (868) at least one clinically significant symptom. Figure 1 demonstrates the association among different types of PFD. In the majority of cases (58%), participants reported associated primary symptoms from more than one section. Thus, simultaneously, two types of PFD were reported by 37% (445) participants, three by 19% (232) and four by 2% (22).

3.4.1 Urinary Dysfunction

In the urinary section, 61% (900) of all participants reported at least one primary symptom, among them 21% (318) of all participants or 35% of symptomatic patients showed clinically significant symptoms. There was a high prevalence of various UD symptoms (Table 3.3): 24.5% of all participants were incontinent of urine, 8.8% having clinically significant symptoms. Looking at the structure of UI we found that SUI alone was present in 50% (181), urge urinary incontinence (UUI) alone in 20% (73) and mixed urinary incontinence (MUI) in 30% (110) of all UI participants. We found an association between symptom severity and total section score, as well as presence of bother, where severely affected patients had higher values (Table 3.4).

3.4.2 Faecal Dysfunction

In this section, 605 (41%) patients were symptomatic for primary symptoms; 18% (260) of all participants and 42% of those symptomatic had clinically significant symptoms. FI was reported by 79 (5.3%), flatus incontinence by 36.8% (540) and obstructed defaecation by 5.5% (80) (Table 3.3). Clinically significant symptoms were encountered by 2.4% (35), 15.5% (230) and 3.2% (47) accordingly. Again, we found an association between severity of symptoms/presence of bother and total section score (Table 3.4).

3.4.3 Pelvic Organ Prolapse

POP symptoms were reported by 4.8% (70) of women, where 1.2% (18) of all or 26% of symptomatic patients were clinically significant. The most commonly reported symptom was vaginal pressure or heaviness, which was present in 3.3% participants (Table 3.3).

3.4.4 Sexual Dysfunction

In this cohort, 41% (608) mentioned at least one primary SD symptom, of which 11% (162) of all or 27% of those symptomatic were clinically significant. The most commonly reported primary symptom was dyspareunia (31%), followed by vaginal tightness/vaginismus (25%) and vaginal laxity (5%) (Table 3.3). In general, dyspareunia was reported as mild, and similar rates of superficial and deep dyspareunia were noted (Table 3.5). As with previous sections, we found an association between symptom severity and total section score (Table 3.4).

3.4.5 Impact of symptoms on grade of bother

Some degree of bother was reported by 37% (519) of all symptomatic participants. A significant relationship was found between each section's total score (Table 3.1) and grade of bother; bother score increased with increasing total section score (Table 3.6).

Eleven percent of women reporting urinary symptoms considered that their symptoms disturbed them, and 5% claimed that symptoms had an impact on their QoL. A positive correlation was found between bother grade and total urinary section score (Table 3.6). The highest bother due to symptoms among all sections was noted in the FD group. One in four women (26%) reported associated bother in this section. Bothersome symptoms from prolapse and SD were reported by approximately 1% and 10% of participants, respectively (Table 3.3).

3.5 Discussion

This is one of the few studies to cover all four domains of prepregnancy PFD, specifically in relatively young women, who were recruited in early pregnancy. Although it included the entire age range of premenopausal women, 87% (1,285) were <34 years old, which is the first cut-off point for age when participants were classified into age categories in previous studies[6, 57]. There was at least one of four types of PFD present in 57.6% of participants. This is comparable with data presented by a large population-based study from Australia (46%)[6], which is the only other study covering all four types of PFD. However, that study concerned the general population and was not confined to nulliparous women. Some of our figures seem to be slightly higher compared with previous studies, probably because we described more types of PFD and thus more

symptoms, such as frequency, urgency, obstructed defaecation etc. Also, some studies investigated all women, including postsurgical and medically treated women[57].

3.5.1 Urinary and Prolapse Dysfunction

We found a high prevalence of UD in this cohort, in which one third had clinically significant symptoms. Urinary frequency and urgency, which have not been described previously in nulliparous women, were more prevalent than UI. Our findings correlate with data from the Finnish National Nocturia and Overactive Bladder (FINNO) study showing a prevalence of urgency of 57% and UUI of 25%; however, we cannot compare those studies directly because they targeted the general population, not nulliparous women only [131]. The prevalence of UI varies in different studies from 17% to 45% due to different grades of severity used for definition[6]. Thus, we compared our data in two ways: overall prevalence and clinically significant prevalence, as described in the "Methods" section. The overall prevalence of UI in our study was 24%, which is comparable with data from another big nulliparous cohort reporting a UI rate up to 21.5%[70], but it was higher than in the nulliparous group from EPINCONT (8–15%) or NHANES (6.5%). However, our prevalence of clinically significant UI (8.8%) correlated well with data from both studies[57, 68]. Also, we found good correspondence with EPINCONT in ratios of various types of UI (SUI 50 %, UUI 14 %, MUI 36 %)[132].

One in 20 participants in our study reported POP symptoms and 1.2% of the total cohort clinically significant symptoms. However, the number of women who reported POP symptoms was small, and results should be interpreted with caution. Also, there is a potential for confusion, as some bowel- or bladder-related symptoms may resemble prolapse. Even though the prevalence appeared low, it was comparable with result for

nulliparous women from the NHANES study— 0.6%—where they examined clinically significant symptoms only[57]. The two fold difference could be explained by the fact that the nulliparous group in their study included postsurgical patients, which was mentioned in their limitations.

3.5.2 Faecal Dysfunction

The present study is not the first to describe bowel related problems in nulliparous women. However, it is probably one of most comprehensive studies to date, covering a wide range of bowel disorders. The FD section had the highest median total section scores for primary symptoms and highest occurrence of bother of symptoms among all sections. This could be partially explained by high prevalence of pre-existing bowel pathology. In this study 11% of women had medical history of irritable bowel syndrome, additional 6 respondents had coeliac disease and another 6 - inflammatory bowel disease. However the rates of defaecation straining, constipation and faecal urgency were 4–6 folds higher than number of patients with medical history of bowel problems.

Our rate of FI, 5.3% was comparable with data from NHANES study (6.3%) and with Australian Survey reporting the prevalence in general population—3.5%[6]. Similarly with the latter, we had comparable prevalence of significant flatus incontinence —15% vs. 11%. Unfortunately we could not weigh our findings of flatus incontinence and Obstructed Defaecation (OD) against other studies reporting similar data in nulliparous women, since we could not find such publications. However, we think this is an important aspect to be considered, when describing PFD of the posterior compartment. Usually flatus incontinence is considered to be as a result of severe perineal trauma or

pudendal nerve damage in labour and delivery, but this could be also a congenitally determinate condition or predisposition to it.

3.5.3 Sexual Dysfunction

We found a high prevalence of SD in nulliparous women, not reported previously. Nearly half of participants had at least one primary SD symptom, where more than a quarter were clinically significant. Whereas we would expect up to one third of participants to complain of dyspareunia, an interesting finding was vaginal laxity in 4.8% and coital UI in 1.8% of respondents. This is consistent with data from previous studies for general population showing a vaginal laxity prevalence of 5.2%[6] and coital incontinence of 2%[133]. Regarding dyspareunia, in many cases it is thought to be caused by endometriosis, which has been shown to be more prevalent in nulliparous women (56% of all affected) and dyspareunia was one of the leading symptoms present in 55% of patients with SD[89]. We could not identify studies specifically describing SD in nulliparous women. The majority of studies focused on prenatal versus postnatal sexual satisfaction or comparison of SD following different modes of delivery. SD in the general population has a reported prevalence of 19–50%[58], which correlates with our findings.

3.5.4 Quality of life and degree of bother

A large pan-European study demonstrated that UI symptom severity was the most important predictor of QoL and bother[134]. Indeed, many clinicians consider that presence of bother is more important than the absolute score in predicting severe PFD. It has been observed that the degree of bother is a more useful parameter in identifying patients who may require surgical treatment[135]. Our study shows a strong correlation

between symptom severity reported bother scores, which emphasises the role of using questionnaires to assess degree of bother in addition to symptom severity.

3.5.5 Correlation among different types of PFD

This study demonstrates that in the majority of nulliparous women with PFD, the disorder affects more than one pelvic floor compartment simultaneously. BMI, age, chronic cough etc. could be common risk factors for UD, FD, POP and SD. Moreover, sometimes there is an overlap among symptoms presented from different sections. For instance, dyspareunia could reflect a uterine, bladder or bowel prolapse, obstructed defaecation with incomplete bowel emptying or recurrent lower urinary tract infection. This fact emphasises the role of comprehensive investigation of pelvic floor status in order to diagnose and address all issues leading to PFD. Detailed questionnaires covering all four sections involved in PFD are appropriate for achieving this goal.

The high prevalence of PFD and multicompartment involvement in nulliparous women could possibly suggest that congenital factors play an important role in PFD development. In order to understand the real role of childbearing in pelvic floor morbidity, it is important to elucidate the natural history of PFD by studying primiparous women before and after first delivery. Very few studies specifically target premenopausal nulliparous women in detail, often having a very narrow angle of view by describing UI only[68, 70, 76]. Others describe PFD in nulliparous women regardless of age, which is a major confounder[6, 57] or compare incontinence status before and during pregnancy[76]. Our study aimed to fill the existing gaps in understanding PFD and add to the knowledge base of PFD in women before their first pregnancy. Our main goal was to elucidate the prevalence of all components of PFD specifically in premenopausal,

relatively young nulliparous women and to describe the relationship between them. Associated risk factors is another important topic to be described in the future but was beyond the goals of this article. Further research is needed to clarify the role of childbearing on PFD development in nulliparous women and specifically investigating the correlation between pre- and postnatal pathology, rates of postnatal persistence of prepregnancy pathology and difference in severity between de novo and persistent postnatal pathology. Ideally, epidemiological studies should be combined with clinical examinations. This knowledge would help identify the group of patients at higher risk of severe PFD and possibly implement some measures to prevent it.

3.5.6 Study strengths and limitations

The main strength of this study is the large number of nulliparous participants comprising extensive and detailed demographic characteristics and medical history of participating women. In addition, we used a validated questionnaire, correlating with clinical findings and comprehensively covering all areas of PFD, including presence of bother due to symptoms. Although we have no detailed characteristics of the general nulliparous population, this study can be considered representative of an entire population from a statistical point of view. For studies >300 participants, a sample size of 10 % is considered to represent the population with an acceptable error of <3 %[136]. The SCOPE Ireland database included 17% of all nulliparous women who delivered during study period in our maternity hospital. The 4P study sampled 13% of nulliparous women and had no difference in maternal characteristics with SCOPE study (Table 3.2 and Appendix III). Another strength is high homogeneity of the study population, which allows overcoming naturally occurring confounders for PFD like

advanced age and interracial differences. The majority were relatively young (87% <34y.o.) and Caucasian (98%). There are numerous studies mentioning interracial difference in pelvic floor anatomy and prevalence of PFD, with white women being considered more prone to develop prolapse and UI[8, 137].

The main limitation of this study is that patients were not clinically examined to verify the questionnaire's findings. Additionally, participants completed questionnaires in early pregnancy, and we cannot rule out the potential for confusion or recall bias, as questions pertained to prepregnancy status only. However, as incontinence is such an important event for women, it is unlikely this information would be prone to recall bias[138]. This is a common limitation for such studies, and other research groups collected prepregnancy data in the same way[76]. In addition, we are not aware of any evidence that pelvic floor status is affected in early pregnancy.

3.6 Conclusion

We confirmed the high prevalence of different types of incontinence in nulliparous women and found good correlation with previously reported data. However, the spectrum of PFD symptoms in our study was larger than has been shown previously. There seems to be a higher correlation among studies when prevalence of moderate and severe symptoms are compared. One third of participants had clinically significant symptoms, showing an association between severity of primary symptoms from questionnaire results of total sections and bother scores. A total section score cut-off value could be determined used to screen patients in order to identify those at higher risk of severe PFD. SD had a high prevalence in nulliparous women. The majority of patients had more than one component of PFD affected simultaneously. A

comprehensive approach to investigating nulliparous women is required to elucidate the natural history of PFD. Postnatal follow-up is needed to detect the role of prepregnancy PFD in the structure of postnatal pathology and delineate the group of patients who could be at higher risk of severe postnatal PFD.

Figure 3.1: Prevalence of symptoms and association of various types of PFD

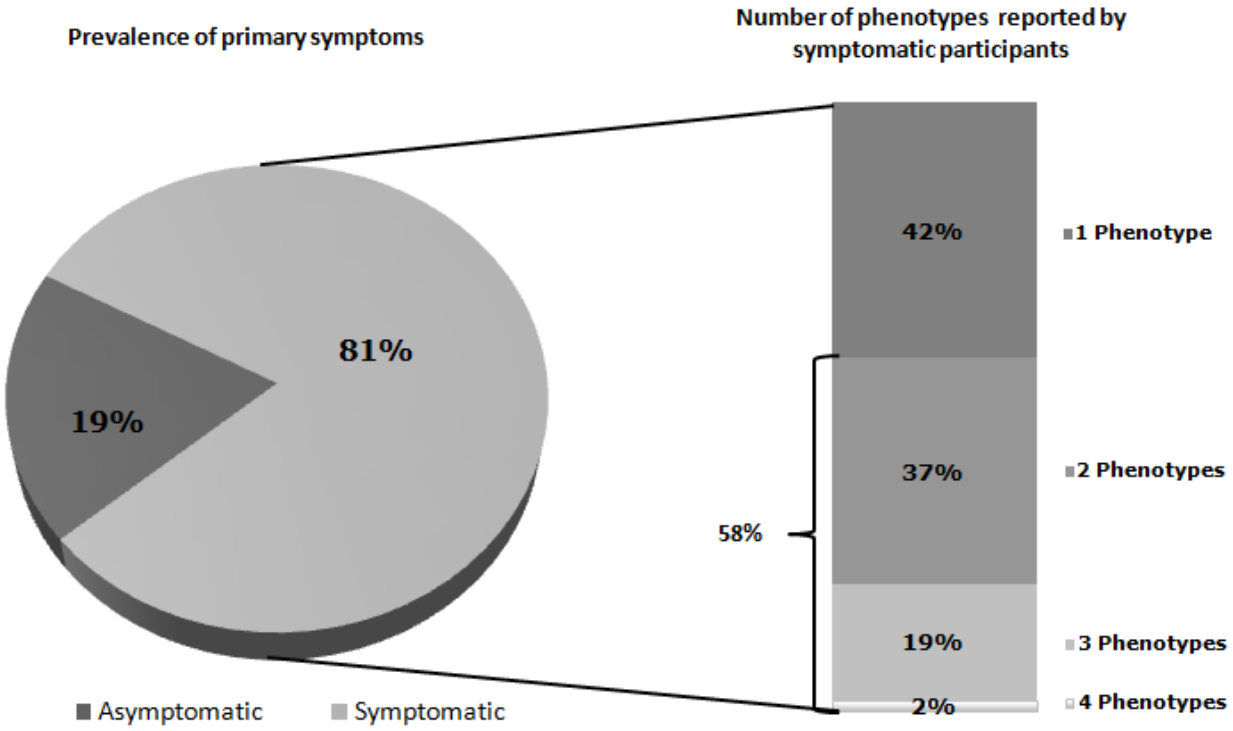


Table - 3.1 Commonly used definitions in this chapter

Primary Symptoms - symptoms contained in the ICS definitions or core symptoms for a specific type of PFD

Secondary Symptoms - symptoms not mandatory present for diagnosis of PFD, but their association adds to the understanding of severity of primary symptoms

Mild Symptoms - symptoms reported as severity grade 1 and no associated bother present

Severe Symptoms - symptoms reported as severity grade 2 or 3

Clinically Significant Symptoms - symptoms reported as grade 2, 3 or 1 with associated bother

Total Section Score - a sum of all individual symptom scores within one questionnaire's section

Table 3.2 Demographic characteristics of the 4P-Study population and Scope Ireland study

	4P-Study (n=1484)	**SCOPE Ireland (n=1774)**
Caucasians	1450(97.7%)	1733(97.7%)*
Age in years		
17-24	170(11.4%)	207(11.7%)
25-29	440(29.7%)	545(30.6%)
30-34	675(45.5%)	787(44.4%)
35-45	199(13.4%)	235(13.3%)
BMI		
Underweight	19(1.3%)	22(1.2%)
Normal	867(58.5%)	1036(58.4%)
Overweight	412(27.8%)	495(27.9%)
Obese	184(12.4%)	221(12.5%)
Education		
≤12 years	185(12.5%)	230(13%)
>12 years	1297(87.5%)	1544 (87%)
Smoking		
Non smokers	1088(73.4%)	1285(72.4%)
Smokers	394(26.6%)	489(27.6%)
Alcohol consumption		
No	289(19.5%)	339(19.1%)
Yes	1193(80.5%)	1435(80.9%)
Mean values [A]		
Age in years	30. 0(4.5)	29.9(4.5)
BMI	24.9(4.1)	24.9(4.2)
Weight in kg.	67.5(12.1)	67.5(12.2)

* All values presented as number of cases and (%) of total

A Data presented as mean value and Standard Deviation (SD)

Table 3.3 Prevalence of individual PFD Symptoms (n=1485)

	Total * Symptomatic	Clinically * Significant Symptomatic
Urinary Dysfunction		
Urinary Frequency [A,B]	**29.2%(431)**	**11%(162)**
Nocturia	**17.6%(260)**	**8.3%(123)**
Nocturnal enuresis	0.3%(4)	0.2%(3)
Urgency	**42%(619)**	**12.5%(184)**
Urge Incontinence	**12.4%(183)**	**5.4%(79)**
Stress Incontinence	**19.7%(291)**	**6.3%(93)**
Weak Stream	24.3%(358)	7.7%(113)
Incomplete Bladder Emptying	24.9%(367)	8.7%(128)
Strain to Empty	14.1%(207)	4.7%(69)
Pad Usage	6.5%(96)	3.1%(46)
Reduced Fluid Intake	4.9%(72)	3.2%(47)
Recurrent UTI	14.3%(211)	5.1%(75)
Dysuria	9.4%(139)	3.3%(49)
Impact on Social Life	4.7%(69)	3.5%(51)
Bladder - How much of a bother	N/A	11.1%(163)
Faecal Dysfunction		
Defaecation Frequency	19.8%(290)	10.1%(147)
Consistency of Bowel Motion	52.5%(771)	18.4%(270)
Defaecation Straining	59.9%(880)	23.9%(351)
Laxative Use	7.9%(116)	5.6%(83)
Do You Feel Constipated	51.6%(757)	23.6%(346)
Flatus incontinence	**36.8%(540)**	**15.7%(230)**
Faecal Urgency	46.6%(683)	18.3%(269)
Faecal Incontinence with diarrhoea	**4.8%(71)**	**2%(30)**
Faecal Incontinence with normal stool	**1.2%(18)**	**0.6%(9)**
Incomplete Bowel Evacuation	41.2%(603)	20.9%(305)
Obstructed Defaecation	**5.5%(80)**	**3.2%(47)**
Bowel - How much of a bother	N/A	26%(380)

Prolapse Dysfunction		
Prolapse sensation	**1.1%(16)**	**0.3%(5)**
Vaginal Pressure or heaviness	**3.3%(48)**	**0.8%(12)**
Prolapse reduction to void	**0.3%(5)**	**0.3%(5)**
Prolapse reduction to defaecate	**1%(14)**	**0.5%(7)**
Prolapse - How much of a bother	N/A	0.9%(13)
Sexual Dysfunction		
Sufficient lubrication (No)	18.4%(263)	22.4%(321)
During intercourse vaginal sensation is (abnormal)	12.7%(183)	9.1%(131)
Vaginal Laxity	**4.8%(70)**	**1.2%(17)**
Vaginal tightness/vaginismus	**25.1%(363)**	**8.4%(121)**
Dyspareunia	**31%(449)**	**9.6%(139)**
Coital Incontinence	1.8%(26)	0.3%(5)
Sexual Function - How much of a bother	N/A	9.9%(143)

* - In both columns figures are given out of total participants

A - The symptoms are worded similarly as seen in the questionnaire (however in the questionnaire they have extra explanation in layman terms)

B – Primary symptoms are highlighted in bold

Table 3.4 Primary symptoms matched against the median section scores and associated bother

Primary symptoms	Severity Grade	Median section score and IQR M(IQR)	*Prevalence of associated bother
Urinary			
Urinary Frequency	Mild	4(0-8)	61((18.5%)
	Severe [A]	7(0-14)	40(39.6%)
Nocturia	Mild	5(1-9)	44(24%)
	Severe	8(2-14)	29(37%)
Urgency	Mild	3(0-6)	80(16%)
	Severe	9(3-15)	53(51%)
Urge Incontinence	Mild	6(2-10)	51(33%)
	Severe	9(3-15)	13(46%)
Stress Incontinence	Mild	5(1-9)	60(23%)
	Severe	9(2-16)	18(55%)
Faecal			
Flatus incontinence	Mild	5(1-9)	147(33%)
	Severe	8(3-13)	38((46%)
Faecal Incontinence with normal stool	Mild	7(4-10)	5(39%)
	Severe	6.5(0-13.5)	1(25%)
Faecal Incontinence with diarrhoea	Severe	7(4-10)	25(40%)
	Mild	14(6-22)	5(100%)
Obstructed Defaecation	Mild	7(3-10)	58(54%)
	Severe	11(2-20)	8(100%)
Prolapse			
Vaginal Pressure or heaviness	Mild	1(0-2)	6(14%)
	Severe	2(1-3)	1(17%)
Sexual			
Vaginal Laxity	Mild	2(0-4)	12(19%)
	Severe	3(0-3)	0(0%)
Vaginal tightness/vaginismus	Mild	2(1-3)	65(21%)
	Severe	6(2-10)	71(73%)
Dyspareunia	Mild	2(0-4)	106(26%)
	Severe	8(5-11)	32(97%)

* - The prevalence of associated bother out of total affected in the respective group: mildly or severely affected accordingly

[A] - Moderate and severe symptoms were grouped together, in order to reflect the prevalence of significant pathology

Table 3.5 Dyspareunia in nulliparous population (n = 1447)

Grade of dyspareunia	
Severity	**Cases (%)**
No	1012(70%)
Mild	402(28%)
Moderate	28(2%)
Severe	5(1%)
Type of dyspareunia	
Superficial	218(50%)
Deep	172(40%)
Mixed	45(10%)

Table 3.6 Grade of bother correlated to total section scores (n=1484)

Grade	Total section score & prevalence							
	Urinary *		Faecal *		Prolapse *		Sexual *	
0	1(0-3) [A]	1312(89%) [B]	2(1-4)	1081(74%)	0(0-0)	1440(99%)	0(0-1)	1305(90%)
1	8(5-10)	136(9%)	7(5-8)	290(20%)	3(2-3)	290(0.7%)	4(3-6)	116(8%)
2	11(10-15)	21(1.5%)	10(8-12)	73(5%)	5.5(4.5-6.5)	73(0.3%)	8(7-9)	23(1.7%)
3	11.5(9-20)	6(0.5%)	13(10-14)	17(1%)			11(8.5-13)	4(0.3%)

* Spearman correlation test showed a significant relationship between the bother grade and section symptoms score the in each subsection ($p<0.001$)

[A] Median section symptom score and Interquartile Range M(IQR);

[B] Prevalence shown as: № of cases (% of total)

Chapter 4

Study 2

The role of prepregnancy pelvic floor dysfunction in postnatal pelvic morbidity in primiparous women

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Durnea CM, Khashan AS, Kenny LC, Tabirca SS, O'Reilly BA. The role of prepregnancy pelvic floor dysfunction in postnatal pelvic morbidity in primiparous women
Int Urogynecol J 2014;25:1363-1374

4.1 Abstract

Introduction Little is known about the natural history of pelvic floor dysfunction (PFD).We investigated the association between prepregnancy and postnatal PFD in premenopausal primiparous women and the associated effect of mode of delivery.

Methods A prospective cohort study, nested within the parent Screening for Pregnancy Endpoints (SCOPE) study, was performed in a tertiary hospital with approximately 9,000 deliveries per annum. The validated Australian pelvic floor questionnaire was completed by 872 nulliparous women at 15weeks' gestation, at the time of recruitment to the SCOPE study and 1 year postnatally. The questionnaire contained four sections with questions about urinary, faecal, prolapse and sexual dysfunction.

Results One year postnatally urinary dysfunction was present in 73%, faecal in 49%, prolapse in 14% and sexual in 58% of participants. Prepregnancy PFD persistent postnatally constituted more than half of total PFD. The majority of affected (71%) had multicompartment involvement. Participants with persistent PFD had higher prevalence of severe symptoms and bothersome symptoms within the group. Severity of prepregnancy PFD worsened in <15% cases postnatally.

Conclusions The main damage to the pelvic floor seems to occur in the majority of patients before first pregnancy, where first childbearing does not worsen prepregnancy PFD in the majority of cases. Pregnancy appears to affect more preexisting symptoms of urgency and urge incontinence comparing to stress incontinence. Caesarean section seems to be more protective against postnatal worsening of prepregnancy PFD comparing to de novo onset pathology. However, larger studies are needed to confirm these findings.

4.2 Introduction

The association between childbearing and pelvic floor dysfunction (PFD) is commonly recognised[6, 8, 11-12]. Although vaginal delivery is considered one of the most significant risk factors for PFD, urinary incontinence (UI) is common in nulliparous women as well as in primiparous women post caesarean section (CS)[12, 47]. There is a body of evidence demonstrating that initial onset of PFD during the first pregnancy is more likely to be associated with persistent postnatal PFD compared to de novo postnatal onset[49-51]; however, the natural history of PFD is poorly understood[75]. Despite the fact that many studies investigated the correlation between the onset of UI during the pregnancy and its correlation with postnatal PFD, there are no researches at the moment on the relationship between the prenatal and postnatal pathology in nulliparous women. Such a study would add to the understand-ding of the natural history of PFD.

We hypothesised that prepregnancy PFD in nulliparous women plays an important role in postnatal prevalence of pelvic morbidity, which is worsened by childbearing and reflects a congenital predisposition to pelvic floor weakness.

In the present 4P study (Prevalence and Predictors of Pelvic floor dysfunction in Primips), we aimed to investigate the correlation between the prepregnancy and postnatal PFD in premenopausal primiparous women, by assessing all four types of PFD: urinary, faecal, prolapse and sexual dysfunctions. Additionally, we intended to investigate the persistence rate of prepregnancy pathology postnatally, its relation-ship with mode of delivery (MOD) and the association among all four types of PFD.

4.3 Materials and methods

The 4P is a prospective cohort study, nested within the larger parent international, multicentre Screening for Pregnancy Endpoints study (SCOPE, www.scopestudy.net), which has been described previously along with inclusion/exclusion criteria and detailed methodology for the 4P study[139]. SCOPE Ireland was performed in a tertiary maternity hospital with approximately 9,000 deliveries a year, with a 40–42% rate of nulliparous women.

The present study, consisting of two parts, was approved by the Clinical Research Ethics Committee of the Cork Teaching Hospitals (CREC), Ireland. The first stage was a questionnaire-based survey. In the second phase, we performed a detailed clinical assessment involving family and personal history of collagen-related diseases collection, joint hypermobility assessment, collagen type III quantification, Pelvic Organ Prolapse Quantification (POP-Q) assessment and 3D transperineal ultrasound scan approximately at 12 months post delivery. This article describes the first phase only: questionnaire findings analysis.

The validated Australian pelvic floor questionnaire was used in the first phase to assess PFD[28]. Specifically, this questionnaire was chosen because it covers all four compartments of PFD plus associated bother due to symptoms. Additionally, it is a validated questionnaire, showing a very good correlation with other questionnaires and an association with urodynamic findings[28]. The questionnaire was answered twice: on the day of recruitment and at 15 weeks' gestation by 1,484 (83%) and at 1 year post delivery by 1,060 (60%) from all SCOPE participants. Of those who were recruited for the 4P study (1,484), 424 (28%) were excluded from postnatal analysis due to failure to

complete the postnatal questionnaire and another 188 (12%) due to second ongoing pregnancy (Appendix II).

Less than 1% of PFD answers were missing at the time of completion; therefore, women with missing data on specific variables were excluded from the analysis of these variables. The recruitment phase occurred between February 2008 and March 2011. At recruitment all participants were specifically asked about prepregnancy symptoms, the questionnaire stating (verbatim): "All these questions pertain to the period BEFORE you were pregnant", additionally being verbally instructed to ignore any symptoms newly developed in pregnancy. Postnatal questionnaires were completed at 1 year postnatally, in order to exclude postpartum short-term transitory changes in the pelvic floor.

There are four sections in this questionnaire, assessing all types of PFD. Each section contains 10–15 questions (Appendices III & IV). All answers are graded from 0 to 3, where 0 means no symptom present and 3 indicates most frequent or severe symptom. Additionally, each section contains a question about the grade of bother due to symptoms, rated similarly from 0 to 3. Not each separate question from the questionnaire has an individual clinical value when assessing PFD. That is why the questions from each section can be logically divided into primary symptoms, mandatory to diagnose a type of dysfunction and secondary symptoms, giving extra information on the severity of those primary symptoms like reduced fluid intake, pad usage, laxative use, grade of bother etc. The primary symptoms from the questionnaire were selected for analysis according to International Continence Society (ICS) definitions for faecal (FD) or urinary (UD) dysfunction. Because we aimed to comprehensively investigate all possible types of symptoms and dysfunctions, besides incontinence commonly described in other studies, we investigated symptoms related to overactive bladder

(OAB) in the UD section and obstructed defaecation (OD) in the FD section. Dyspareunia, vaginal laxity and tightness were used as primary symptoms for the sexual dysfunction (SD) section. All questions included in the pelvic organ prolapse (POP) section can be regarded as primary symptoms, as they were included in the Pelvic Floor Distress Inventory and used in other studies[8, 11]. Additionally, this questionnaire contains a total section score for UD, FD, POP and SD, which is meant to better characterise the severity of primary symptoms rather than representing a scale score[28]. It is calculated by adding all individual symptom scores in each section (Table 4.3 & Appendix III). In our analysis we considered clinically severe symptoms those rated as grade 2 or 3 severity (meaning symptom present at least once weekly). The assessed PFD was classified into general, de novo postnatal onset PFD (DNPFD) and prepregnancy PFD persisting postnatally (PPFD). The main outcome measures were: total prevalence of various symptoms of all PFD, DNPFD and PPFD and prevalence of clinically severe symptoms, persistence of prepregnancy symptoms postnatally, prevalence of persistent symptoms which worsened postnatally, characteristics of women in whom prepregnancy symptoms worsened postnatally, characteristics of women in whom prepregnancy symptoms worsened postnatally, quantification of multiple compartment involvement and the effect of MOD on postnatal PFD.

4.3.1 Statistical analysis

All statistical analyses were performed using Stata Software 10.0. Descriptive statistics were used to analyse the median score value and interquartile range [M (IQR)] for the primary symptoms in each section of the questionnaire (Table 4.3). All statistical tests were two-sided and a p value<0.05 was considered statistically significant. Log-linear

binomial regression was used to estimate the relative risk (RR) of having Denovo or worsening postnatal symptoms in relation to MOD. RR were adjusted for maternal age, body mass index (BMI), education, smoking and marital status. When convergence was not achieved — a recognised problem with this model —log-linear Poisson regression with "robust" estimation variance was used[125].

4.4 Results

The study population consisted of 98.4% Caucasian women, with a mean age of 30.5 years and mean BMI of 25 kg/m2. All demographic characteristics of women who participated in the 4P study were similar to the SCOPE study (Table 4.1). It has been previously demonstrated that the SCOPE cohort is representative of the study population[139].

Table 4.2 demonstrates the prevalence of all questionnaire's symptoms at 1 year post delivery in three columns: the general prevalence of symptoms, DNPFD and PPFD. Each column has two sets of data, showing the total prevalence of symptoms in the group and prevalence of severe symptoms present ≥1 a week. Additionally, we marked primary symptoms (described in the "Materials and methods" section) for clarity.

Overall only 10% (88) of all participants were asymptomatic for primary symptoms, whereas 90% (784) reported at least one symptom and 31% (268) at least one severe symptom. Among postnatally symptomatic women, 71% reported primary symptoms from>1 section of the questionnaire: 31% (272) had primary symptoms from two sections, 24% (213) from three and 8% (69) from four sections (Figure 4.1). The correlation between primary symptoms with related section scores for DNPFD and

PPFD groups, and postnatal persistence rate of prepregnancy symptoms, is presented in Table 4.3. In order to comprehensively describe the PFD in the following results' sections, we are presenting the data as total prevalence in the cohort, prevalence of severe symptoms in the same cohort out of all participants and percentage of severely affected out of those symptomatic only.

4.4.1 Urinary dysfunction

UD was solely present in 17% of cases only, in the remaining cases being associated with other types of PFD (Fig. 1). At least one primary UD symptom was reported by 73% (640) of all participants; among them 17% (146) of total or 23% of symptomatic participants presented severe symptoms. Of those 640 participants with postnatal UD, 67% (429) had PPFD and 33% (210) DNPFD (Section Score in Table 4.2). UI was present in 54 % (465) of all participants, where 18% (83) of those affected or 9.6% of all presented severe symptoms (Table 4.2). Of all 4P study participants, stress urinary incontinence (SUI) was present in 24% (204), urge urinary incontinence (UUI) in 8% (72) and mixed urinary incontinence (MUI) in 22% (189), giving a ratio of 44/15/41 % in urinary incontinent women. It is worth mentioning that 63% of incontinent women had de novo onset symptoms; however, the prevalence of severe UI was nearly similar in the DNPFD and PPFD groups, giving a higher rate of severe UI within the PPFD group (Table 4.2). The total urinary section score was also higher in PFD (Table 4.3). In contrast to UI, symptoms related to OAB, frequency, nocturia and urgency, were more prevalent in the PPFD group. Severe symptoms were at least twice more prevalent than in DNPFD (Table 4.2). Interestingly, prepregnancy symptoms of UD persisted postnatally on average in 61% of participants; however, initial pathology worsened postnatally in 16% of cases of PPFD only (Table 4.3).

4.4.2 Faecal dysfunction

Primary FD symptoms were reported by 49 % (425), where 10 % (87) of all participants or 21 % of those symptomatic had severe symptoms. PPFD was present in 57 % (429) of all affected (Table 4.2). Flatus incontinence (Fl.I) was more prevalent in the PPFD group, whereas faecal incontinence (Fe.I) and OD were more prevalent in the DNPFD group, though the prevalence of severe pathology was similar in both groups; the only exception was Fl.I, which was higher in the persistent group. In the FD section the difference in section scores between DNPFD and PPFD groups was minimal. Prepregnancy symptoms persisted postnatally on average in 50%, where they worsened after first childbearing in 15 % only (Table 4.3).

4.4.3 Prolapse dysfunction

Only 0.2% of all participants indicated POP as the single presenting symptom, whereas in the majority it was combined with symptoms from other compartments (Fig. 4.1). POP symptoms were reported by 14% (121) of women, where in 3% (24) of all or 20% of symptomatic participants they were severe. DNPFD was most prevalent at 87% (105) (Table 4.2). Most commonly reported symptoms were “vaginal pressure or heaviness” present in 11% (94) and “prolapse sensation” (feeling a lump) in 7% (57) of study participants (Table 4.2). In those affected, severe symptoms were present in 18% (17) and 25% (14) respectively. All symptoms were more severe in the DNPFD group.

4.4.4 Sexual dysfunction

At least one primary SD symptom was reported by 58% (504), of which 10% (91) of total and 18% of symptomatic participants had severe symptoms. PPFD constituted

53% (268) of those affected. The most prevalent primary symptom in all participants was dyspareunia 44% (367), followed by vaginal tightness 29% (244) and vaginal laxity 21% (180) (Table 4.2). Severe forms of pathology in those affected were reported by 14% (50), 2 % (49) and 13% (23) accordingly. Similar rates and severity of superficial and deep dyspareunia were noticed in both DNPFD and PPFD groups (Table 4.2). The median section score was similar in both groups; prepregnancy symptoms persisted postnatally on average in 59% and worsened in 12% compared to baseline prechildbearing status (Table 4.3).

4.4.5 Impact of symptoms on grade of bother

Some degree of bother was reported by 52 % (406) of symptomatic participants (784). The prevalence of the associated bothersome symptoms in different sections ranged between 21 and 24 % (Table 4.2). There was a trend towards a higher disturbance from symptoms in the DNPFD group. Severe bother due to symptoms was more prevalent in UD and FD groups (Table 4.2).

4.4.6 PFD and mode of delivery

We evaluated the effect of MOD on postnatal PFD for the Denovo and persistent groups separately. The main aim for the PPFD group was to investigate the impact of MOD on worsening postnatal symptoms, thus only cases where postnatal score worsened compared to prepregnancy were included in the analysis. Since CS is considered to be protective against PFD, the women who delivered by CS were chosen as reference group.

Postnatal symptoms worsened only in 14% of PPFD (Table 4.3), that is why sometimes the number of observations was low to reach statistical significance. However we are reporting data for majority of primary symptoms, to show the general tendency (Table 4.4). In an attempt to address this issue, in addition to separate primary symptoms, we are presenting the Relative Risk (RR) for a combination of all primary symptoms within the relevant section. There was a consistency between the findings for each separate primary symptom and the whole section analysis, with forceps delivery increasing the risk for the majority of primary symptoms followed by spontaneous vaginal delivery (SVD) and vacuum delivery (Table 4.4). A trend towards higher increase of RR of PFD from vaginal delivery was observed in PPFD vs DNPFD for urinary urgency, SUI and Fl.I; however, the number of observations was too small to allow a definite conclusion. Participants with PPFD which worsened postnatally had a trend towards a higher rate of prepregnancy bothersome symptoms and more types of simultaneous prepregnancy PFDs (Table 4.5).

4.5 Discussion

There are no previous studies, to our knowledge, investigating the relationship between all types of prepregnancy and postnatal PFD, specifically in relatively young primiparous women. While our study included all premenopausal women, 85% (739) were less than 34 years old, which is the first cut-off point for age, when participants were classified into age categories in other studies[6, 57]. There are several studies investigating the postnatal prevalence of UI at different periods of time in primiparous women[77], correlation between the prepregnancy onset of UI and its persistence during pregnancy[76] or de novo onset of symptoms in pregnancy and postnatal persistence[49, 51];

however, no studies have described the role of prepregnancy PFD in postnatal pelvic floor morbidity. The main goal of our study was to investigate the difference between de novo and persistent postnatal PFD, besides describing the prevalence and severity. The associated risk factors is another important topic to be described in the future; however, it was beyond the goal of the present article.

4.5.1 Urinary and prolapse Dysfunction

Although it has been previously demonstrated that UI first diagnosed in pregnancy plays an important role in development of persistent postnatal pathology, it is important to consider that a part of these symptoms could have existed prepregnancy. This is consistent with our findings, showing a high prevalence of persistent pathology.

The highest prevalence of PPFD was found In this section, which exceeded DNPFD (Table 4.2). The prevalence of UI varies in different studies from 17 to 45% due to the use of different grades of severity for definition of UI[6]. The prevalence of any UI in the 4P study was comparable with data from the National Health and Nutrition Examination Survey (NHANES) presenting only severe pathology— 9.7%[57]. Also we found a good correspondence with the Epidemiology of Incontinence in the County of Nord-Trøndelag (EPINCONT) study in correlation with various types of UI (SUI43 %, UUI 16%, MUI 4%)[132]. The prevalence of de novo SUI and UUI was nearly double compared to persistent; however, the percentage of severe pathology was nearly similar in both groups (Table 4.2). It is interesting to mention that the majority of prepregnancy UI (76%) persisted postnatally and total urinary section score was higher in the PPFD group, reflecting a more severe pathology (Table 4.3).

We found a high prevalence of symptoms of OAB (urinary urgency and UUI) , which is consistent with data from the Finnish National Nocturia and Overactive Bladder (FINNO) study, where urgency was present in 54.7% of respondents and UUI in 25.7%. Interestingly, in contrast to UI, the prevalence of both total and severe urinary urgency was higher in the PPFD group compared to DNPFD. The bother from symptoms was higher in the PPFD as well. For both UUI and urgency, vaginal delivery seemed to increase the RR at least by 50% with a trend to a higher risk in the persistent group with worsened symptom score postnatally (Table 4.4). However, the numbers were too small to allow a firm conclusion. The highest impact on UI and OAB was noted from forceps delivery.

The prevalence of postnatal POP in our study is comparable with data for primiparous women from the NHANES study - 2.5% - reporting severe pathology only[57]. However, the results here should be interpreted with caution, since the number of women who reported POP symptoms was small. Also there is a potential for confusion, since some bowel- or bladder-related symptoms may resemble prolapse. The highest increase in prolapse symptoms from vaginal delivery was found in the DNPFD group with virtually no protection from CS in the PPFD group (Table 4.4). A higher grade of bother was also noted in the DNPFD group (Table 4.2).

4.5.2 Faecal Dysfunction

FD, similar to the previous section, had a higher overall prevalence of PPFD compared to the DNPFD group. Our prevalence of Fe.I was similar to that reported by the NHANES study (8.8%) and comparable with the Childbirth and Pelvic Symptoms study (8.2–17%)[74]. The majority of cases of Fe.I had de novo onset. Also, we detected a high rate of

Fl.I, and the majority had PPFD with a high postnatal persistence rate. The rate of severe Fl.I is comparable with previous studies showing a prevalence of 10.9–19.2%[6, 49]. OD appeared to be a prevalent symptom in our study at 6.4 % (0.7 %) with approximately similar distribution between PPFD and DNPFD. We could not compare our findings of OD against other studies reporting similar data in primiparous women, since we could not find such publications.

Usually Fl.I is put on account of severe perineal trauma or pudendal nerve damage in labour and delivery, but this could be also a congenitally determined condition. A similar causative factor could be in the case of OD. Murad-Regadas et al. showed that in women with OD there is no statistical difference in rectocele, enterocele, intussusception and anismus among nulliparous women, post vaginal delivery and post CS[82]. Dietz and Clarke reported a 12% prevalence of rectocele with disruption of septal integrity in nulliparous women and hypothesised that the problem could be congenitally determined[54].

4.5.3 Sexual Dysfunction

The rate of SD, apart from vaginal laxity, was similarly distributed between DNPFD and PPFD. However, a higher prevalence of severe dyspareunia and vaginal tightness was noticed in the PPFD group. Entirely, the risk of SD was minimally affected by the MOD, vaginal laxity only achieving statistical significance and being substantially affected by vaginal route of delivery (Table 4.4). Interestingly, prepregnancy vaginal laxity did not worsen postnatally, de novo only pathology being affected by MOD.

4.5.4 PFD as integrity

The present study demonstrated a high rate of various PFD symptoms at 1 year postnatally. Our prevalence seems to be higher compared to previous studies, probably because we included more types of PFD containing more symptoms such as frequency, urgency and OD. Also previous studies investigated all women, including those post surgical and medical treatment.

However, when we compared our PFD rates using the same definition criteria with previous studies, without including OAB symptoms and SD and excluding mild pathology, as in the NHANES study, we got comparable estimates of PFD at 13.2 vs 18.4 %, considering that our primiparous population is relatively young.

Multicompartment PFD was preponderant in primiparous women with the majority having persistent PFD. There was a high persistence rate of prepregnancy symptoms, on average 60 %; however, only in a minority of cases did severity of prepregnancy pathology worsen postnatally (Table 4.3). The vaginal route of delivery increased the risk of different types of PFD, to a higher degree in those in whom the prepregnancy symptoms worsened postnatally (Table 4.4). The latter group seemed to have more bother from prepregnancy symptoms and more coexisting types of PFD (Table 4.5), which could be potentially used as a prediction tool. However, future research with a larger number of participants is needed, in order to better understand the natural history of PFD and to develop prediction criteria for those with persistent PFD symptoms worsening postnatally.

4.5.5 Strengths and limitations

Among the strengths of this study is the large number of well phenotyped nulliparous participants, followed up to 1 year postnatally. The use of a validated questionnaire, correlating with clinical findings and comprehensively covering all areas of PFD, including questions on the presence of associated bothersome symptoms, is another strength. Previously it has been demonstrated that participants of the 4P study prepregnancy were representative of the entire population[139]. In the present follow-up study, characteristics of our participants do not differ from initial subjects. High homogeneity of the study population is another strength of the present project, which allows overcoming naturally occurring confounders for PFD like advanced age and interracial differences. The majority was relatively young (85 % <34 years of age) and Caucasian (98 %). Several studies mentioned interracial differences in pelvic floor anatomy and prevalence of PFD, with white women being considered more prone to develop prolapse and UI[8, 137].

The fact that patients were not clinically examined to verify questionnaire findings is the main limitation of this study. Regarding the prepregnancy questionnaires, which were completed in early pregnancy, there is a potential for confusion and recall bias since questions pertained to prepregnancy status. However, PFD and especially incontinence is a very important event for woman and it is unlikely to be prone to recall bias[138]. This is a common limitation for this type of study and other research groups collected prepregnancy data in the same way[76]. A part of our participants have undergone clinical examination at 1 year postnatally. Those, in whom symptoms improved postnatally, confirmed that this is not a bias. This could probably be partially explained by lifestyle alteration due to childbearing, such as reduced smoking and

alcohol consumption, more physical activity while looking after a newborn baby and doing pelvic floor exercises, which could also potentially play a role as naturally occurring confounders. Another important limitation is the loss to follow-up in 28%and occurrence of second pregnancy in another 12 % of participants. Finally, for some analyses the sample size was small, which prevented robust conclusions. However, for the main analyses, the study provided adequate statistical power.

4.6 Conclusion

Prepregnancy PFD plays an important role in postnatal pelvic floor morbidity, where the majority of patients have persistent pathology. However, in a minority only the prepregnancy symptoms worsen postnatally. The main damage to the pelvic floor is probably made before first pregnancy due to congenital intrinsic weakness of pelvic floor structures. Childbearing seems to affect more substantial pre-existing symptoms of urgency and urge incontinence comparing to stress incontinence. PPFD has a higher prevalence of severe symptoms compared to DNPFD and higher grade of associated bothersome symptoms. The majority of affected patients have more than one compartment affected, and a comprehensive approach is needed when PFD is evaluated. CS seems to be protective against the development of some symptoms of PFD, and even more protective in the case of PPFD. However, from this study there is no strong evidence that CS significantly reduces the risk of severe postnatal PFD in those affected prepregnancy. Though, women with high grade of bother, especially with symptoms of OAB or UUI and multiple PFD types present prepregnancy, need to be counselled on an individual basis regarding the potential benefit of CS, in particular considering the actual obstetric approaches offering CS on demand. However, larger studies are needed

to confirm this trend and to determine characteristics of women being at higher risk of worsened postnatal PFD.

Figure 4.1: Prevalence of primary symptoms for various types of PFD and their combinations

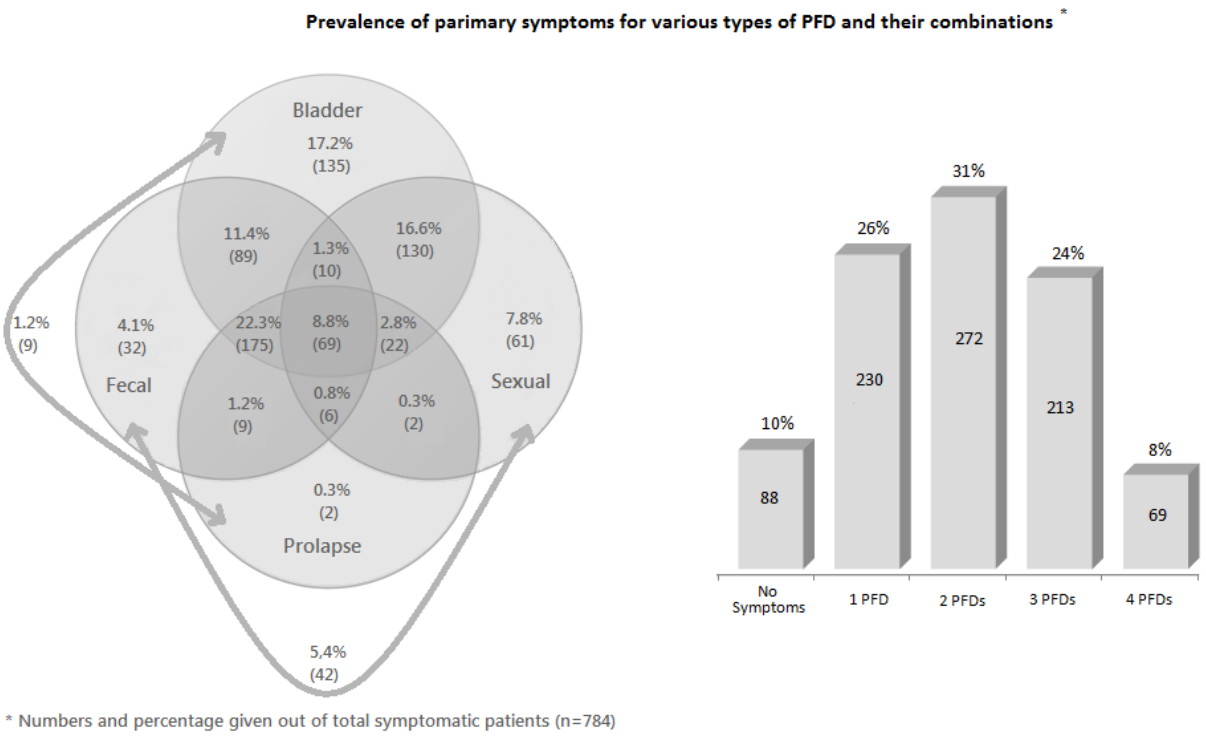

Table 4.1 Demographic characteristics of the population in the 4P-Study and SCOPE Ireland study

	4P-Study (n=872)	SCOPE Ireland (n=1774)
Caucasians	858(98.4%)*	1450(97.7%)
Age in years		
17-24	73(8.4%)	207(11.7%)
25-29	251(28.8%)	545(30.6%)
30-34	415(47.6%)	787(44.4%)
35-45	133(15.3%)	235(13.3%)
BMI		
Underweight	12(1.4%)	22(1.2%)
Normal	489(56.1%)	1036(58.4%)
Overweight	259(29.7%)	495(27.9%)
Obese	112(12.8%)	221(12.5%)
Education		
≤12 years	101(12%)	230(13%)
>12 years	771(88%)	1544 (87%)
Smoking		
Non smokers	661(75.8%)	1285(72.4%)
Smokers	211(24.2%)	489(27.6%)
Alcohol consumption		
No	176(20.2%)	339(19.1%)
Yes	696(79.8%)	1435(80.9%)
Mean values [a]		
Age in years	30.5 0(4.2)	29.9(4.5)
BMI	25.0(4.1)	24.9(4.2)
Weight in kg.	67.8(11.8)	67.5(12.2)

* All values presented as number of cases and (%) of total

[a] Data presented as mean value and Standard Deviation (SD)

Table 4.2 Prevalence of PFD at 12 months postnatally* (n = 872)

	Total PFD prevalence				Denovo PFD				Persistent PFD			
	Tot PFD		Severe PFD		Tot PFD		Severe PFD		Tot PFD		Severe PFD	
	%*	(№)	%*	(№)	%*	(№)	%*	(№)	%*	(№)	%*	(№)
Urinary Dysfunction												
Urinary Frequency[a]	21,1%	(184)	2.4%	(21)	9.4%	(81)	0.8%	(7)	11.9%	(103)	1.6%	(14)
Nocturia[a]	8,8%	(77)	1.6%	(14)	3.8%	(33)	0.6%	(5)	5.1%	(44)	1.0%	(9)
Nocturnal enuresis	0,8%	(7)	0.2%	(2)	0.6%	(5)	-	-	0.2%	(2)	0.2%	(2)
Urgency	49,6%	(432)	9.4%	(82)	20.1%	(175)	1.6%	(15)	29.6%	(257)	7.6%	(67)
Urge Incontinence[a]	29,8%	(261)	5.3%	(47)	21.0%	(183)	3.1%	(27)	8.7%	(77)	2.2%	(19)
Stress Incontinence[a]	45,1%	(393)	7.5%	(66)	29.7%	(258)	3.7%	(32)	15.4%	(135)	3.8%	(33)
Weak Stream	23,8%	(207)	2.8%	(24)	13.8%	(119)	1.9%	(16)	10.2%	(88)	0.9%	(8)
Incomplete Bladder Emptying	27,6%	(240)	3.8%	(33)	15.5%	(135)	1.5%	(13)	12.0%	(105)	2.3%	(20)
Strain to Empty	14,8%	(129)	1.7%	(15)	10.3%	(89)	1.0%	(9)	4.6%	(40)	0.7%	(6)
Pad Usage	14,3%	(125)	6.0%	(52)	10.7%	(94)	4.9%	(42)	3.6%	(31)	1.2%	(10)
Reduced Fluid Intake	6,3%	(55)	2.2%	(19)	3.7%	(32)	1.7%	(15)	2.6%	(23)	0.5%	(4)
Recurrent UTI	9,4%	(82)	0.8%	(7)	5.0%	(43)	0.2%	(2)	4.5%	(39)	0.6%	(5)
Dysuria	7,8%	(68)	0.9%	(8)	5.7%	(50)	0.8%	(7)	2.0%	(18)	0.1%	(1)
Impact on Social Life	8,7%	(76)	1.0%	(9)	6.9%	(60)	0.7%	(6)	1.7%	(16)	0.3%	(3)
Bladder - How much of a bother	20,9%	(182)	3.8%	(33)	14.4%	(125)	1.6%	(14)	6.4%	(57)	2.2%	(19)
Bladder section overall [b]	73.3%	(640)	16.6%	(146)	32.8%	(210)	10.6%	(92)	49.2%	(429)	6.1%	(53)

Faecal Dysfunction

Defaecation Frequency	13,7%	(119)	2.2%	(19)	5.1%	(45)	0.3%	(3)	8.5%	(74)	1.9%	(16)
Consistency of Bowel Motion	50,3%	(438)	0.7%	(6)	17.6%	(153)	0.0%	(0)	32.8%	(285)	0.7%	(6)
Defaecation Straining	60,8%	(523)	7.1%	(61)	17.7%	(153)	0.8%	(7)	42.9%	(370)	6.3%	(54)
Laxative Use	6,8%	(59)	0.6%	(5)	4.1%	(35)	0.5%	(4)	2.8%	(24)	0.1%	(1)
Do You Feel Constipated	46,7%	(407)	5.0%	(43)	11.9%	(104)	0.7%	(6)	35.0%	(303)	4.3%	(37)
Flatus incontinence[a]	44,8%	(385)	9.3%	(80)	20.1%	(173)	3.7%	(32)	24.7%	(212)	5.6%	(48)
Faecal Urgency	53,7%	(467)	8.4%	(72)	19.4%	(168)	0.9%	(8)	34.5%	(299)	7.4%	(64)
Faecal Incontinence with diarrhoea[a]	7,2%	(63)	0.5%	(4)	5.7%	(49)	0.2%	(2)	1.5%	(14)	0.2%	(2)
Faecal Incontinence with normal stool	1,9%	(16)	-	-	1.9%	(16)	-	-	-	-	-	-
Incomplete Bowel Evacuation	41,5%	(356)	4.7%	(40)	16.0%	(137)	1.2%	(10)	25.5%	(219)	3.5%	(30)
Obstructed Defaecation	6,4%	(55)	0.7%	(6)	3.7%	(32)	0.3%	(3)	2.7%	(23)	0.3%	(3)
Bowel - How much of a bother	24,1%	(209)	4.8%	(41)	10.4%	(90)	1.5%	(13)	13.6%	(119)	3.3%	(28)
Bowel section overall [b]	48.7%	(425)	10.0%	(87)	21.1%	(184)	8.4%	(73)	27.6%	(241)	1.6%	(14)

Prolapse Dysfunction

Prolapse sensation[a]	6,6%	(57)	1.6%	(14)	6.1%	(53)	1.4%	(12)	0.2%	(4)	0.2%	(2)
Vaginal Pressure or heaviness[a]	10,9%	(94)	2.0%	(17)	9.6%	(83)	1.6%	(14)	1.1%	(11)	0.4%	(3)
Prolapse reduction to void[a]	1,5%	(12)	0.2%	(2)	1.1%	(9)	0.2%	(2)	0.2%	(3)	0.0%	(0)
Prolapse reduction to defaecate[a]	2%	(17)	0.5%	(4)	1.5%	(14)	0.4%	(3)	0.2%	(3)	0.1%	(1)
Prolapse - How much of a bother	4,1%	(35)	1.4%	(12)	3.4%	(29)	1.2%	(10)	0.4%	(6)	0.2%	(2)
Prolapse section overall [b]	13.9%	(121)	2.8%	(24)	12.0%	(105)	2.5%	(22)	1.8%	(16)	.2%	(2)

Sexual Dysfunction												
Sufficient lubrication (No)	23,9%	(196)	-	-	16.0%	(133)	-	-	7.6%	(63)	-	-
During intercourse vaginal sensation is (Abnormal)	21,2%	(176)	7.7%	(64)	15.7%	(130)	5.5%	(46)	5.5%	(46)	2.2%	(18)
Vaginal Laxity[a]	21%	(180)	2.7%	(23)	18.3%	(155)	2.5%	(21)	2.7%	(25)	0.2%	(2)
Vaginal tightness/Vaginismus[a]	29,1%	(244)	5.6%	(49)	15.5%	(130)	2.4%	(20)	13.6%	(114)	3.2%	(29)
Dyspareunia[a]	43,6%	(367)	5.9%	(50)	22.1%	(186)	2.1%	(18)	21.5%	(181)	3.7%	(31)
Dyspareunia Superficial	18,9%	(159)	2.9%	(24)	10.0%	(84)	1.1%	(9)	8.9%	(75)	1.7%	(14)
Dyspareunia Deep	16,0%	(135)	1.1%	(9)	7.8%	(66)	0.4%	(3)	8.2%	(69)	0.7%	(6)
Dyspareunia Mixed	6,9%	(58)	1.9%	(16)	2.9%	(24)	0.7%	(6)	4.0%	(34)	1.2%	(10)
Dyspareunia Unknown	1.8%	(15)	0.1%	(1)	1.4%	(12)	-	-	0.4%	(3)	0.1%	(1)
Coital Incontinence	5%	(43)	0.5%	(4)	4.4%	(37)	0.4%	(3)	0.6%	(6)	3.3%	(1)
Sexual Function - How much of a bother	23,7%	(203)	5.9%	(50)	18.6%	(158)	4.3%	(36)	5.1%	(45)	1.7%	(14)
Sexual section overall [b]	57.8%	(504)	10.4%	(91)	27.1%	(236)	8.5%	(74)	30.7%	(268)	1.9%	(17)
Combined data for various incontinences												
Urge Urinary Incontinence	8.3%	(72)	2.1%	(18)	4.2%	(36)	1.4%	(12)	4.2%	(36)	0.7%	(6)
Stress Urinary Incontinence	23.6%	(204)	4.3%	(37)	12.8%	(111)	2.0%	(17)	10.8%	(93)	2.4%	(20)
Mixed Urinary Incontinence	21.9%	(189)	3.2%	(28)	17.0%	(147)	1.7%	(15)	4.9%	(42)	1.5%	(13)
Any Urinary Incontinence	53.9%	(465)	9.6%	(83)	34.1%	(294)	5.1 %	(44)	19.8%	(171)	4.5%	(39)
Faecal Incontinence	9.1%	(79)	0.5%	(4)	7.5%	(65)	0.2%	(2)	1.6%	(14)	0.2%	(2)

[*] Percentage is given out of total participants
[a] Primary symptoms are marked
[b] Section scores include primary symptoms only

Table 4.3 Median section scores corresponding to various primary symptoms at 12 months postnatally and the rate postnatal persistence of prepregnancy symptoms

	Denovo PFD		Persistent PFD		Persistence rate		Persistent [1] worsened	
	M	[IQR]*	M	[IQR]	%	N	%	N
Urinary Symptoms								
Frequency	5	[0-11]	4	[0-10]	44.6%	103	8.7%	9
Nocturia	6	[0-12]	6.5	[0.5-12.5]	32.1%	44	9.1%	4
Urgency	4	[0-8]	5	[0-10]	74.2%	256	17.6%	45
Urge Incontinence	5	[1-9]	8	[3-13]	70.1%	75	32%	24
Stress Incontinence	4	[0-9]	6	[0-12]	82.6%	133	11.3%	15
Faecal Symptoms								
Flatus Incontinence	5	[0-10]	6	[2-10]	64.8%	212	17.5%	37
Faecal Incontinence with diarrhoea	8	[3-13]	9	[6-12]	36.1%	13	15.4%	2
Faecal Incontinence with solid stool	7	[2-12]	-	-	-	-	-	-
Obstructed Defaecation	7	[3-11]	8	[4-12]	48.9%	23	13%	3
Prolapse Symptoms								
Prolapse Sensation	2	[0-6]	6	-	22.2%	2	50%	1
Vaginal Pressure or heaviness	2	[0-4]	1	[0-4]	34.6%	9	33.3%	3
Prolapse reduction to void	3	[0-7]	4	-	100.0%	3	-	-
Prolapse reduction to defecate	3	[0-6]	6.5	-	20.0%	2	-	-
Sexual Symptoms								
Vaginal Laxity	3	[1-5]	3	[0-6]	56.1%	23	4.4%	1
Vaginal Tightness/Vaginismus	3	[0-6]	3	[0-6]	52.3%	114	16.7%	19
Dyspareunia	3	[1-5]	3	[0-6]	68.0%	181	14.9%	27

* Median Section Score and Interquartile Range M[IQR]

[1] Postnatal score worse than prenatal in the PPFD group

Table 4.4 The Relative Risk (RR) of getting de novo primary PFD symptoms postnatally or worsening of prepregnancy symptoms postnatally in relation to mode of delivery

Primary Symptom		Total Denovo or worsened postnatally PFD *							Denovo PFD							Persistent PFD worsened postnatally						
		RR	CI	p=	RR	CI	p=	№	RR	CI	p=	RR	CI	p=	№	RR	CI	p=	RR	CI	p=	№
		Unadjusted			Adjusted				Unadjusted			Adjusted				Unadjusted			Adjusted			
Urinary dysfunction symptoms																						
Urinary Section	**SVD**	1.2	(1.1-1.38)	0.000	1.3	(1.15-1.45)	0.000	172	1.4	(1.13-1.83)	0.003	1.6	(1.29-2.08)	0.000	58	1.1	(0.99-1.23)	0.084	1.1	(1-1.26)	0.046	114
	Vacuum	1.1	(1-1.3)	0.042	1.2	(1.05-1.37)	0.008	145	1.2	(0.87-1.53)	0.328	1.3	(0.95-1.7)	0.102	46	1.1	(1-1.27)	0.044	1.2	(1.02-1.3)	0.024	99
	Forceps	1.4	(1.2-1.54)	0.000	1.4	(1.21-1.55)	0.000	90	1.7	(1.31-2.21)	0.000	1.8	(1.36-2.31)	0.000	32	1.2	(1.04-1.33)	0.009	1.2	(1.03-1.3)	0.014	58
Urinary Frequency	**SVD**	1.1	(0.64-1.95)	0.686	1.1	(0.64-2.02)	0.665	31	1.1	(0.59-1.9)	0.854	1.1	(0.57-1.95)	0.873	25	3.4	(0.41-28.41)	0.255	3.2	(0.31-32.24)	0.333	6
	Vacuum	1.2	(0.67-2.24)	0.517	1.3	(0.7-2.47)	0.389	21	1.2	(0.66-2.29)	0.51	1.3	(0.68-2.46)	0.437	20	1.2	(0.07-18.99)	0.903	0.4	(0.02-13.09)	0.642	1
	Forceps	1.9	(1.01-3.62)	0.047	1.9	(0.98-3.64)	0.057	17	1.9	(1-3.73)	0.05	1.9	(0.96-3.68)	0.067	16	2.2	(0.14-35.05)	0.579	0.3	(0.01-14.53)	0.58	1
Nocturia	**SVD**	1.1	(0.47-2.57)	0.831	1.3	(0.51-3.08)	0.617	13	1.1	(0.45-2.77)	0.818	1.3	(0.5-3.47)	0.572	11	1.1	(0.1-11.79)	0.957	0.3	(0.01-13)	0.543	2
	Vacuum	0.9	(0.35-2.55)	0.919	1	(0.36-2.86)	0.978	7	1	(0.33-2.76)	0.936	1.1	(0.36-3.38)	0.854	6	0.9	(0.06-15.02)	0.965	0.7	(0.02-28.75)	0.857	1
	Forceps	2.1	(0.8-5.38)	0.133	2	(0.75-5.46)	0.164	8	2.4	(0.89-6.35)	0.083	2.4	(0.87-6.81)	0.09	8	-	-	-	-	-	-	0
Urinary Urgency	**SVD**	1.4	(0.98-2)	0.063	1.6	(1.1-2.3)	0.014	87	1.4	(0.95-2.09)	0.085	1.5	(1.02-2.34)	0.039	69	1.6	(0.68-3.61)	0.29	1.9	(0.77-4.61)	0.164	18
	Vacuum	1.2	(0.83-1.85)	0.302	1.3	(0.86-1.99)	0.209	48	1.2	(0.76-1.86)	0.458	1.2	(0.77-1.99)	0.378	37	1.6	(0.64-3.93)	0.324	1.7	(0.65-4.44)	0.278	11
	Forceps	1.8	(1.19-2.82)	0.006	1.9	(1.21-2.92)	0.005	37	1.8	(1.09-2.86)	0.02	1.8	(1.1-2.99)	0.02	29	2.2	(0.84-5.98)	0.106	2.2	(0.79-6.02)	0.134	8
Urge Urinary Incontin.	**SVD**	1.7	(1.14-2.44)	0.08	1.8	(1.2-2.64)	0.004	84	1.7	(0.17-2.6)	0.007	1.9	(1.26-2.89)	0.002	80	1.2	(0.26-5.28)	0.828	1.4	(0.19-9.7)	0.761	4
	Vacuum	1.5	(0.96-2.24)	0.079	1.5	(0.97-2.35)	0.071	46	1.5	(0.92-2.29)	0.107	1.6	(0.96-2.51)	0.071	41	2.1	(0.49-8.65)	0.32	2.8	(0.42-18.07)	0.291	5
	Forceps	1.8	(1.15-2.96)	0.011	1.9	(1.16-3.04)	0.011	30	1.9	(1.14-3.16)	0.012	1.9	(1.16-3.27)	0.012	27	1.9	(0.39-9.6)	0.418	2.2	(0.29-16.55)	0.445	3
Stress Urinary Incontin.	**SVD**	1.7	(1.26-2.42)	0.001	1.9	(1.36-2.68)	0.000	120	1.7	(1.22-2.4)	0.002	1.9	(1.32-2.66)	0.000	107	2.8	(0.8-9.91)	0.105	3.7	(0.9-15.23)	0.07	13
	Vacuum	1.5	(1.05-2.18)	0.026	1.6	(1.09-2.34)	0.015	65	1.4	(0.98-2.1)	0.062	1.6	(1.07-2.37)	0.023	59	2.6	(0.65-10.42)	0.176	3.2	(0.65-15.31)	0.154	6
	Forceps	2	(1.33-2.97)	0.001	2	(1.3-2.95)	0.001	44	2	(1.34-3.07)	0.001	2	(1.3-3.04)	0.001	42	1.5	(0.25-9.03)	0.652	1.7	(0.26-11.78)	0.569	2

Faecal dysfunction symptoms

Faecal	**SVD**	1.1	(0.95-1.34)	0.172	1.2	(0.99-1.41)	0.062	145	1.3	(0.93-1.7)	0.138	1.2	(0.89-1.65)	0.231	29	1.1	(0.91-1.32)	0.337	1.2	(0.95-1.41)	0.150	116
Section	**Vacuum**	1	(0.82-1.22)	0.993	1	(0.85-1.27)	0.718	93	1	(0.68-1.4)	0.878	1	(0.67-1.39)	0.847	38	1.1	(0.9-1.36)	0.347	1.1	(0.91-1.39)	0.290	55
	Forceps	1	(0.83-1.33)	0.696	1	(0.83-1.33)	0.690	51	1.2	(0.81-1.74)	0.380	1.2	(0.81-1.73)	0.383	28	1.2	(0.89-1.5)	0.28	1.1	(0.87-1.44)	0.374	23
Flatus	**SVD**	1.4	(1-2.03)	0.048	1.4	(0.97-2.01)	0.075	89	1.3	(0.88-1.91)	0.185	1.3	(0.87-1.93)	0.205	73	1.9	(0.77-4.57)	0.164	1.6	(0.62-4.12)	0.327	16
Incontin	**Vacuum**	1	(0.68-1.58)	0.866	1.1	(0.69-1.63)	0.797	40	0.9	(0.57-1.43)	0.666	0.9	(0.59-1.52)	0.816	33	1.4	(0.5-4.1)	0.498	1.4	(0.45-4.12)	0.576	7
	Forceps	1.7	(1.07-2.6)	0.023	1.7	(1.06-2.61)	0.026	34	1.3	(0.77-2.05)	0.355	1.3	(0.76-2.06)	0.381	27	3.4	(1.19-9.69)	0.022	3.3	(1.11-10.13)	0.032	7
Faecal	**SVD**	0.8	(0.36-1.59)	0.46	0.9	(0.4-1.86)	0.713	14	0.8	(0.37-1.68)	0.536	0.9	(0.41-1.95)	0.785	14	-	-	-	-	-	-	0
Inc. with	**Vacuum**	1.3	(0.64-2.74)	0.451	1.5	(0.71-3.24)	0.28	15	1.4	(0.68-3.02)	0.34	1.6	(0.76-3.56)	0.206	15	-	-	-	-	-	-	0
Diarrhoea	**Forceps**	1.3	(0.56-3.17)	0.52	1.7	(0.69-4.12)	0.25	8	1.2	(0.49-3.09)	0.655	1.6	(0.62-4.05)	0.343	7	-	-	-	-	-	-	1
Obstruc-ted	**SVD**	1.4	(0.6-3.32)	0.433	1.3	(0.55-3.24)	0.531	15	1.5	(0.6-3.67)	0.396	1.4	(0.56-3.71)	0.443	14	-	-	-	-	-	-	1
Defaecation	**Vacuum**	1.5	(0.6-3.82)	0.386	1.4	(0.52-3.56)	0.535	10	1.5	(0.57-4.1)	0.402	1.4	(0.49-3.81)	0.549	9	-	-	-	-	-	-	1
	Forceps	0.6	(0.12-2.73)	0.491	0.5	(0.11-2.47)	0.409	2	0.6	(0.13-3.1)	0.583	0.6	(0.12-2.81)	0.498	2	-	-	-	-	-	-	0

Prolapse symptoms

Prolapse	**SVD**	3	(1.7-5.23)	0.000	3.4	(1.97-6.01)	0.000	50	4.2	(2.09-8.33)	0.000	4.7	(2.31-9.49)	0.000	48	0.7	(0.29-1.74)	0.45	0.9	(0.08-10.8)	0.959	2
Section	**Vacuum**	2.3	(1.21-4.2)	0.011	2.7	(1.47-4.97)	0.001	26	3.1	(1.45-6.47)	0.003	3.5	(1.66-7.37)	0.001	23	1	(0.36-2.79)	1	0.8	(0.2-2.96)	0.698	3
	Forceps	4.3	(2.35-7.93)	0.000	4.1	(2.17-7.79)	0.000	26	6.4	(3.1-13.34)	0.000	6.3	(2.96-13.61)	0.000	24	0.5	(0.13-1.96)	0.321	0.4	(0.07-2.2)	0.285	2
Prolapse	**SVD**	3.8	(1.45-9.87)	0.007	4.4	(1.62-11.8)	0.004	25	3.8	(1.46-9.95)	0.006	4.4	(1.63-11.87)	0.003	25	-	-	-	-	-	-	0
Sensation	**Vacuum**	2.7	(0.92-7.65)	0.07	2.8	(0.95-8.46)	0.062	11	2.7	(0.92-7.66)	0.07	2.8	(0.93-8.3)	0.068	11	-	-	-	-	-	-	0
	Forceps	5.6	(1.97-15.9)	0.001	4.9	(1.68-14.05)	0.004	12	5.3	(1.83-15.16)	0.002	4.5	(1.54-13.28)	0.006	11	-	-	-	-	-	-	1

Sexual dysfunction symptoms

Sexual	**SVD**	1.2	(1.06-1.42)	0.008	1.2	(1.03-1.4)	0.018	156	1.4	(1.1-1.81)	0.007	1.4	(1.05-1.74)	0.019	87	1.1	(0.92-1.27)	0.347	1.1	(0.93-1.31)	0.266	69
Dysfunc.	**Vacuum**	1.1	(0.92-1.3)	0.292	1.1	(0.91-1.29)	0.382	113	1.1	(0.82-1.49)	0.496	1.1	(0.8-1.47)	0.605	51	1.1	(0.94-1.33)	0.228	1.1	(0.93-1.35)	0.223	62
Section	**Forceps**	1.2	(0.98-1.45)	0.082	1.2	(0.95-1.42)	0.135	64	1.4	(1.02-1.93)	0.036	1.4	(1.02-1.93)	0.038	32	1	(0.81-1.28)	0.853	1	(0.8-1.27)	0.943	32
Vaginal	**SVD**	4.3	(2.41-7.82)	0.000	4.5	(2.45-8.12)	0.000	75	4.3	(2.36-7.66)	0.000	4.4	(2.4-7.95)	0.000	74	-	-	-	-	-	-	1
Laxity	**Vacuum**	3.7	(1.99-6.94)	0.000	3.7	(1.98-7.1)	0.000	40	3.7	(1.99-6.95)	0.000	3.8	(1.99-7.16)	0.000	40	-	-	-	-	-	-	0
	Forceps	4.8	(2.46-9.23)	0.000	4.7	(2.41-9.2)	0.000	27	4.6	(2.37-8.9)	0.000	4.5	(2.3-8.81)	0.000	27	-	-	-	-	-	-	0
Vaginal	**SVD**	1	(0.67-1.54)	0.928	0.9	(0.58-1.37)	0.605	53	1	(0.68-1.63)	0.834	1	(0.63-1.55)	0.947	48	0.8	(0.22-2.67)	0.683	0.4	(0.09-1.79)	0.232	5
Tightness /	**Vacuum**	1.3	(0.87-2.07)	0.181	1.2	(0.75-1.86)	0.47	43	1.3	(0.83-2.1)	0.247	1.2	(0.75-2)	0.408	37	1.5	(0.46-4.89)	0.507	0.9	(0.23-3.22)	0.826	6
Vaginism.	**Forceps**	0.8	(0.45-1.53)	0.554	0.8	(0.46-1.57)	0.597	14	0.8	(0.39-1.53)	0.468	0.8	(0.4-1.59)	0.515	11	1.3	(0.3-5.28)	0.75	1.5	(0.33-7)	0.597	3
Dyspare-	**SVD**	1	(0.72-1.44)	0.92	0.9	(0.63-1.28)	0.563	76	1.1	(0.76-1.58)	0.634	1	(0.67-1.43)	0.911	69	0.7	(0.24-1.98)	0.498	0.5	(0.16-1.71)	0.288	7
unia	**Vacuum**	1	(0.71-1.53)	0.845	0.9	(0.63-1.4)	0.761	48	1	(0.69-1.56)	0.87	1	(0.62-1.46)	0.832	42	1	(0.35-3.12)	0.931	0.9	(0.24-3.12)	0.814	6
	Forceps	1.4	(0.88-2.08)	0.169	1.3	(0.84-2.03)	0.228	33	1.3	(0.8-2.08)	0.293	1.3	(0.81-2.16)	0.259	26	2	(0.71-5.78)	0.186	1.9	(0.61-5.63)	0.272	7

***Total PFD includes all DNPFD and PPFD only worsened postnatally**

Table 4.5 Prepregnancy PFD characteristics in PPFD group with worsened and unchanged symptoms postantally.

		PPFD prevalence		Bother presence in affected		1 Compartment Affected		> 1 Compartment Affected	
		№	% of all	№	%	N	%	N	%
Stress Incontinence	Worsened PPFD	24	2.8	9	37.5	4	16.0	20	84
	Unchanged PPFD	137	15.7	35	25.5	32	23.4	105	76.6
Urge Incontinence	Worsened PPFD	15	1.7	9	60	3	20.0	12	80
	Unchanged PPFD	92	10.6	28	30.4	16	17.4	76	82.6
Urinary Frequency	Worsened PPFD	9	1	2	22.2	4	44.4	5	55.6
	Unchanged PPFD	222	25.5	47	21.3	74	33.3	148	66.7
Urgency	Worsened PPFD	45	5.2	15	33.3	9	20.0	36	80
	Unchanged PPFD	300	34.4	58	19.3	80	26.7	220	73.3
Nocturia	Worsened PPFD	4	0.5	1	25	1	25.0	3	75
	Unchanged PPFD	133	15.3	33	24.8	39	29.3	94	70.7
Flatus incontinence	Worsened PPFD	37	4.2	17	45.9	3	8.1	34	91.9
	Unchanged PPFD	290	33.3	94	32.5	50	17.2	240	82.8
Fecal Incontinence with diarrhoea	Worsened PPFD	2	0.2	1	50	1	50.0	1	50
	Unchanged PPFD	34	3.9	15	43.7	3	8.8	31	91.2
Vaginal tightness/ vaginismus	Worsened PPFD	19	2.2	6	31.6	6	31.6	13	68.4
	Unchanged PPFD	203	23.3	55	27.1	44	21.7	159	78.3
Dyspareunia	Worsened PPFD	27	3.1	9	33.3	5	18.5	22	81.5
	Unchanged PPFD	244	28	71	29.1	46	18.9	198	81.1

Chapter 5

Study 3

Prevalence, aetiology and risk factors of pelvic organ prolapse in premenopausal primiparous women

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5.1 Abstract

Introduction The natural history of pelvic organ prolapse (POP) is poorly understood. We investigated the prevalence and risk factors of postnatal POP in premenopausal primiparous women and the associated effect of mode of delivery.

Methods We conducted a prospective cohort study in a tertiary teaching hospital attending 9,000 deliveries annually. Collagen-diseases history and clinical assessment was performed in 202 primiparae at ≥1 year postnatally. Assessment included Pelvic Organ Prolapse Quantification (POP-Q), Beighton mobility score, 2/3D-transperineal ultrasound (US) and quantification of collagen type III levels. Association with POP was assessed using various statistical tests, including logistic regression, where results with $p<0.1$ in univariate analysis were included in multivariate analysis.

Results POP had a high prevalence: uterine prolapse 89%, cystocele 90%, rectocele 70% and up to 65% having grade two on POP-Q staging. The majority had multi-compartment involvement, and 80% were asymptomatic. POP was significantly associated with joint hypermobility, vertebral hernia, varicose veins, asthma and high collagen type III levels ($p<0.05$). In multivariate analysis, only levator ani muscle (LAM) avulsion was significant in selected cases ($p<0.05$). Caesarean section (CS) was significantly protective against cystocele and rectocele but not for uterine prolapse.

Conclusions Mild to moderate POP has a very high prevalence in premenopausal primiparous women. There is a significant association between POP, collagen levels, history of collagen disease and childbirth-related pelvic floor trauma. These findings support a congenital contribution to POP aetiology, especially for uterine prolapse; however, pelvic trauma seems to play paramount role. CS is significantly protective against some types of prolapse only.

5.2 Introduction

The association between childbearing and pelvic organ prolapse (POP) giving rise to symptoms of pelvic floor dysfunction (PFD) is commonly recognised[8, 57, 140]. However, POP is present not only in women giving birth but also in premenopausal, nulliparous women, in whom the prevalence of prolapse is similar to women post-Caesarean section (CS), with the latter delivery mode considered to be partially protective compared with vaginal delivery[118, 141]. Initially it was shown that POP is associated with reduction in total collagen content, with higher levels of weaker immature collagen and no change in collagen type I/III ratios[18]. However, a later study demonstrated that levels of collagen type I(providing strength and being mainly present in bone structures and, to a lesser extent, in soft tissue) is minimally changed in women with POP; collagen type III (providing elasticity) is increased, leading to decreased collagen I/III ratio[110]. POP is also associated with joint hypermobility and various medical conditions linked with abnormal collagen[17, 116]. All these factors are indicative of the systemic manifestation of collagen abnormalities and suggest a role for congenital predisposition in POP aetiology [86, 118-119]. Additionally, prolapse is associated with levator ani muscle (LAM) trauma[142].

We hypothesised that postnatal POP in premenopausal primiparous women is not a condition caused by pregnancy alone but could be a clinical manifestation of a pre-existing, undiagnosed condition or a congenital predisposition triggered by pregnancy and delivery. The 4P-study reported here (Prevalence and Predictors of Pelvic Floor Dysfunction in Primips) aimed to elucidate the natural history of POP by investigating the role of a congenital component in postnatal POP in premenopausal primiparous women while at the same time considering such major confounding factor as LAM trauma .

5.3 Materials and Methods

The 4P is a prospective cohort study nested within the parent Screening for Pregnancy Endpoints (SCOPE Ireland study; www.scopestudy.net), previously described in detail[139]. The study was approved by the Clinical Research Ethics Committee of the Cork Teaching Hospitals (CREC) Ireland and performed in a tertiary maternity hospital attending approximately 9,000 deliveries a year. All participants, 872 nulliparous women, completed the Australian Pelvic Floor Questionnaire[28] in early pregnancy and 1 year postnatally. The recruitment phase occurred between February 2008 and March 2011. All participants were invited for clinical follow-up between March and December 2012. We had a response rate of 60.8% (530), and the proposal for follow-up was accepted by 46.8% (408). Participants who had more than one delivery or were repeatedly pregnant at the time of follow-up [23.6% (206)] were excluded from the study (Appendix II). Clinical follow-up of 202 (23.2% of all invited) participants who met the inclusion criteria consisted of POP-Q assessment measured on rest and on maximal Valsalva, joint hypermobility assessment using the Beighton score, transperineal 2D/4D ultrasound (US) scan for prolapse quantification, blood serum collection for procollagen quantification and a collection of personal and/or family history of collagen-related or other diseases previously shown to be associated with PFD and POP (Appendix VI). The Beighton joint mobility score is a system proposed to quantify joint hypermobility and is mainly used in rheumatological and orthopaedic practice. A generalised joint laxity is considered to be present with a score of four or more[143].

According to Dietz and Lekskulchai, POP can be quantified on 2D transperineal US scan (Tp-USS)[42]. Two images are acquired—one at rest and one at maximal Valsalva maintained for not less than 6 s in order to achieve the greatest pelvic organ descent[117].

The inferior margin of the pubic bone is considered as a reference line. The distance from the most distant bladder point or anorectal junction is measured to the reference line. Prolapse is then classified into significant and nonsignificant categories. For significant cystocele, we proposed a cut-off level of 10 mm below the symphysis pubis (outside the pelvis) and 15 mm for rectocele; there was no cut-off level for uterine prolapse. LAM trauma, especially its puborectalis aspect, has a recognised association with POP. US-diagnosed avulsion is considered to be present if the urethro-LAM insertion distance is >25 mm on tomographic US investigation (TUI) [15]. We measured procollagen type III N-terminal propeptide (PIIINP) level in 96 participants, using commercial enzyme-linked immunosorbent assay (ELISA) tests by Uscn Life Science Inc. Wuhan. Participants with highest and lowest values for point C (leading edge of cervix on POP-Q assessment) were selected from the cohort for procollagen quantification. The main outcome measures were cystocele, rectocele and uterine prolapse.

5.3.1 Statistical analysis

All statistical analyses were performed using IBM SPSS 19 and Stata Software 10.0. All statistical tests were two sided, and a p value <0.05 was considered statistically significant. Log-linear binomial regression was used to estimate the relative risk (RR) of developing various types of POP in relation to mode of delivery (MoD). All regression models were adjusted for maternal age, body mass index (BMI), education, smoking and marital status. When convergence was not achieved, a recognised problem with this model, log-linear Poisson regression with "robust" estimation variance was used[125]. In separate models, we classified MoD into spontaneous vaginal, instrumental vaginal and CS deliveries to increase statistical power of the analysis. The association between various POP types and collagen level was assessed using Student's t test. The association

between POP and various medical conditions was analysed using chi-square test. Correlation between Beighton hypermobility score and POP was tested with Kruskal–Wallis test and Spearman rank correlation, as appropriate. We investigated the correlation between hypermobility score and presence of various types of prolapse in isolation as well as in combination. An ordered logistic regression was used to assess the impact of LAM trauma and MoD, among other risk factors (RFs), on main outcome measures. RFs investigated were: LAM hiatus >25 cm2, LAM avulsion, subpubic arch angle, collagen type III level, family and personal history of collagen diseases, foetal birthweight and head circumference, duration of first and second stage of labour, MoD, type of maternity care, induction of labour, acceleration of labour with oxytocin, epidural analgesia, perineal tear, episiotomy and perineal suturing. As a reference group, we used patients with no prolapse, who had a vaginal delivery, had an intact LAM, a levator hiatal area <25 cm2, absence of any medical history of collagen disease, no induction of labour, no epidural analgesia, no episiotomy etc. and who had a subpubic angle >90° and <100°.

5.4 Results

Clinical follow-up was attended by 202 participants (33.3% of all eligible for follow-up). The study population consisted of 99.5% Caucasian women with mean age 31.2 years, mean BMI 25.1 kg/m2 and mean weight 68.0 kg. All demographic characteristics of women who participated in the 4P clinical follow-up study were similar to those in participants of the Screening for Obstetric and Pregnancy Endpoints (SCOPE) Ireland (Table 5.1).

We found a high prevalence of various types of POP. Most prevalent was cystocele, present in 90% of participants, followed by uterine prolapse (89%) and rectocele (70%). None of the participants had prolapse grade 3 or higher (Table 5.2).

In the majority of cases (65%), there was a coexistence of the anterior-, central- and posterior-compartment prolapse. Two-compartment involvement was the second most common (25%), with cystocele and uterine prolapsed being the most frequently associated conditions. Solitary POP was the rarest finding in this study group (Table 5.3).

Despite the high prevalence of POP on POP-Q examination, only 20% of participants with prolapse were symptomatic. The prevalence of symptoms is presented in Table 5.4 as binary variables. There was a better association between prolapse diagnosis and presence of symptoms on Tp-USS, which outlines patients with significant prolapse only. On Tp-USS, 33% of participants with POP were symptomatic (Table 5.4). We found a statistically significant correlation between procollagen type III (PIIINP) levels and uterine prolapse. Mean PIIINP level (SD) was higher in participants with uterine vs. nonuterine prolapse: 101(39) μg/ml vs. 69 (25) μg/ml. Mean difference was 32 μg/ml [95% confidence interval (CI) 3–60, p=0.01)] However, there was no significant association between collagen type III levels and presence of cystocele or rectocele.

On examining risk factors in medical history, we found a statistically significant association between various types of POP and family history of uterine prolapse, cystocele, varicose veins and personal history of vertebral hernia, varicose veins and asthma ($p<0.05$) (Appendix VI). A statistically significant association was found between Beighton score and rectocele (p=0.036) but not for cystocele and uterine prolapse. However, when we analysed the correlation with a combined score for all prolapses, a statistically significant association was detected (p=0.022). We analysed the correlation between various POPs and different risk factors (Table 5.5). A particular POP was associated with presence of other types of prolapse; however, the most persistent and

significant risk factor was LAM trauma. During analysis of the impact of MoD on prolapse, in order to increase statistical power, we combined all instrumental deliveries and all CS (Table 5.6).We found that CS reduced the risk of cystocele and rectocele but not of uterine prolapse. Instrumental deliveries slightly but not significantly reduced the risk of rectocele.

5.5 Discussion

In this study, we aimed to evaluate the role of childbirth in the development of postnatal POP by assessing primiparous women only at least 1 year postnatally to exclude transitional postnatal changes in the pelvic floor. Additionally, we intended to test the hypothesis stating that POP is a congenitally determined condition rather than a result of childbearing alone and especially of vaginal delivery. We hypothesised that if the condition were congenitally determined and caused by abnormal collagen quantity or quality, this change should have a systemic pattern, involving other parts of the body, as well having a family history of collagen-related disorders.

The prevalence of different types of POP appeared very high in our study. However, in the majority, prolapse grade was I–II and was asymptomatic. Our data are consistent with previous epidemiological studies, and the question of changing the prolapse classification to a more clinically relevant one has been raised in the past [55]. There seems to be a better clinical correlation between presence of prolapse symptoms and US findings, where prolapse is classified into clinically significant or nonsignificant[42]. The actual POP-Q system comprehensively describes different types of POP. However, the system has a poor association with clinically meaningful prolapse, resulting in labelling

the majority of patients as having prolapse and causing unnecessary anxiety and sometimes even surgical interventions.

Collagen plays an important role in the human body, offering biomechanical strength and elasticity to connective tissue. The process of collagen synthesis consists of five steps. The first two are intracellular, occurring in fibroblasts; the remaining three are extracellular[120]. When a procollagen molecule leaves the cell, it is transforming from procollagen into tropocollagen by proteolytic cleavage of carboxy and amino terminals. These terminals can be detected and quantified as markers of collagen synthesis in blood serum or frozen tissue homogenates[121]. Procollagen N-terminal propeptides (PNP) and C-terminal propeptides (PCP) are specific to collagen type and can be quantified by radioimmunoassay [46] or ELISA test[122]. There are 28 types of collagen; however only types I, II and III are major supporting collagens[144]. Type I is the most prevalent and widespread in the body, constituting 90% of total body collagen, especially being abundantly present in bone tissue, where strength is required. Collagen type II is mostly found in cartilage and type III in soft tissue, e.g. skin, ligaments[144-145]. There is controversy regarding collagen content in patients with prolapse, the consensus being collagen type I is minimally changed or has a tendency to slightly lower levels in severely prolapsed patients; collagen type III seems to undergo the most important change, and its concentration appears to be significantly increased, which changes the type I/III ratio[111, 120]. Edwall et al. suggested this finding may be due to an increased collagen turnover in patients with prolapse following intensive breakdown, especially for collagen type III.

In our study, the majority of participants were relatively young (78% <34 years), and POP was only grade I–II. We decided to investigate the synthesis of collagen type III only

because, according to previous studies, this is where we would expect to find the most significant change[111, 120]. Our results were consistent with previous findings, showing a statistically significant increase in collagen type III synthesis in participants with uterine prolapse. However, we found no statistically significant association with cystocele or rectocele. This may be due to the fact that the dry weight of uterine attachment ligaments comprises 70– 80% collagen, where collagen type III has the highest content in the body; in fascial tissue, such as vesicovaginal or rectovaginal septum, collagen III content is lower[46, 144].

Collagen abnormality appears to be a systemic issue. Although genes coding collagen synthesis may have different expressions in various tissues, there is a body of evidences indicating that collagen-related problems seem to have a systemic manifestation. It has been demonstrated that POP is associated with joint hypermobility; abdominal, inguinal and vertebral hernias; varicose veins; mitral valve prolapse etc[17, 46, 115-116]. Our results are consistent with these findings, showing a statistically significant association between POP and various family and personal medical history risk factors. In clinical practice, introducing a relatively simple investigation for collagen levels, such as ELISA of blood serum, could help identify antenatally the patients at higher risk of POP. However, larger studies are needed to confirm the potential benefit of this investigation, which demonstrates that uterine prolapse, for instance, is associated with pregnancy per se, rather than with MoD.

A multivariate analysis was performed to assess the correlation of significant risk factors described above and the impact of LAM trauma and MoD on POP, excluding most common confounders. The analysis showed that the associations between collagen level and family and personal history of collagen-related diseases were confounded. In

multivariate analysis, levator avulsion was significantly associated with different types of POP, and the presence of rectocele was associated with uterine prolapse. The latter partially confirms the role of multicompartment involvement of POP in the majority of participants as a reflection of generalised pelvic floor weakness. Low yield of statistically significant results in multivariate analysis could probably be explained by the limited number of observations of these variables in our study. Multivariate analysis did not demonstrate that vaginal delivery increases the risk POP; however, surprisingly, we found that CS is significantly protective against the development of rectocele and cystocele only and does not affect the occurrence of uterine prolapse (Table 5.6). Attempting to explain this selective impact of MoD on different types of POP, we hypothesised that the significantly protective effect of CS against cystocele and rectocele, in contrast to uterine prolapse, could possibly be explained by the different attachment mechanism of the uterus on the one hand and vagina on the other. The main uterine support consists of cardinal and uterosacral ligaments. Their insertion point is concentrically focussed the around lower uterus and is perpendicular to the birth canal axis. Paravaginal support was demonstrated by DeLancy to have three levels of attachment[146]. Although level one, which is similar to the uterine attachment, plays an important supportive role, the area of level two is much larger. It consists of vesicovaginal fascia and rectovaginal septum, both running parallel to the birth canal axis. Level two resembles a sail framed by arcus tendineus and fascia of levator ani muscles. Thus, vesicovaginal fascia and rectovaginal septum are peripherally attached, whereas the midline part, projecting on the urogenital hiatus, is the most mobile and exposed area. In addition, there is a different distribution of pressure vectors during labour on supportive structures through the birth canal. During vaginal delivery, the uterine pressure vector is directed along the longitudinal uterine axis. Suspension

ligaments, focussed around the exit of the fully dilated uterus, have opposing contradirectional resistance in a parallel plane. In the vagina, the pressure vector is perpendicular to vesicovaginal fascia and rectovaginal septum[147]. The main impact on uterine position appears to result from pregnancy, during which gravitation facilitates continuous overdistension of the uterine ligaments, which contain a higher level of abnormal collagen type III. In the case of rectocele and cystocele, damage is probably produced during labour, when the foetal head is progressing through the birth canal and is overstretching the vagina. This can lead to avulsion injury of the paravaginal supportive structures. Considering this, additional strategies apart from CS must be investigated to prevent POP and especially uterine prolapse; such strategies include education around avoiding risk factors, such as smoking, which has been shown to impair collagen quality[148], or performing life-long pelvic floor exercises to reinforce the pelvic floor.

5.5.1 Strengths and limitations

The main strength of our study is its comprehensive approach to the investigation of POP. It included detailed family and personal history of related medical conditions, use of a validated questionnaire, POP-Q assessment, transperineal scan and collagen quantification. Additionally, this study encompasses a large number of well-phenotyped nulliparous participants followed up to 1 year postnatally and is representative of the entire population. Although we had a clinical follow-up rate of 33% of eligible participants, demographic characteristics of these women was similar to the SCOPE cohort (Table 5.1), which has been shown prepregnancy to be representative of the entire nulliparous population[139]. High homogeneity of the study population is another

strength, allowing us to overcome naturally occurring confounders for POP, such as advanced age and interracial differences. The majority of participants was relatively young (78% <34 years) and Caucasian (99%), which enables a better understanding of the natural history of POP. Previous studies have shown that white women are considered more prone to develop prolapse and urinary incontinence (UI)[8, 137]. All patients were delivered in the same hospital following similar protocols and obstetric approaches, which excludes various obstetric management confounders. The main limitation of the study is that our participants did not have a POP-Q and Tp-USS assessment in early pregnancy, i.e. at the time of recruitment. Also, we recognize that our study could be underpowered for making a definite conclusion on the impact of MoD on POP. The low clinical follow-up rate due to high exclusion numbers as a result of the next ongoing pregnancy is another limitation. This could also explain why the number of participants >34 years was slightly higher than in SCOPE data. However, we dealt with this issue by doing a multivariate logistic regression, including age as a confounder. The slight difference with SCOPE demographics can be also explained by the fact that all participants were at least 1 year older than at recruitment. In addition, we investigated the association between POP and 35 medical conditions. We acknowledge that having so many tests creates a possibility of chance findings. However, we investigated only conditions previously shown to be associated with POP.

5.6 Conclusion

POP has a very high prevalence among premenopausal primiparous women, with the majority having multicompartmental involvement. In the majority of our patients, prolapse was asymptomatic; however, it may well contribute to future pelvic floor

morbidity in the postmenopausal period. The relationship between POP and family and personal history of collagen abnormalities, the association between uterine prolapse and collagen level and the lack of correlation between MoD and uterine prolapse grade is suggestive of an important congenital contribution to POP aetiology. Similarly, LAM trauma proved to be a paramount risk factor. CS seems to be protective against cystocele and rectocele, with no effect on uterine prolapse; this issue warrants further research. POP-Q is a very comprehensive classification system; however, we agree that perhaps it has a more valuable role in research than in clinical settings in which grade I–II prolapse is assessed. Considering the fact that POP seems to have a strong congenital predetermination, a thorough analysis of risk factors could help identify women at a higher risk of POP and implement some preventive measures.

Table 5.1 Demographic characteristics of the population in the 4P-study and Scope Ireland study

	4P/PFD study (n=202)	SCOPE Ireland (n=1775)
Caucasians	201(99.5%)*	1450(97.7%)
Age in years		
17-24	19(9.4%)	207(11.7%)
25-29	49(24.3%)	545(30.6%)
30-34	89(44.16%)	787(44.4%)
35-45	45(22.3%)	235(13.3%)
BMI		
Underweight	4(2%)	22(1.2%)
Normal	103(51%)	1036(58.4%)
Overweight	70(34.7%)	495(27.9%)
Obese	25(12.4%)	221(12.5%)
Education		
≤12 years	28(13.9%)	230(13%)
>12 years	174(86.1%)	1544 (87%)
Smoking		
Non smokers	148(73.3%)	1285(72.4%)
Smokers	54(26.8%)	489(27.6%)
Alcohol consumption		
No	39(19.3%)	339(19.1%)
Yes	163(80.7%)	1435(80.9%)
Mean values [A]		
Age in years	31.2(4.7)	29.9(4.5)
BMI	25.1(4.1)	24.9(4.2)
Weight in kg.	68.0(11.3)	67.5(12.2)

* All values presented as number of cases and (%) of total

[A] Data presented as mean value and Standard Deviation (SD)

Table 5.2 Prevalence of various types of POP* (N = 202)

Prolapse Grade	Cystocele		Rectocele		Uterine prolapse	
0	20	(9.9%) [A]	60	(29.7%)	22	(10.9%)
1	64	(31.7%)	95	(47.0%)	178	(88.1%)
2	118	(58.4%)	47	(23.3%)	2	(0.9%)
Total prolapsed	182	(90.1%)	142	(70.3%)	180	(89.1%)

* Prolapse quantified according to POP-Q

[A] All percentage given out of total participants

Table 5.3 Number of POP compartments involved (N = 197)

3 Compartments prolapsed	129	(65.5%)
Cystocele + Uterine prolapse	39	(19.8%)
Cystocele + Rectocele	7	(3.6%)
Uterine prolapse + Rectocele	4	(2%)
Uterine prolapse	11	(5.6%)
Cystocele	6	(3.1%)
Rectocele	1	(0.5%)

Table 5.4 Prevalence of prolapse symptoms in association with various types of prolapse (N = 202)

	POP-Q assessment								Ultrasound assessment*	
	Cystocele		Rectocele		Uterine prolapse		All prolapses		Cystocele	Rectocele
	Total	Grade 2	Total	Grade 2	Total	Grade 2	Total	Grade 2		
Asymptomatic [A]	142(78.0%)	28(23.7%)	98(69%)	34(72.3%)	131(72.3%)	N/A[C]	158(80.2%)	94(75.2%)	18(66.7%)	35(68.6%)
Prolapse sensation [A]	18(9.9%)	15(12.7%)	17(12%)	8(17.0%)	17(9.4%)	N/A	19(9.6%)	15(12%)	5(18.5%)	8(15.7%)
Vaginal Pressure or heaviness [A]	27(14.8%)	22(18.6%)	20(14.1%)	8(17.0%)	26(14.4%)	N/A	30(15.2%)	23(18.4%)	8(29.6%)	12(23.5%)
Prolapse reduction to void [A]	6(3.3%)	5(4.2%)	5(3.5%)	3(6.4%)	4(2.2%)	N/A	5(2.5%)	5(4.0%)	1(3.7%)	2(3.9%)
Prolapse reduction to defecate [A]	2(1.1%)	1(0.9%)	2(1.4%)	1(2.1%)	2(1.1%)	N/A	2(1.1%)	2(1.6%)	0(0%)	0(0%)
Associated bother [A]	12(6.6%)	9(7.6%)	11(7.8%)	4(8.5%)	10(5.6%)	N/A	13(6.6%)	10(8.0%)	3(11.1%)	6(11.8%)
Prolapse present [B]	182(90.1%)	118(58.4%)	142(70.3%)	47(23%)	180(89.1%)	2(1%)	197(97.5%)	125(61.9%)	27(13.4%)	51(25.3%)

* Significant only prolapse presented according to Dietz's criteria[16]

[A] Percentage given out of total prolapsed within the group (last line in each column)

[B] Percentage given out of total participants

[C] Two participants only had uterine prolapse grade two

Table 5.5 Correlation between different types of POP and various risk factors

	Univariate analysis			Multivariate analysis		
	OR	CI (95%)	p=	OR	CI (95%)	p=
		Cystocele				
Uterine prolapse	5.8	(2.61-12.73)	0.000			
Rectocele	12.8	(4.93-33.26)	0.000			
LAM* avulsion	4.3	(1.55-11.78)	0.005	2.86	(1.20-6.85)	0.018
High collagen Type III levels	1	(0.99-1.01)	0.944			
Family history of collagen diseases	0.9	(0.52-1.59)	0.736			
Personal history of collagen diseases	1.2	(0.62-2.16)	0.647			
		Rectocele				
Uterine prolapse	2	(1.01-3.84)	0.046			
LAM* avulsion	1.1	(0.52-2.44)	0.767			
High collagen Type III levels	1	(0.98-1)	0.082			
Family history of collagen diseases	1	(0.6-1.74)	0.945			
Personal history of collagen diseases	1	(0.57-1.8)	0.976			
		Uterine prolapse				
Cystocele	5.7	(2.18-15.11)	0.000			
Rectocele	1.9	(0.94-3.96)	0.071	15.1	(5.62-40.35)	0.000
LAM* avulsion	2.4	(1.14-5.06)	0.021	6.15	(2.03-18.56)	0.001
High collagen Type III levels	1	(0.98-1)	0.278			
Family history of collagen diseases	1.3	(0.78-2.21)	0.312			
Personal history of collagen diseases	0.9	(0.51-1.59)	0.726			

* LAM - levator ani muscle

Table 5.6 Correlation between various types of POP and mode of delivery *

Type of POP	Mode of delivery	№	Unadjusted			Adjusted		
			RR	95% (CI)	p =	RR	95% (CI)	p =
Cystocele	Vacuum	23	0.9	(0.67-1.24)	0.560	0.9	(0.62-1.19)	0.363
	Forceps	24	1.1	(0.84-1.43)	0.487	1.0	(0.74-1.32)	0.919
	Em. Caesarean Sections	8	0.6	(0.34-1.06)	0.078	0.6	(0.35-1.08)	0.089
	El. Caesarean Sections	12	0.5	(0.33-0.86)	0.011	0.4	(0.27-0.7)	0.001
	All Instrumental deliveries	47	1.0	(0.79-1.26)	0.996	0.9	(0.72-1.19)	0.540
	All Caesarean Sections	20	0.6	(0.38-0.82)	0.003	0.5	(0.33-0.73)	0.000
Rectocele	Vacuum	9	0.8	(0.39-1.47)	0.416	0.7	(0.36-1.49)	0.394
	Forceps	10	1.0	(0.52-1.8)	0.929	0.8	(0.42-1.64)	0.595
	Em. Caesarean Sections	2	0.3	(0.08-1.25)	0.101	0.3	(0.1-1.12)	0.076
	El. Caesarean Sections	2	0.2	(0.05-0.76)	0.019	0.2	(0.03-0.66)	0.012
	All Instrumental deliveries	19	0.9	(0.52-1.43)	0.557	0.8	(0.46-1.36)	0.397
	All Caesarean Sections	4	0.2	(0.09-0.65)	0.005	0.2	(0.08-0.56)	0.002
Uterine prolapse	Vacuum	32	0.9	(0.82-1.08)	0.402	0.9	(0.79-1.08)	0.349
	Forceps	28	0.9	(0.79-1.08)	0.304	1.0	(0.81-1.11)	0.498
	Em. Caesarean Sections	19	1.0	(0.91-1.16)	0.626	1.1	(0.93-1.24)	0.351
	El. Caesarean Sections	29	0.9	(0.79-1.08)	0.322	1.0	(0.84-1.12)	0.632
	All Instrumental deliveries	60	0.9	(0.83-1.04)	0.227	0.9	(0.83-1.06)	0.302
	All Caesarean Sections	48	1.0	(0.86-1.08)	0.531	1.0	(0.9-1.13)	0.913

*Spontaneous vaginal delivery – used as reference group

Chapter 6

Study 4

The status of the pelvic floor in young primiparous women

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6.1 Abstract

Objectives: To investigate the postnatal prevalence of sonographically diagnosed pelvic floor trauma, and the correlations with various antenatal/intrapartum predictors in primiparous women.

Methodology: A prospective cohort study, performed in a tertiary hospital with 9000 deliveries per annum. 202(23.2% of those recruited) primiparous participants were clinically assessed at least one year postnatally, with Pelvic Organ Prolapse Quantification (POP-Q), 2/3D-transperineal ultrasound (TpUS) and collagen type III levels quantification.

Results: Clinically significant POP had a high prevalence on POP-Q staging: uterine prolapse-63%, cystocele-42%, rectocele-23%. Ballooning of the levator ani muscle (LAM) hiatus was detected in 33.2% and LAM avulsion in 29% of participants, with partial LAM avulsion in 15% and complete in 14%. Postnatal POP symptoms were positively associated with similar prepregnancy symptoms (OR [95% CI]) (OR 7.2 [1.19-44.33]), LAM avulsion (OR 4.8 [1.99-11.34]), forceps delivery (OR 1.8 [0.96-3.25]) and negatively associated with Caesarean Section (CS) (OR-0.2 [0.09-0.63]). LAM abnormality was associated with forceps delivery (OR 4.9 [1.44-16.97]) and prolapse (OR between 6.8 and 11.7 [2.34-78.51]), whereas collagen levels did not play a role 1.007 [0.99-1.02].

Conclusion: Clinically significant POP was common in relatively young premenopausal primiparae. A partial or full levator avulsion was seen in 29% of participants, being associated with POP and symptoms related to it. Congenital factors seem to play little role in the aetiology of levator muscle trauma, whereas the main risk factor seems to be

forceps delivery. Avoidance of difficult vaginal deliveries may prevent severe pelvic floor trauma.

6.2 Introduction

Pelvic floor dysfunction (PFD) is a common problem, with childbearing recognised as one of the major risk factors[6]. Numerous epidemiological and clinical studies have been undertaken on various aspects of PFD, such as urinary and faecal incontinence, prolapse or sexual dysfunction. There has been increasing interest over the last decade in innovative methodologies investigating morphological changes of pelvic floor, especially 3D transperineal ultrasound (3D-TpUS). This technique has good test-retest and intra-observer repeatability and is considerably cheaper and in some aspects superior to magnetic resonance imaging (MRI), especially when assessing dynamic images, eg for the investigation of prolapse[16, 104, 149]. Several groups have examined the role of trauma to the puborectalis aspect of the levator ani muscle (LAM) in development of PFD[100, 108]. The appearances of LAM avulsion seem to be very uncommon in nulliparous women, however it is present in 12-36% of women after first vaginal delivery[106]. Additionally, transperineal ultrasound allows visualisation of bladder neck mobility, urethral length, assessment and quantification of pelvic organ prolapse (POP), measurement of subpubic angle and assessment of the anal sphincter complex[40, 103, 150].

The present ultrasound study is a part of the 4P-study (Prevalence and Predictors of Pelvic floor dysfunction in Primips), which is designed to comprehensively assess changes in the pelvic floor after first pregnancy and delivery. In this study we aimed to investigate the postnatal prevalence of sonographically diagnosed morphological

alterations of pelvic floor functional anatomy and their correlations with various antenatal and intrapartum predictors in primiparous women.

6.3 Methodology

The 4P is a prospective cohort study, nested within the parent SCOPE Ireland study (Screening for Pregnancy Endpoints, www.scopestudy.net), which has previously been described in detail[151]. It was approved by Clinical Research Ethics Committee of the Cork Teaching Hospitals (CREC) Ireland and performed in a tertiary maternity hospital with 9000 deliveries per annum.

All 4P participants, 1484 nulliparous women (84% of those recruited for SCOPE), completed the validated Australian Pelvic Floor Questionnaire[28] in early pregnancy at 14- 15 weeks. Same questionnaire was answered one year postnatally by 1060 women (71% of those who completed the prepregnancy one), however only 872 (59%) were included in the study analysis and constituted the core of 4P-Study, since 188 (13%) were excluded due to a second ongoing pregnancy. The recruitment phase occurred between February 2008 and March 2011. All 872 participants included in the initial analysis were invited for clinical follow up between March and December 2012. We received answers from 530 (60.8%) participants, the proposed follow-up being accepted by 408 (46.8%). Participants who had more than one delivery, or were repeatedly pregnant at the time of follow up 23.6% (206), were excluded from the study (Figure 1). The clinical follow up was attended by 202 (23.2% of all invited) participants between May and November 2012. All attendees had a POP-Q assessment, transperineal 2D/4D ultrasound scan for quantification of POP and pelvic morphology evaluation, a blood serum collection for pro- collagen quantification and a collection of personal history

and/or family history of connective tissue conditions, shown previously to be associated with PFD and POP (Appendix VI).

POP-Q measurements were obtained on maximal Valsalva with an effort duration of at least 6 seconds, in order to achieve maximal pelvic organ descent[117]. Pb and Gh lengths were additionally measured at rest. The POP-Q classification does not specify what grade of prolapse should be considered significant, however it has been suggested that POP-Q Stage 1 may be considered part of the normal range[152]. This may not be correct for the central compartment however, where stage 1 prolapse seems strongly associated with symptoms of prolapse[152]. Hence, we defined 'clinically relevant prolapse' as cystocele and rectocele ≥ Stage 2, uterine prolapse ≥ stage 1. For ultrasound POP investigation on 2D transperineal ultrasound scan (2D-TpUS) and 3D-TpUS, two images were acquired – at rest and on maximal Valsalva. To estimate the extent of prolapse, we measured the distance from the most distal part of the bladder or anorectal junction to a horizontal line placed through the inferior margin of the pubic bone[153].

There are no studies to date correlating the degree of prolapse diagnosed on POP-Q vs. ultrasound. However, previous studies reported a better correlation between presence of symptoms and grade of ultrasound prolapse[154]. We used an ultrasound POP classification categorising prolapse into clinically significant and non-significant[42]. A cut-off level of 10mm below the symphysis pubis was proposed for definition of significant cystocele and 15 mm below the SP for significant rectocele. We used the reference line (that is a cut-off of 0) as the definition of significant uterine prolapse based on unpublished data provided by HP Dietz as there is currently no published cut- off for central compartment descent.

LAM integrity was assessed using 3D-TpUS in tomographic ultrasound imaging (TUI) mode, the image being acquired on maximum pelvic floor muscle contraction. The plane of minimal hiatal dimension was selected as reference plane. To cover the whole width of LAM, five tomographic slices cephalad to the reference plane, with a slice thickness of 2.5 mm, were included in the analysis. A LAM avulsion was diagnosed if the gap between the centre of the urethra and the LAM insertion (Levator- urethra gap or LUG) was ≥25 mm[101]. A complete LAM avulsion was diagnosed if a gap ≥ 25 mm was observed in the reference slice and in the two slices cephalad to it. Any other combination of abnormal slices was considered a partial LAM avulsion[102]. We also assessed ballooning of the levator hiatus, which is defined as distension of hiatal area >25cm^2 and has been shown to be associated with LAM trauma and symptoms and signs of prolapse[45]. The subpubic arch angle was measured in the axial plane close to the plane of minimal hiatal dimensions, where the pubic rami join. The image was manipulated to obtain maximal pubic rami length[103].

We measured the Procollagen type III N-Terminal Propeptide (PIIINP) level in 96 participants, using commercial ELISA tests manufactured by Uscn Life Science Inc. Wuhan. Participants with highest and lowest value for point C (leading edge of cervix on POP-Q assessment) were selected from the cohort for procollagen quantification. The methodology was described in detail previously[154].

6.3.1 Statistical analysis

Statistical analysis was performed using IBM SPSS 19 and Stata Software 10.0. All statistical tests were two-sided and a p-value <0.05 was considered statistically significant. To investigate the effect of potential risk factors (RFs) on PFD, stepwise

ordinal logistic regression was used to calculate the Odds Ratio (OR) and 95% Confidence Interval (95% CI). In ordinal logistic regression, the outcome measure was ordinal with more than two categories. RFs with borderline statistical significance ($p<0.1$) were used for multivariate logistic regression. Main outcome measures were, rectocele, uterine prolapse, LAM trauma, and LAM hiatal ballooning. The examined risk factors were subpubic arch angle, collagen type 3 levels, personal / family history of collagen related diseases, induction of labour, mode of delivery, Oxytocin augmentation, duration of labour, foetal head circumference and birthweight.

6.4 Results

Clinical follow up was attended by 202 primiparous women (33.3% of all eligible for follow up). Among our participants 99.5% were Caucasian, with mean age 31.2 years, mean BMI of 25.1 kg/m^2 and mean weight 68.0 kg. Demographic characteristics of women who participated in 4P-study clinical follow up and SCOPE Ireland were similar (Table 6.1). The SCOPE cohort has been shown previously to be representative for the entire population[151].

In order to avoid transitory postnatal pelvic floor changes, participants were invited for clinical follow up at least one year postnatally. The average delivery to clinical assessment interval was 1 year and 9 months (ranging from 1.1 to 4.1 years). Of all participants 158 (80.2%) were asymptomatic, 19 (9.6%) complained of symptoms of a vaginal lump or bulge, 30 (15.2%) of vaginal pressure or heaviness, 4 (2.2%) of prolapse reduction to void, 10 (5.6%) of prolapse reduction to defecate and 10 (5.6%) reported associated bother due to prolapse symptoms.

On clinical examination the Mean (Standard Deviation) POP-Q values for various points on maximal Valsalva were as following: Ba -1.21 (0.84)cm, Bp -1.92 (0,75)cm, C -5.23 (1.03)cm. On 2D-TpUS maximal descent of the bladder on Valsalva was to 0.45 (SD 1.16) cm below the symphyseal reference line. Maximal descent of the rectal ampulla was to 0.46 (SD 1.17) cm above the reference line.

The prevalence of various types of POP on POP-Q and 3D-TpUS is presented in Table 6.2. Clinically significant uterine prolapse (Stage 1 or higher) on POP-Q measurement (described in methods section) was present in 63% participants. Clinically significant cystocele (stage 2 or higher) was 3 fold higher on POP-Q examination compared to the finding of a significant cystocele on ultrasound (bladder 10 mm or more below the SP) at 41.6% vs. 13.9%. Significant posterior compartment descent (ICS POP-Q stage 2 or higher, or descent of the ampulla to 15 mm below the SP or more) was similar for both diagnostic methods – around 24%.

The 3D-TpUS revealed that nearly one third of participants (29.2%) had some sort of abnormal LAM morphology. The rate of partial LAM avulsion was one third higher comparing to complete avulsion (21.8% vs. 14.4%) right sided avulsion being more common that left sided (10.9% vs. 2.5%), and bilateral avulsion being common at 15.8%). One third of participants (67; 33.2%) had ballooning of LAM hiatus, of which 38 (56%) had associated LAM avulsion.

Analysing the factors associated with presence of prolapse symptoms we found statistically significant correlations with prepregnancy presence of prolapse symptoms (OR 2.7 - 7.2), complete LAM avulsion (OR 4.8 - 9.5), LAM hiatal ballooning (OR 2.5 – 5.2) and forceps delivery (OR 1.8). Caesarean Section delivery was protective (OR 0.2 – 0.4) (Table 6.3).

Additionally, we analysed the association of various antepartum and intrapartum factors with LAM trauma and ballooning of LAM hiatus. On univariate analysis we found statistically significant or borderline significance correlation between any LAM trauma and use of Oxytocin in labour (OR 1.8), duration of 2nd stage of labour (OR 1.008), forceps delivery (OR 4.5), episiotomy (OR 4.2) and presence of cystocele postnatally (OR 4.2) (Table 6.4).

Ballooning of LAM hiatus was associated with forceps delivery (OR 4.8), episiotomy (OR 1.9), presence of postnatal cystocele, rectocele and uterine prolapse – (OR 7.5, 2.6 and 7.6 respectively), and LAM avulsion (OR 2.8 for partial and 17.4 for complete avulsion) (Table 6.5).

On multivariate analysis LAM avulsion was statistically significant associated with duration of 2nd stage of labour (OR 1.01), forceps delivery (OR 4.9), postnatal presence of uterine prolapse (OR 6.84) and cystocele (OR 11.7) (Table 6.4). Ballooning of LAM hiatus was significantly associated with uterine prolapse (OR 7.6) and LAM avulsion (OR 3.2 for partial and 12.2 for complete avulsion). Forceps delivery had borderline significance here (OR 4.0 (p=0.074)) (Table 6.5).

We did not find any association between LAM abnormality and foetal birthweight or head circumference, duration of labour, subpubic arch angle, collagen levels, or collagen disease history. Also the time interval from delivery to 3D-TpUS did not significantly influence the presence of LAM pathology. Caesarean Section (CS) appeared protective, however not statistically significant.

6.5 Discussion

In the present study we investigated the postnatal prevalence of the pelvic floor trauma using 3D-TpUS in primiparous women Different from previous studies, we intended to describe the ultrasound appearance of the pelvic floor in primiparas at one year after childbirth and to link it to potential prepregnancy and intrapartum contributing factors[107]. We intentionally used this cut-off for time limit, in order to avoid inclusion of transitory pelvic floor changes in our study, which can persist up to 6 months postnatally or even more[71].

We found pelvic organ prolapse to be very common in primiparous women, with clinically significant cystocele being more prevalent on POP-Q assessment, and rectocele having similar detection rates on POP-Q and 3D-TpUS investigation. Around half of participants had clinically significant cystocele or uterine prolapse and one quarter had clinically significant posterior compartment descent, although nobody had any type of prolapse greater than stage 2 (Table 6.2). It is recognised that the correlation of POP findings between POP-Q assessment and on TpUS are fair to good[153]. However it has also been demonstrated that TpUS is more likely to avoid the potential confounding effect of important factors such as levator co-activation, full bladder or rectum (which can be directly visualised on the screen and dealt accordingly), whereas clinical examination additionally is able to displace one compartment to allow other compartments to descend[155].

Prolapse symptoms were not uncommon (even though 80% of participants with objective prolapse were asymptomatic), and were associated with LAM trauma and forceps delivery, whereas CS had a protective effect[154]. The prevalence of ultrasound diagnosed complete LAM avulsion obtained in this study is well within the range of data

reported previously, with 14.4% being close to figures reported recently in studies using an identical methodology[41, 156]. Our rate of partial avulsion is higher than demonstrated in previous studies, however similar to previous reports we found that right sided trauma is more common than left sided[105]. This is probably due to the fact that in Ireland active management of labour is advocated with high rate of forceps delivery. Slightly more than half of cases with ballooning of levator hiatus were associated with LAM trauma. A significant association was found between presence of prolapse symptoms and forceps delivery, whereas CS was protective. Our data from univariate analysis corresponded well with previous studies showing an association between LAM trauma with length of 2nd stage of labour, mode of delivery and episiotomy, where forceps was most predictive of trauma [41, 108, 156]. In contrast to other reports we did not find a significant association with foetal birthweight and foetal head circumference[108]. This could probably reflect different obstetric practices, as active management of labour is largely used in Ireland and there is a high rate of instrumental deliveries, or else be due to power issues. In addition, definitions of avulsion vary in the published literature, which may explain some of the differences in results.

The logistic regression analysis did not demonstrate an association between congenital non-modifiable factors such as subpubic arch angle, collagen levels or collagen related disease with LAM pathology, which most likely occurs due to mechanical impact of vaginal delivery, rather than due to the pelvic weakness. This conclusion confirms the results from previous studies using 3D-TpUS intrapartum and in early postnatal period, which demonstrated that crowning of the head is the immediate cause of avulsion of the levator ani muscle[157]. Additionally other research groups have demonstrated that hiatal dimensions, bladder neck descent, subpubic arch angle and other anthropometric

parameters were not associated with avulsion. Our results are in keeping with these data and suggest that antenatal prediction of LAM trauma may be impossible[158].

6.5.1 Strengths and limitations

The main strength of our study is the fact that it was nested within the SCOPE study, giving access to a detailed database containing information about well phenotyped nulliparous women and intrapartum risk factors. The present study is likely to be representative for the entire study population which is homogeneous and which has been shown to be representative of the Irish population overall. All participants were relatively young women, who delivered their babies in the same hospital, following similar obstetric management principles and protocols. A potential congenital predictor of pelvic organ support, Procollagen III, was included in the study design to investigate naturally occurring confounders. All participants were assessed both clinically by ICS POP-Q and by translabial ultrasound in order to comprehensively describe the state of pelvic organ support.

The lack of baseline assessments remains a major limitation, especially when interpreting clinical symptoms. Another limitation is the limited number of observations due to attrition, which may limit the conclusions that can be drawn from our results, although the participants' demographic characteristics in the present study were reasonably similar to the Cork SCOPE population. The study had limited statistical power due to small sample size and this is reflected in the wide 95% confidence intervals for some ORs. For example, family history of collagen diseases, induction of labour and oxytocin use during labour were not statistically significant in the univariate models

despite the elevated OR. This warrants further investigation of these risk factors in larger cohorts.

6.6 Conclusion

More than half of relatively young premenopausal primiparous women were shown to have some form of clinically significant POP at 1-4 years after their first delivery. This is likely to contribute to the development of PFD later in life. One third showed some degree of LAM trauma, which is associated with the presence of POP and symptoms related to it in later life. Congenital factors seem to play little role in the aetiology of levator muscle trauma, whereas the main risk factor seems to be forceps delivery. Caesarean Section was demonstrated to be protective for presence of some symptoms. Avoidance of difficult vaginal deliveries may prevent severe pelvic floor trauma and associated symptoms.

Table 6.1 Demographic characteristics of the population in the 4P-study and Scope Ireland study

	4P/PFD study (n=202)	SCOPE Ireland (n=1774)
Caucasians	201(99.5%)*	1450(97.7%)
Age in years		
17-24	19(9.4%)	207(11.7%)
25-29	49(24.3%)	545(30.6%)
30-34	89(44.16%)	787(44.4%)
35-45	45(22.3%)	235(13.3%)
BMI		
Underweight	4(2%)	22(1.2%)
Normal	103(51%)	1036(58.4%)
Overweight	70(34.7%)	495(27.9%)
Obese	25(12.4%)	221(12.5%)
Education		
≤12 years	28(13.9%)	230(13%)
>12 years	174(86.1%)	1544 (87%)
Smoking		
Non smokers	148(73.3%)	1285(72.4%)
Smokers	54(26.8%)	489(27.6%)
Alcohol consumption		
No	39(19.3%)	339(19.1%)
Yes	163(80.7%)	1435(80.9%)
Mean values †		
Age in years	31.2(4.7)	29.9(4.5)
BMI	25.1(4.1)	24.9(4.2)
Weight in kg.	68.0(11.3)	67.5(12.2)

*All values presented as number of cases and (%) of total

† Data presented as mean value and Standard Deviation (SD)

Table 6.2 Prevalence of various types of POP on POP-Q and 3D transperineal US assessment (№ 202)

Prolapse Presence	Cystocele		Rectocele		Uterine prolapse	
	POP-Q*	3D-TpUS†	POP-Q*	3D-TpUS†	POP-Q‡	3D-TpUS†
No	118(58.4%)	174(86.1%)	155(76.7%)	153(75.7%)	75(37%)	-
Yes	84(41.6%)	28(13.9%)	47(23.3%)	49(24.3%)	127(63%)	-

* Prolapse grade 2 only according to POP-Q shown as prolapse present

† Significant only prolapse according to Dietz et al. shown as prolapse present (Dietz et al [42])

‡ Prolapse grade 1- 2 according to POP-Q shown as prolapse present (according Dietz et al [152])

Table 6.3 Correlation of prolapse symptoms with various risk factors (n=202)

	OR	CI (95%)	p=
Vaginal pressure or heaviness			
Pre-pregn. vaginal pressure/heaviness	4.4	(0.77-24.8)	0.096
Pre-pregn. total prolapse score	4.4	(2.30-8.30)	<0.0001
Forceps delivery	1.7	(0.96-2.94)	0.071
Emergency CS	0.4	(0.18-0.86)	0.019
Elective CS	0.2	(0.09-0.52)	0.001
Partial LAM avulsion	1.1	(0.35-3.70)	0.820
Complete LAM avulsion	5.3	(2.14-13.3)	<0.0001
Ballooning of LAM hiatus	3.9	(1.73-8.58)	0.001
Prolapse sensation			
Pre-pregn. vaginal pressure/heaviness	3.5	(1.13-10.66)	0.029
Pre-pregn. prolapse score	2.7	(1.10-6.85)	0.03
Forceps delivery	0.3	(0.12-0.99)	0.048
Partial LAM avulsion	3.2	(0.84-11.92)	0.089
Complete LAM avulsion	9.5	(3.08-29.26)	<0.0001
Ballooning of LAM hiatus	3.2	(1.21-8.28)	0.019
Presence of multiple prolapse symptoms			
Pre-pregn. vaginal pressure/heaviness	7.2	(1.19-44.33)	0.032
Pre-pregn. total prolapse score	4.8	(2.37-9.55)	<0.0001
Forceps delivery	1.8	(0.96-3.25)	0.069
Emergency CS	0.3	(0.12-0.83)	0.019
Elective CS	0.2	(0.09-0.63)	0.004
Partial LAM avulsion	1.6	(0.61-4.12)	0.340
Complete LAM avulsion	4.8	(1.99-11.34)	<0.0001
Ballooning of LAM hiatus	2.5	(1.24-5.15)	0.011
Bother due to prolapse symptoms			
Pre-pregn. total prolapse score	4.2	(1.52-11.51)	0.006
Partial LAM avulsion	1.7	(0.32-9.40)	0.519
Complete LAM avulsion	7.4	(2.07-26.21)	0.002
Ballooning of LAM hiatus	5.2	(1.53-17.54)	0.008

Table 6.4 Correlation between ultrasound diagnosed LAM avulsion and various antenatal / intrapartum factors (n= 202)

Factors	Univariate analysis			Multivariate analysis		
	OR	CI (95%)	p=	OR	CI (95%)	p=
Subpubic arch angle	0.98	(0.95-1.02)	0.290			
High collagen T3 levels	1.01	(0.99-1.02)	0.224			
Family history of collagen diseases	1.5	(0.8-2.81)	0.209			
Personal history of collagen diseases	0.9	(0.45-1.76)	0.743			
Private maternity care	0.99	(0.47-2.09)	0.991			
Induction of labour	1.4	(0.77-2.59)	0.265			
Use of Oxytocin in labour	1.8	(0.97-3.45)	0.063	0.7	(0-1.63)	0.435
Regional analgesia	0.9	(0.47-1.75)	0.779			
Duration of 1st stage of labour	0.99	(0.91-1.10)	0.988			
Duration of 2nd stage of labour	1.01	(1.00-1.01)	0.003	1.01	(1.00-1.02)	0.019
Vacuum delivery	1.9	(0.87-4.23)	0.108	1.3	(0.48-3.52)	0.599
Forceps delivery	4.5	(1.99-10.22)	<0.0001	4.9	(1.44-16.97)	0.011
Emergency CS	0.6	(0.47-1.63)	0.352			
Elective CS	0.7	(0.25-1.98)	0.507	0.4	(0.04-4.08)	0.450
Perineal tear	0.9	(0.65-1.25)	0.524			
Episiotomy	4.2	(2.24-7.78)	<0.0001	1.8	(0.66-4.77)	0.251
Foetal birthweight	1.0	(0.99-1.01)	0.450			
Foetal head circumference	1.1	(0.91-1.39)	0.296			
Delivery/assessment time interval	0.99	(0.99-1.00)	0.342			
Cystocele	4.2	(0.94-19.14)	0.061	11.7	(1.73-78.51)	0.012
Rectocele	1.3	(0.58-2.71)	0.569			
Uterine prolapse	1.6	(0.76-3.30)	0.218			

Table 6.5 Correlation between ultrasound diagnosed ballooning of LAM hiatus and various antenatal/intrapartum factors (n= 202)

Factors	Univariate analysis			Multivariate analysis		
	OR	CI (95%)	p=	OR	CI (95%)	p=
Subpubic arch angle	1.01	(0.98-1.05)	0.459			
High collagen T3 levels	0.99	(0.98-1.01)	0.514			
Family history of collagen diseases	1.5	(0.79-2.73)	0.230			
Personal history of collagen diseases	1.5	(0.77-2.83)	0.245			
Private maternity care	1.1	(0.51-2.26)	0.860			
Induction of labour	1.3	(0.7-2.38)	0.413			
Use of Oxytocin in labour	1.7	(0.89-3.21)	0.111			
Regional analgesia	0.9	(0.45-1.69)	0.686			
Duration of 1st stage of labour	1.1	(0.98-1.19)	0.102			
Duration of 2nd stage of labour	1.0	(1.00-1.01)	0.303			
Vacuum delivery	1.5	(0.67-3.37)	0.326			
Forceps delivery	4.8	(1.91-11.82)	0.001	4.0	(0.87-18.56)	0.074
Emergency CS	0.5	(0.12-1.77)	0.264	0.5	(0.07-2.98)	0.418
Elective CS	0.6	(0.24-1.64)	0.340	0.7	(0.13-3.33)	0.633
Perineal tear	0.9	(0.68-1.31)	0.725			
Episiotomy	1.9	(1.05-3.52)	0.035	0.6	(0.17-1.88)	0.353
Foetal birthweight	1.01	(1.00-1.00)	0.049	1.0	(0.99-1.001)	0.192
Foetal head circumference	1.2	(0.94-1.45)	0.169			
Delivery/assessment time interval	0.73	(0.42-1.26)	0.263			
Cystocele	7.5	(1.65-33.59)	0.009	2.1	(0.35-12.03)	0.422
Rectocele	2.6	(1.15-5.79)	0.022	1.8	(0.57-6.59)	0.311
Uterine prolapse	7.6	(3.21-17.93)	<0.0001	6.8	(2.34-20.01)	<0.0001
Partial LAM avulsion	2.8	(1.25-6.24)	0.012	3.2	(1.20-8.69)	0.020
Complete LAM avulsion	17.4	(6.11-49.87)	<0.0001	12.2	(3.22-46.00)	<0.0001

Chapter 7

Discussion

Several population based studies have investigated the association between PFD and childbirth. However, very few studies have targeted a nulliparous population. To our knowledge, this is the first large, comprehensive, prospective cohort study focused specifically on prepregnancy pelvic floor status in nulliparous women and the correlation of prepregnancy PFD with postnatal pelvic floor morbidity.

7.1 Urinary Dysfunction (UD)

The prevalence of various UD symptoms in nulliparous women, apart from urinary incontinence (UI), is unknown. There are some studies, like NHANES or EPINCONT, reporting the prevalence of urinary incontinence in nulliparous women as part of bigger cohorts, classifying participants by parity, age etc[57, 68]. We found a high prepregnancy prevalence of UD in this nulliparous cohort. Urinary urgency (UU) was present in 42%, nocturia in 17.6%, urgency urinary incontinence (UUI) in 12.4%, and stress urinary incontinence (SUI) in 19.7% of participants. Overall prepregnancy UI was reported by 24% of participants. One third of participants had clinically significant symptoms, where higher severity was associated with higher grade of bother score due to symptoms. UI had the following distribution by types: SUI/UUI/MUI (mixed urinary incontinence) – 50%/30%/20%. There could be an opinion that findings reported in the present study are unrealistically high, taking into account that these women have never been pregnant and childbearing is considered one of the most important risk factors. However, the results obtained in the current research on UI correlated very well with the above mentioned NHANES and EPINCONT studies, and the results regarding overactive bladder (OAB) symptoms were in line with the FINNO study prevalence of OAB for the general population[131]. Additionally, several studies have demonstrated that UI and prolapse are

not exclusively observed in parous women. A good example, as mentioned in previous chapters, is Bucshbaum's study investigating PFD in parous / nulliparous sets of identical twins[86]. Another study assessed the prevalence of SUI in young, nulliparous, and physically fit students. They reported a 38% rate of SUI and 15% of urethral sphincter incompetence[159].

On analysing postnatal UD, it was noticed that the prevalence rose compared to prepregnancy UD. Postnatally 73% of participants had at least one primary symptom of UD, of which 25% were severe. Postnatal UI was present in 54% of participants with SUI/UUI/MUI ratios being slightly changed in favour of MUI with a drop in UUI rate: 44%/15%/41%. It is interesting to mention, that 63% of all incontinent women had postnatal Denovo onset Pelvic Floor Dysfunction symptoms (DNPFD), whereas in those with severe UI the rate of DNPFD and Persistent prepregnancy onset PFD (PPFD) symptoms was similar, which means that a higher rate of severe UI was noticed in the PPFD group. In the PPFD group prepregnancy UUI persisted in 70%, UU in 74% and SUI in 83% postnatally, whereas they worsened in 16% only. Symptoms related to OAB: frequency nocturia and urgency, in contrast to UI, were more prevalent in PPFD group. However, the same group of symptoms was most prone to worsen as a result of difficult vaginal delivery and had maximum protection from an elective CS.

7.2 Faecal dysfunction (FD)

Although this study is not the first to describe bowel related problems in nulliparous women[57], it is one of most comprehensive studies to date, covering a large spectrum of bowel disorders, with previous studies primarily focusing on FI. FD before first pregnancy and delivery was present in 41% of participants, where nearly half of them

had clinically significant symptoms. The prepregnancy FD section had the highest median score for symptoms and highest occurrence of bother among all sections. Bothersome symptoms were reported by 26% of study participants. FI was reported by 5.3%, flatus incontinence (Fl.I.) by 36.8%, and obstructed defaecation (OD) by 5.5%.

Postnatal anal sphincter disruption with FI has an obvious association with traumatic instrumental vaginal delivery. However this was not the case for prepregnancy pathology and other types of bowel dysfunction. As described in previous chapters, there is no statistical difference in prevalence of OD due to rectocele, enterocele, intussusception and anismus among nulliparous women, those who have had vaginal delivery or CS[82]. Dietz and Clarke have examined 178 nulliparous young women using 3D ultrasound for rectovaginal septal integrity. Twelve percent showed signs of rectocele with disruption of septal integrity. As a result the authors hypothesised that the problem could be congenitally determined[54].

At one year postnatally the prevalence of FD has not changed dramatically, 49% reporting FD symptoms of which 21% had severe symptoms. FI and OD were most prevalent in the DNPFD group, whereas Fl.I in the PPFD. Overall prepregnancy FD persisted postnatally in 50%, where they worsened in 15% only. Vacuum delivery and CS were associated with a decreased risk of FD.

7.3 Pelvic Organ Prolapse (POP)

In the present study POP symptoms were not widespread in nulliparous women, with 4.8% (70) of participants only reporting them. However in 26% (18) of participants they were clinically significant. The most commonly reported symptom was “vaginal pressure or heaviness” – 3.3%. Postnatally POP symptoms were reported by 14% of participants,

which in 20% of cases were severe. The most prevalent were "Vaginal pressure or heaviness" reported by 11% and prolapse sensation by 7% of participants.

Interestingly, various types of prolapse appeared to be very prevalent in young primiparous women on POP-Q assessment. Cystocele was present in 90% (grade 2 in 58%), rectocele in 70% (grade 2 in 23%), and uterine prolapse in 88% (grade 2 in 1%). In the majority of cases it was asymptomatic. The POP tended to present as a combination of various types of prolapse, with the most prevalent combination being uterine prolapse and cystocele (20%).

The prevalence of POP in nulliparous and primiparous women has been reported previously. As it has been shown earlier, in absence of any obvious risk factors UI is present in every fifth woman and asymptomatic prolapse stage two or less in every second young and physically fit women[84]. As well, POP is associated with operations for abdominal hernias and varicose veins and chronic pulmonary disease, where weak collagen may be a congenital risk factor for POP in up to one third of women[98]. Thus, familial predisposition might play an important role in the development of UI and POP[85, 160]. This aetiological aspect of collagen abnormality and congenital RFs was tested in the present study. I found that collagen type III had a higher concentration in women with uterine prolapse and no association was found with cystocele and rectocele. Additionally, an association was found between joint hypermobility score with rectocele and composite prolapse score – summing up all prolapse types present in the participant. An association was also found between various types of prolapse and family history of uterine prolapse, vertebral hernia, cystocele, and personal history of varicose veins, vertebral hernia and asthma.

The association between POP and levator ani muscle (LAM) avulsion is well recognised[161]. This aspect was also investigated in the present project. The results from 3D transperineal scans showed that some sort of LAM avulsion was present in 30% of participants and in 14% a complete avulsion was diagnosed. In the multivariate logistic regression models forceps delivery was associated with a statistically significant increased odds of all types of prolapse, whereas CS was protective only for cystocele and rectocele, but not for uterine prolapse. Additionally POP was associated with 3rd degree perineal tear. No association was found with previously reported foetal birthweight, head circumference or long second stage of labour.

7.3 Sexual dysfunction (SD)

At least one primary symptom of SD was reported prenatally by 41% of participants, of which 27% were clinically significant. Dyspareunia had a prevalence of 31%, vaginal tightness/vaginismus – 25%, vaginal laxity - 5%. In the majority of cases dyspareunia was mild, with similar rates of superficial and deep types. SD has a reported prevalence of 19-50%[58] in the general population. We could not identify studies specifically describing baseline SD in the nulliparous population. The majority of studies focused on prenatal versus postnatal sexual satisfaction or comparison of SD following different modes of delivery.

As mentioned previously, endometriosis is more common in nulliparous women with dyspareunia being one of the leading symptoms[89]. This may partially explain the findings of the present study, as dyspareunia was the most commonly reported SD symptom affecting 1 in 3 nulliparous women. An unexpected finding in our study was coital UI, present in 1.8% of respondents. These data are in keeping with a Danish population-

based study, performed on a sample of 2860 randomly selected women, which showed a prevalence of coital incontinence in 2% of the general population and 12% in patients with UI[133]. Postnatal SD had a prevalence of 58%, with 18% of participants mentioning severe symptoms. Dyspareunia was reported by 44%, vaginismus by 29% and vaginal laxity underwent a dramatic increase to 21%. Similar rates and severity of superficial and deep dyspareunia were noticed in both DNPFD and PPFD groups. Prepregnancy symptoms overall persisted postnatally in 59% and worsened in 12% only. CS delivery was protective against SD.

7.4 PFD as integrity

This research project has shown that 70% of young non-pregnant women had baseline PFD before their first pregnancy and 90% after first childbirth. This is a surprisingly large number of women and it has never been described previously. The majority of women with prepregnancy PFD had a variation of symptoms but these symptoms were described as mild with low bothersome scores. However, the prepregnancy affected women constituted the majority of those who developed postnatal PFD. Moreover, prenatal PFD persisted in approximately 80% of cases postnatally. Postnatal PFD was more severe and more disturbing in those affected prepregnancy versus those with a Denovo postnatal condition.

The majority of participants with PFD had multicompartment involvement. CS proved to be protective against urinary and prolapse dysfunction but with minimal effect on faecal and sexual postnatal pathology. Forceps delivery was a significant risk factor in the univariate analyses, however in the multivariate logistic regression analyses it remained statistically significant for POP only.

Data from the objective POP-Q assessment have shown further interesting findings. The majority of postnatal women had some sort of POP at 1 year postnatally, however only 43% of them were symptomatic, with the majority of symptoms being mild.

7.5 Strengths & limitations

Strengths:

The main strength of this study is the prospective design, large number of nulliparous patients within the cohort and the extensive and detailed characteristics and medical history of the participating women undertaken. In addition, a validated, comprehensive questionnaire covering all areas of PFD was used, which in addition included questions regarding the severity or bothersome nature of symptoms and the impact of PFD on patients' daily living. The nulliparous cohort recruited for the present research project, was shown to be likely to represent the population in general. The research population was very homogenous, consisting of nulliparous women, with the majority being relatively young (83% <34 years old) and Caucasian (99%). There are numerous studies mentioning interracial differences in pelvic floor anatomy and prevalence of PFD [8, 137, 162-163]. White women are considered more prone to develop prolapse and UI. This point confers extra strength to our study, by giving robust information on the magnitude of PFD prevalence in a nulliparous Caucasian population, without confounding interracial factors. Additionally, all participants were delivered in the same hospital using similar obstetric approaches and protocols, what excludes a possible obstetric management confounder. More than a quarter of participants attended for clinical follow up to confirm the questionnaire based findings. In the present study data regarding pelvic floor status were collected in early first pregnancy and at one year postnatally. By

comparing these findings the real impact of childbearing on pelvic floor morbidity could be estimated and help to elucidate the natural history PFD.

Limitations:

This was an opportunistic study using the SCOPE Ireland cohort study. A power calculation could not be performed as a result. Although the majority of previous PFD studies have a similar number of participants (≈800-1500 in average) to the present study, the present project demonstrated that in some cases our numbers were not large enough to achieve adequate statistical power. Particularly this was seen in the second paper, when assessing the effect of the mode of delivery on worsening of some particular persistent symptoms postnatally. However, this could guide future studies on sample size planning and power calculation.

Another limitation is the high attrition rate. It may appear at a glance that the clinical follow up of 4P-Study was attended only by 8.5% (202) of participants from the total number of recruited for the SCOPE Ireland study (2579). However it is necessary to mention that the two studies were not connected and simply shared the same cohort of participants. From those recruited for the 4P-Study (1484) the final clinical follow up was attended by 13.6% (202), or 23% from those eligible - who completed the prepregnancy and postnatal questionnaire and constituted the core of the study. Such a low figure can be explained by the fact that 26% (394) of participants were already pregnant in their next pregnancy and another 28% (424) did not answer the second questionnaire, making them ineligible for clinical follow up. This is always a risk in attempting to survey women within the first year of childbirth.

The SCOPE cohort, which is likely to be representative for the entire population (discussed in the limitations section of paper 1), was used as a benchmark to compare with the demographic characteristics of the 4P-Study participants at different research stages. The difference in demographic characteristics between SCOPE Ireland and 4P-study participants never exceeded 3% (Table 6.1), which demonstrates that even the smallest group of 202 participants who attended the clinical follow up study had similar characteristics to the participants from the SCOPE study and accordingly with the entire population. Albeit, it is important to mention that in the final stages the attrition rate within the 4P-Study was quite high and the final obtained data may not be representative to the entire population. The Australian Pelvic Floor Questionnaire is a comprehensive tool for the assessment of PFD, however some of its questions are not very well focussed. Additionally, its symptom's severity grading system is suboptimal for differentiating mild pathology from symptoms occurring occasionally. Grade one severity (mild), is asking if the symptom is present less than once a week and this could result in a large spectrum of interpretations. Although the International Continence Society does not specify the frequency of symptoms while defining incontinence, many researchers would report only symptoms occurring once a month or less as presence of disease. However despite this limitation, our findings are in line with previous studies. Also participants completed prenatal questionnaires in early pregnancy, where there is a potential for confusion reporting prepregnancy symptoms incorrectly. However, this issue was dealt with and it was demonstrated in the first and second studies that the chance of recall bias is minimal. It has been shown previously that remembering an important health event is not prone to be affected by recall bias[138]. Additionally, it is worth mentioning that this is a common limitation in observational research. Another limitation is the fact that patients were not clinically examined at recruitment to verify

questionnaire findings, since symptoms from different compartments may coexist and overlap. Also, it should be acknowledged that it is not possible to exclude that some risk factors did not reach statistical significance in the multivariate logistic regression models due to the limited number of observations for some outcomes, as well as the fact that some risk factors could become significant due to chance, considering that so many risk factors were included in the analysis simultaneously.

Chapter 8

Conclusion

This research project confirmed the previously reported high prevalence of PFD in nulliparous women. Additionally, it has shown that there is a larger spectrum of symptoms than those reported previously in women who have not yet embarked on their first pregnancy. Up to a quarter of these women had bothersome symptoms. The most common symptoms were urinary and faecal urgency and frequency, incomplete bladder and bowel evacuation, weak stream, UI, defaecation straining, constipation, vaginal heaviness and dyspareunia. The majority of nulliparous women with PFD had multicompartment involvement. Sometimes symptoms from different compartments may overlap with a potential of misdiagnosis. For this reason a comprehensive investigation of PFD is required, in order to identify and treat the real causative factor. The majority of prepregnancy symptoms persisted postnatally, however only 10 to 15 percent of them worsened as a result of first childbirth. The main damage to the pelvic floor was probably done before the first pregnancy and can be attributed to intrinsic pelvic floor weakness. The group of patients with Prepregnancy Persistent PFD (PPFD) had a higher prevalence of severe and bothersome symptoms compared to Denovo postnatal onset PFD (DNPFD). In the logistic regression models CS delivery seemed to have a higher protective effect on preventing postnatal worsening of prepregnancy symptoms compared to DNPFD. Interestingly, this finding had a higher magnitude in the case of OAB compared to SUI. Vaginal delivery, including instrumental, did not increase the risk of PFD, apart from prolapse section, which was mostly affected by forceps delivery. In contrast to vaginal delivery, CS delivery was protective for all types of PFD.

POP was an extremely common finding in the present study. On POP-Q assessment some degree of POP was present in 90% of participants who attended for clinical follow up, with no cases of prolapse bigger than grade 2 and very few only being symptomatic. The majority of participants with POP had multicompartment involvement in different

combinations. Although POP-Q is a very comprehensive classification system, it does not define clinically meaningful prolapse and a revision from this point of view would be very welcome by practicing clinicians. There was a significant association between uterine prolapse and high collagen type III levels. The same association was obtained for presence of family history for a set of collagen related medical conditions, as well as with joint hypermobility. All these findings are very suggestive of congenital contribution to the aetiology of POP and could lead to development of prevention strategies. CS delivery seems to be protective for development of cystocele and rectocele, but not for uterine prolapse.

3D-Transperineal scan is a very efficient and novel methodology in detecting pelvic floor trauma. Some degree of LAM trauma was detected in 1:3 women after the first childbearing. A complete LAM avulsion was diagnosed in 1:6 participants, most commonly on the right side. LAM trauma was associated with POP presence and POP related symptoms. Also it was positively associated with forceps delivery and its risk being reduced by CS. No statistically significant link was found between LAM trauma and family history of collagen disease, and collagen levels.

Recommendations for future research:

This study could potentially have a big impact on future PFD research in nulliparous women. To our knowledge, this is the first study comprehensively describing PFD in all four compartments, specifically in nulliparous women. The prevalence findings could well contribute to the planning of future studies investigating various symptoms of PFD before and after first childbearing. A research group have already contacted us after the first publications to inquire about additional details, in order to design their study.

In the present work for the first time it was outlined that more than half of postnatal PFD in primiparous women has a prepregnancy origin, while the first childbearing has a negative impact on 15% of cases only of persistent PFD. These patients should be the main target population for future research, since this is the group where the most significant protection from CS could be expected. The present study was suggestive of this, however the sample size was too small to achieve statistical significance and to investigate characteristics specifically of these women. LAM trauma is a potential confounder for appearance of prolapse symptoms and this should be taken in consideration in the future. Additionally, the potential protective effect of CS delivery on persistent OAB, and development of cystocele and rectocele, needs confirmation in future research and could potentially outline the group of patients who can benefit from it.

APPENDICES

APPENDIX I: INTRODUCTION (CHAPTER 1) TABLES

Abbreviations used in Appendix I

UD – urinary dysfunction
FD – faecal dysfunction
POP – pelvic organ prolapse
SD – sexual dysfunction
UI – urinary incontinence
SUI - stress urinary incontinence
UUI – urge urinary incontinence
FI – faecal incontinence
VD – vaginal delivery
CS – Caesarean section

Table A-1.1: Summary of the studies which investigated the prevalence and risk factors for various types of PFD before and after first pregnancy (continues over 6 pages)

Author and date	Sample Size (N)	Reported data classified by parity	Types of PFD reported	Summary of findings
MacLennan, A.H., et al. (2000[6])	3010	Yes	UD FD POP SD	Pelvic floor disorders are strongly associated with female gender, ageing, pregnancy, parity and instrumental delivery. Caesarean section (CS) vs. vaginal delivery (VD) does not offer significant reduction in long term pelvic floor morbidity.
Hendrix, S. L., A. Clark, et al. (2002[8]).	27,432	No	POP	The prevalence of POP in WHI study is as following: uterine prolapse - 14.2%; cystocele - 34.3%; rectocele - 18.6%. Black women have the lowest risk for POP. Hispanic women have the highest risk for uterine prolapse. Parity and obesity are strongly associated with increased risk for uterine prolapse, cystocele, and rectocele

Casey, B. M., J. I. Schaffer, et al. (2005[10])	3887	Yes	UD	The PFD at 7 months after delivery is greater in women who: received oxytocin, had a forceps delivery, had an infant weighing >4000 g. or who had an episiotomy performed. CS is partially protective for urge and stress UI.
Skoner, M.M., W.D. Thompson, and V.A. Caron (1994[11])	140	No	UD	Main risk factors for stress urinary incontinence (SUI) are VD, episiotomy or tear during delivery (3.78-fold increase), family history of similar condition and multiple urinary tract infections. High parity (four or greater) is not a strong predictor
Buchsbaum, G. M., M. Chin, et al. (2002[48])	149	Yes	UD	Among assessed nulliparous nuns 30% had SUI, 24% UUI, 35% mixed UI, and 11% had urine loss unrelated to stress and urge. Significant risk factors (RFs) for UI were BMI, multiple urinary tract infections, and depression. Childbirth does not seem to be the only most significant RF for presence of urinary symptoms.
Whitehead WE, Borrud L, Goode PS, et al. (2009[53])	2229	No	FD	FD prevalence is 8.3% of which 6.2% is liquid stool,1.6% -, solid stool and 3.1% mucus. Prevalence increases from 2.6% in 20 to 29 year olds up to 15.3% in 70 years and older. FI is significantly associated with advancing age, loose or watery stools and urinary incontinence. Chronic diarrhea is a strong modifiable risk factor.
Swift, S. (2005[55]).	Review	No	POP	In some epidemiological studies up 80-90% of women have prolapse grade I to II on POP-Q assessment.
Uustal Fornell, E., G. Wingren, et al. (2004[67]).	1340	No	UD FD POP	Women with UD are similarly likely to suffer from FD and POP and vice versa. Other associated factors for PFD were obesity, chronic bronchitis, VD and multiparity, age, heredity and diseases suggestive of collagen disorders.
Rortveit, G., Y. S. Hannestad, et al. (2001[68]).	27,900	Yes	UD	Urinary incontinence (UI) was reported by 25% of participants. Prevalences among nulliparous women ranged from 8% to 32%, increasing with age. Only stress and mixed types of incontinence are associated with parity. All effects of parity seem to disappear in older age.
Nygaard, I., et al. (2008[69])	396	Yes	UD FD POP	Prevalence of PFD in nullips is 12.8%, UI 6.5%, faecal incontinence (FI) 6.3%, prolapse 0.6%

O'Halloran, T., et al., (2012[70])	1,002	Yes	UD	The rate of any UI in nulligravid women is 12.6%, incontinence being slightly more common in students 13.2%, with highest rates in students who are sexually active and using combined oral contraception 21.5% .
Fonti Y, et al. (2009[71])	Review	No	PFD	Transitory postnatal pelvic floor changes may persist up to 6 months postnatally or even more.
Chan, S.S., et al. (2012[72])	388	Yes	UD FD	The prevalence of SUI, urge urinary incontinence (UUI), and FI were 25.9 %, 8.2 %, and 4.0 %, respectively, 12 months after delivery. VD, antenatal SUI, and UUI were associated with SUI; antenatal UUI and increasing maternal BMI at the first trimester were associated with UUI. Antenatal FI was associated with FI. Pregnancy, regardless of route of delivery and obstetric practice, had an effect on UI and FI.
Torrisi, G., G. Minini, et al. (2012[73])	744	Yes	UD FD SD	At 3 months postpartum the prevalence of UI is 21.6%, of FI-4.3% (3.2% - liquid; 1.1% solid incontinence), of flatal incontinence 12%, New onset of UI or FI during pregnancy, positive family history and VD are independent risk factors for the persistence of symptoms of UI and FI in the early postpartum period. The sexual score improves in majority 3 months after delivery.
Borello-France, D., et al. (2006[74])	834	Yes	UD FD	In women delivered by CS, UI was reported in 22.9%, whereas FI in 7.6% at six months postpartum.
Fritel, X., V. Ringa, et al. (2012[75]).	Review	Yes	UD	CS is associated with a lower rate of postpartum SUI and less need for surgical correction of SUI later in life. Nevertheless, it is difficult to postulate this association as causal.
Brown, S. J., S. Donath, et al. (2010[76])	1,507	Yes	UD	Prevalence of UI before the index pregnancy was 10.8% increasing to 55.9% in the third trimester. SUI (36.9%) and mixed incontinence (MUI) (13.1%) were more common during pregnancy than urge incontinence (UI) alone (5.9%). UI before pregnancy was associated with childhood enuresis higher maternal and previous miscarriages or terminations. Occasional leakage (<1/ month) before pregnancy is the strongest predictor of UI in pregnancy (OR = 3.6, 95% CI 2.8-4.7).

Gartland, D., S. Donath, et al. (2012[77]).	1507	Yes	UD	Persistent UI at 9 months postanatlly has a prevalence of 25% . It is associated with presence of symptoms in pregnancy, prolonged labour in combination with operative vaginal birth.
Svare, J. A., B. B. Hansen, et al. (2014[78])	575	Yes	UD	UI at one year after the first VD is strongly associated with UI during the pregnancy and inversely associated with oxytocin augmentation.
Ekstrom, A., D. Altman, et al. (2008[79])	435	Yes	UD	A history of SUI before pregnancy (OR 5.2, 95% CI 1.5-19) and at 3 months follow-up (OR 3.9, 95% CI 1.7-8.5) is independent predictors for SUI at 9 months follow-up. VD is associated with an increased risk for lower urinary tract symptoms 9 months after childbirth when compared to elective CS.
Laine K, Skjeldestad FE (2013[80])	2846	Yes	FD	The lowest prevalence of FI was after a previous CS only (6.4%). The highest - after previous delivery complicated by obstetric anal sphincter injury (24.4%). The prevalence of FI in nulliparous women was 7.7%, being associated to low educational level and comorbidity. Other RFS were increased with increasing parity and UI which was associated with anal incontinence in all parity groups.
Brincat, C., C. Lewicky-Gaupp, et al. (2009[81])	240	Yes	FD	The prevalence of faecal incontinence at 12months postpartum is 5.4%
Murad-Regadas, S. M. et al. (2009[82])	105	Yes	FD POP	Presence of obstructed defaecation due to: intussusception, anismus, sigmoidocele and enterocele is not influenced by parity (including nulliparity) or mode of delivery.
Dietz, H.P. and K.P. Mann (2014[83])	764	No	POP	ICS POP-Q staging system requires revision. Stage 1 prolapse of the anterior and posterior vaginal wall should probably be regarded as normal. Stage 1 uterine prolapse as currently defined seems highly relevant.
Larsen, W.I. and Yavorek, T.A. (2006[84])	144	Yes	UD POP	Fifty percent of participants had stage I or II POP, 19% reporting incontinence. Incontinence was associated running, and no risk factors were identified for prolapse. Prolapse stage I and II represents normal support.

Buchsbaum GM, Duecy EE. (2006[85])	101 parous 101 nullips	Yes	POP	There is a 74.3% to 91.1% concordance by compartment in prolapse stage within nulliaprous and parous sister pairs. This high concordance of POP stages suggests a familial predisposition toward developing this condition. However, a more advanced risk POP is associated with VD.
Buchsbaum GM, Duecy EE. (2008[86])	101 parous 101 nullips	Yes	UD POP	All identical twins had identical continence status and pelvic support in all three compartments, regardless of mode of delivery or difference in parity.
Shaw, C. (2002[87])	systematic review	No	SD	The reported prevalence of SD in general population varies between 0.6%-64%. Coital incontinence has a prevalence of 2% in community samples and 10% to 56% in clinical settings.
Stones, R.W. et al. (2006[88])	3,150	No	SD	Prevalence of dyspareunia in Chinese population is 4.7%. Dyspareunia is strongly associated with urinary symptoms, particularly in those with combined urinary urge and incontinence (26.8%). Dyspareunia is associated with early sexual debut, primary level of education, and membership of minority ethnic communities
Bellelis, P., J. A. Dias, Jr., et al. (2010[89])	892	Yes	SD	Chronic pelvic pain is the most prevalent symptom (56.8%) of endometriosis, followed by deep dyspareunia (57.4%). The majority (56.5%) of patients with endometriosis are nulliparous.
Pastor, Z. (2013[90])	systematic review	No	SD	The reported prevalence of coital incontinence is 0.2-66%. It is usually caused by SUI. Urodynamic diagnoses of detrusor overactivity and SUI are observed in orgasmic incontinence.
Hosseini, L., E. Iran-Pour, et al. (2012[91])	114 VD 99 CS	Yes	SD	Two years postpartum there are no significant SD differences between women having CS and VD. This includes: desire, arousal, lubrication, orgasm, pain, and satisfaction. However to note, 80% of women having VD reported vaginal laxity.
Klein, K., C. Worda, et al. (2009[92])	55 44 controls	Yes	SD	Sexual function does not significantly differ at 12-18 months postnatally between women who had VD without episiotomy, heavy perineal laceration, or secondary operative interventions and women having elective CS

Connolly, A., J. Thorp, et al. (2005[93]).	150	Yes	SD	At 6 months postpartum 90% of the women had resumed intercourse, 17% of women reported dyspareunia; less than 5% described the pain as major, 61% of women reported orgasm. Delivery mode and episiotomy were not associated with intercourse resumption or anorgasmia; dyspareunia was only associated with breast-feeding at 12 weeks (RR = 3.36, 95% CI = 1.77-6.37). Sexual function was described as similar to or improved over that prior to pregnancy.
van Brummen, H.J., et al (2006[94])	524	No	SD	Sexual satisfaction does not seem to be associated with antenatal and intrapartum factors. Sexual dissatisfaction at 1 year postpartum was related to sexuall activity in early pregnancy.
Zorn, B. H., H. Montgomery, et al. (1999[95])	115 UI 80 controls	N/A	UD	There is a strong association between depression and UI, where linking factor may be altered serotonin function. This may help explaining the efficacy of serotonergic antidepressants in the treatment of urge incontinence.
Abramov, Y., P. K. Sand, et al. (2005[96])	271	No	FD	Age, menopause, obesity, parity, and stress urinary incontinence are the major risk factors for female anal incontinence. Emergency CS after initiation of labor is associated with a lower prevalence of anal incontinence, whereas no anal incontinence is noted in women who had only elective CSs.
Hojberg KE, Salvig JD, (2000[97])	1726	No	FD	The general prevalence of FI is 8.6%, including: liquid FI 2.3% solid FI 0.6%, flatus incontinence at least once a week - 4.2%. The latter is associated with age > 35 years, previous lower abdominal or urological surgery, anal sphincter tear, birth weight > 4kg and episiotomy. Increasing parity, spontaneous perineal tear were not associated.
Rinne, K. M. and P. P. Kirkinen (1999[98])	85	No	POP	POP is associated with parity, foetal birth weight, operations of abdominal hernias and also had more chronic pulmonary disease, e.g. asthma However, POP is not associated with instrumental and preterm deliveries. About 30%. of patients with POP have familial history of similar condition.
Sze, E.H. and G. Hobbs (2012[99])	101 164 controls	Yes	POP	Vaginal birth has little effect on the pelvic support changes beyond the puerperium while menopause predisposes women to POP outside the hymen.

Table A-1.2: Summary of the studies investigating anatomical changes of pelvic structures using transperineal ultrasound scan

(continues over 2 pages)

Author and date.	Sample Size (N)	Type of research	Investigated structure	Summary of findings
Toozs-Hobson P, Balmforth J, et al. (2008[13])	156	Risk factors	LAM hiatal area measurement Bladder neck mobility	Although VD is associated with more distensible levator hiatus and a greater degree of bladder neck mobility, these changes partially improve at 6 month compared to 6 weeks postnatally.
Shek, K. L. and H. P. Dietz (2010[41])	367	Risk factors	LAM avulsion	Vaginal delivery, forceps and a longer second stage increase the riskof levator trauma. Epidural pain relief may exert a protective effect.
Dietz, H. P. and O. Lekskulchai (2007[42])	735	Methodology & Reliability confirmation	POP quantification	Descent of the bladder on transperineal scan to > or = 10 mm and of the rectum to > or = 15 mm below the symphysis pubis are strongly associated with symptoms, and can be used as cut-offs for the diagnosis of significant prolapse.
Dietz, H. P., C. Shek, et al. (2008[45]).	544	Methodology	LAM distensibility detection	A hiatal area of > 25 cm^2 on Valsalva is defined as abnormal distensibility or 'ballooning' of the levator hiatus.
Zhuang, R.R., et al (2011[100])	69	Reliability confirmation	LAM avulsion	Both MRI and 3D Tomographic perineal scan are reliable methods to assess LAM avulsion with good correlation between methods.
Dietz, H.P., A. Abbu, and K.L. Shek (2008[101])	118	Methodology & Reliability Confirmation	LAM avulsion detection	Levator-urethral gap is a reproducible measurement and strongly associated with LAM avulsion trauma diagnosed on vaginal palpation. A cut-off of 25 mm may be used for the diagnosis of levator avulsion injury.
Dietz, H.P., et al. (2011[102])	736	Methodology	LAM avulsion detection	Abnormality in three central slices on tomographic ultrasound is diagnostic for complete avulsion of the puborectalis muscle.

Choi, S., S. S. Chan, et al. (2013[103])	27	Methodology & Reliability Confirmation	Subpubic arch angle	3DTUS is a reliable method to measure subpubic arch angle with satisfactory intra/inter operator repeatability and reproducibility.
Braekken, I. H., M. Majida, et al. (2008[104]).	17	Reliability confirmation	LAM hiatal area measurement LAM thickness Bladder neck mobility	Perineal ultrasound is a reliable method for quantification of morphology and function of the pelvic floor structures.
Adisuroso, T., K. L. Shek, et al. (2012[105])	497	Reliability confirmation	LAM avulsion	The published methodology of minimal criteria for diagnosis of LAM avulsion is sufficiently robust for clinical practice and highly unlikely to cause false-positive diagnosis.
Dietz HP (2013[106])	Review		LAM avulsion	The reported prevalence of LAM avulsion in primiparous women is 12-36%
Albrich, S. B., R. M. Laterza, et al. (2012[107])	157	Risk factors	LAM avulsion	The risk of levator defect after vaginal delivery is >7 times higher than after caesarean section. However, emergency caesarean section do not completely prevent LAM trauma.
Valsky, D. V., M. Lipschuetz, et al. (2009[108]).	210	Prevalence & Risk factors	LAM avulsion	The prevalence of LAM trauma inprimiparas was 18.8%. The main risk factors were large foetal head circumference and long second stage of labour.
Shek, K. L., V. Chantarasorn, et al. (2012[109])	488	Clinical follow up	LAM avulsion LAM distensibility detection	On comparing imaging data obtained at 3-6 months and 2-3 years postpartum there is no evidence of regression or healing of childbearing related changes to levator distensibility. However, it was documented anatomical improvement in two women diagnosed with levator avulsion at 3-6 months postpartum.

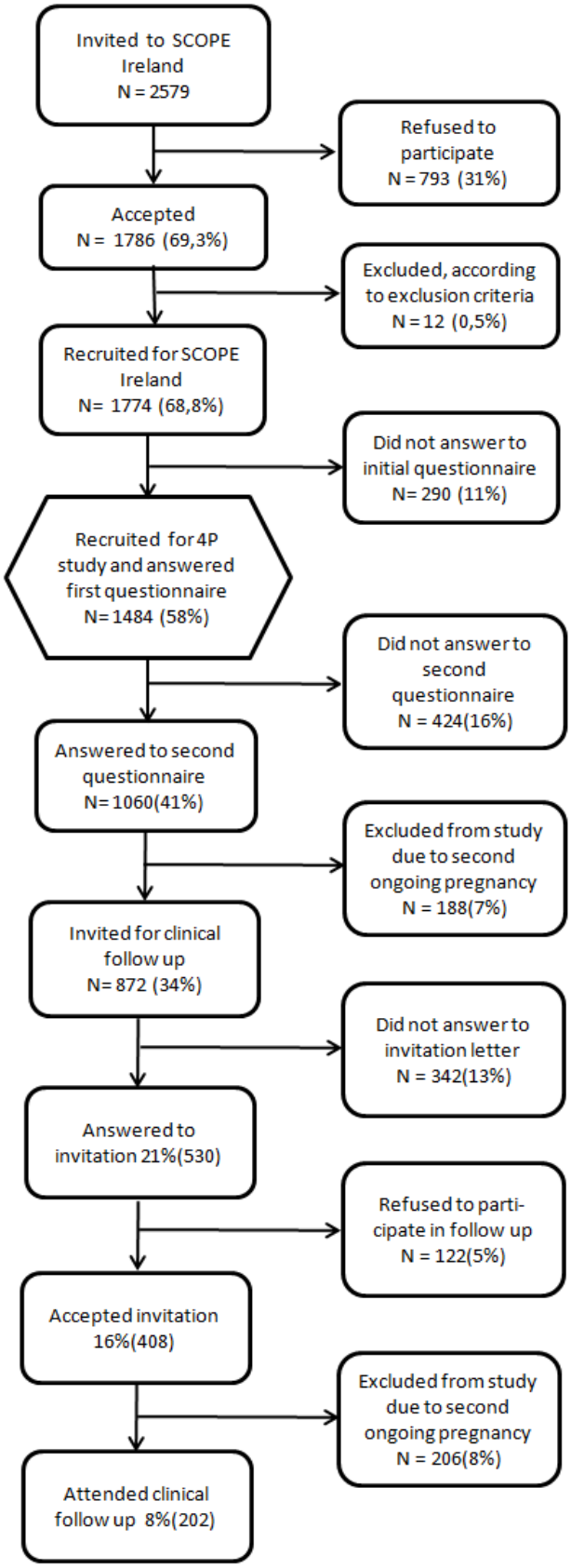
Table A-1.3: Summary of the studies which investigated the association between pelvic organ prolapse and collagen abnormalities

(continues over 2 pages)

Author and date.	Sample Size (N)	Results significance	Sampling side	Summary of findings
Jackson, S. R., N. C. Avery, et al. (1996[18])	Not available	Significant	vaginal epithelium	POP is associated with a reduction in total collagen content. Collagen turnover is up to four times higher in prolapse tissue. Collagen-type ratios, is similar in both groups. Increased collagenolytic activity causes loss of collagen from prolapse tissue.
Keane, D. P., T. J. Sims, et al.(1997[20])	36 SUI 25 Controls	Significant	periurethral Tissue	There is significantly less collagen in the tissues of nulliparous women with SUI. In addition, there was a decreased ratio of type I to type III collagen.
Edwall, L., K. Carlstrom, et al (2008[21])	48 POP 28 controls	Significant	urogenital tissue	In women with POP there is higher tissue concentrations of PICP (procollagen type I carboxyterminal) and especially PIIINP (procollagen type III aminoterminal), suggesting an increased collagen breakdown in POP. There is a different pattern in case of SUI without POP, where tissue levels of collagen turnover markers are low, indicating reduced collagen breakdown.
Knuuti, E., S. Kauppila, et al. (2011[46])	43	Significant	blood serum	Recurrent genital prolapse is more common in women with joint hypermobility as compared to normal mobility. Plain hypermobility is associated with higher concentrations for PICP, whereas combination of recurrent prolapse and joint hypermobility with PIIINP.
Ewies, A. A., F. Al-Azzawi, et al. (2003[110])	25 POP 25 controls	Significant	cardinal ligaments	In women with prolpase there is higher expression of collagen III and tenascin, and lower quantities of elastin. Collagen I expression is directly related to the age and menopausal status rather than to prolapse. In contrast collagen III expression is directly related to the presence of POP rather than age or menopausal status and is suppressed with the use of HRT.

Gabriel, B., D. Denschlag, et al. (2005[111])	25 POP 16 controls	Significant	uterosacral ligaments	In women with POP there is no difference in collagen I expression as compared to those without POP, whereas the collagen III expression was significantly related to the presence of POP rather than age or parity. The higher collagen III expression might be a typical characteristic of POP patients' connective tissue.
Lauer-Fields JL, Juska D, (2002[112])	Review	N/A	Conjunctive tissue	The matrix metalloproteinase (MMP) is implicated in tissue remodeling in different diseases associated with abnormal turnover of extracellular matrix components. Substrate flexibility, MMP active sites, and MMP exosites all contribute to collagen degradation.
Skorupski P, Jankiewicz K, (2013[113])	132	Significant	Blood PCR gene polymorphism assessment	A combination of effects of MMP-1 and -MMP-3 may play a role in the development of POP.
Friedman, D. W., C. D. Boyd, et al. (1993[114]).	9 inguinal hernia 15 controls	Significant	skin fibroblasts	A constitutive and systemic increase in type III collagen synthesis may result in reduced collagen fibril assembly in the abdominal wall, eventually leading to the development of herniation
Strohbehn, K., J. A. Jakary, et al. (1997[115])	647	Significant	N/A	Younger women with POP compared to older once have higher than expected prevalence of congenital anomalies, as well as rheumatologic and neurologic diseases.
Lammers, K., S. L. Lince, et al. (2012[116])	110 POP 110 controls	Significant	N/A	Patients with POP have a higher prevalence of varicose veins, joint hypermobility, rectal prolapse and family members with POP as compared to the controls. POP and other collagen-associated disorders may have a common aetiology, being related to the levels of the collagens.

Appendix II: STARD flowchart indicating recruited numbers



Appendix III: Prepregnancy Australian Pelvic Floor Questionnaire (Page1)

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SCOPE IRELAND FEMALE PELVIC FLOOR QUESTIONNAIRE

All these questions pertain to the period BEFORE you were pregnant

Bladder section ***Q 1-14*** ***Score ____/ 42 = _____***

Urinary frequency How many times do you pass urine in the day? 0 up to 7 1 between 8-10 2 between 11-15 3 more than 15	**Nocturia** How many times do you get up at night to pass urine? 0 0-1 1 2 2 3 3 more than 3 times	**Nocturnal enuresis** Do you wet the bed before you wake up? 0 never 1 occasionally - less than 1/week 2 frequently –once or more/week 3 always – every night
Urgency Do you need to rush/hurry to pass urine when you get the urge? 0 never 1 occasionally – < 1/week 2 frequently -> 1/week 3 daily	**Urge incontinence** Does urine leak when you rush/hurry to the toilet/Can you make it in time? 0 never 1 occasionally – < 1/week 2 frequently -> 1/week 3 daily	**Stress incontinence** Do you leak with coughing, sneezing, laughing, exercising? 0 never 1 occasionally – < 1/week 2 frequently -> 1/week 3 daily
Weak stream Is your urinary stream/flow weak/prolonged/slow? 0 never 1 occasionally – < 1/week 2 frequently -> 1/week 3 daily	**Incomplete bladder emptying** Do you have a feeling of incomplete bladder emptying? 0 never 1 occasionally – < 1/week 2 frequently -> 1/week 3 daily	**Strain to empty** Do you need to strain to empty your bladder? 0 never 1 occasionally – < 1/week 2 frequently -> 1/week 3 daily
Pad usage Do you have to wear pads? 0 none - never 1 as a precaution 2 with exercise/during a cold 3 daily	**Reduced fluid intake** Do you limit your fluid intake to decrease leakage? 0 never 1 before going out/socially 2 moderately 3 daily	**Recurrent UTI** Do have frequent bladder infections? 0 no 1 1-3/year 2 4-12/year 3 > 1/month
Dysuria Do you have pain in your bladder/urethra when you empty your bladder? 0 never 1 occasionally – < 1/week 2 frequently -> 1/week 3 daily	**Impact on social life** Does urine leakage affect your routine activities (recreation, shopping etc.) 0 not at all 1 slightly 2 moderately 3 greatly	**How much of a bother** is your bladder problem to you? 0 no problem 1 slightly 2 moderately 3 greatly
Other symptoms (haematuria, pain etc.)		

Bowel Section ***Q15-26*** ***Score _____/ 36 = _____***

Defaecation frequency How often do you usually open your bowels? 2 < 1/week 1 < every 3 days 0 > 3/week or daily 0 > more than 1/day	**Consistency of bowel motion** How is the consistency of your usual stool? 0 soft 0 firm 1 hard / pebbles 2 watery 1 variable	**Defaecation straining** Do you have to strain a lot to empty your bowels? 0 never 1 occasionally – < 1/week 2 frequently -> 1/week 3 daily
Laxative use: Do you use laxatives to empty your bowels? 0 never 1 occasionally – < 1/week 2 frequently -> 1/week 3 daily	**Do you feel constipated?** 0 never 1 occasionally – < 1/week 2 frequently -> 1/week 3 daily	**Flatus incontinence** When you get wind/flatus, can you control it or does wind leak? 0 never 1 occasionally – < 1/week 2 frequently -> 1/week 3 daily
Faecal urgency Do you get an overwhelming sense of urgency to empty bowels? 0 never 1 occasionally – < 1/week 2 frequently -> 1/week 3 daily	**Faecal incontinence with diarrhoea** Do you leak watery stool when you don't mean to? 0 never 1 occasionally – < 1/week 2 frequently -> 1/week 3 daily	**Faecal inc. with normal stool** Do you leak normal stool when you don't mean to? 0 never 1 occasionally – < 1/week 2 frequently -> 1/week 3 daily

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Appendix III: Prepregnancy Australian Pelvic Floor Questionnaire (Page2)

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SCOPE IRELAND FEMALE PELVIC FLOOR QUESTIONNAIRE

Incomplete bowel evacuation Do have the feeling of incomplete bowel emptying? 0 never 1 occasionally – < 1/week 2 frequently -> 1/week 3 daily	**Obstructed defecation** Do you use finger pressure to help empty your bowel? 0 never 1 occasionally – < 1/week 2 frequently -≥ 1/week 3 daily	**How much of a bother** is your bowel problem to you? 0 no problem 1 slightly 2 moderately 3 greatly
Other symptoms (pain, mucous discharge, rectal prolapse etc.)		

Prolapse section Q27 –31 ***Score _____ / 15 = _____***

Prolapse sensation Do you get a sensation of tissue protrusion in your vagina/lump/bulging? 0 never 1 occasionally – < 1/week 2 frequently -≥ 1/week 3 daily	**Vaginal pressure or heaviness** Do you experience vag. pressure/ heaviness/dragging sensation? 0 never 1 occasionally – < 1/week 2 frequently -≥ 1/week 3 daily	**Prolapse reduction to void** Do you have to push back your prolapse in order to void? 0 never 1 occasionally – < 1/week 2 frequently -≥ 1/week 3 daily
Prolapse reduction to defaecate Do you have to push back your prolapse to empty your bowels? 0 never 1 occasionally – < 1/week 2 frequently -≥ 1/week 3 daily	**How much of a bother** is the prolapse to you? 0 no problem 1 slightly 2 moderately 3 greatly	
Other symptoms (problems sitting/walking, pain, vag. bleeding)		

Sexual function Section Q 32 – ***Score ____ / 19***

Sexually active? Are you sexually active? no < 1/week ≥ 1/week most days / daily	**If NOT, why not:** no partner partner unable vaginal dryness too painful Prolapse embarrassment Prolapse } 19 other	**Sufficient lubrication** Do you have sufficient lubrication during intercourse? 1 no 0 yes
During intercourse vaginal sensation is: 3 none 3 painful 1 minimal 0 normal / pleasant	**Vaginal laxity** Do you feel that your vagina is too loose or lax? 0 never 1 occasionally 2 frequently 3 always	**Vaginal tightness/vaginismus** Do you feel that your vagina is too tight? 0 never 1 occasionally 2 frequently 3 always
Dyspareunia Do you experience pain with intercourse: 0 never 1 occasionally 2 frequently 3 always	**Dyspareunia where** Where does the pain occur no pain at the entrance of the vagina deep inside/ in the pelvis both	**Coital incontinence** Do you leak urine during sex? 0 never 1 occasionally 2 frequently 3 always
How much of a bother are these sexual issues to you? Not applicable 0 no problem at all 1 slight problem 2 moderate problem 3 great problem	**Other symptoms** (coital flatus or faecal incontinence, vaginismus etc.)	

TOTAL Pelvic floor Dysfunction SCORE:_____

2

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Appendix IV: Postnatal Australian Pelvic Floor Questionnaire (Page1)

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SCOPE IRELAND FEMALE PELVIC FLOOR QUESTIONNAIRE

SCOPE ID Number: _____ *Date:* ____/____/____

This questionnaire pertains to the period approximately 12 month after the birth of your baby.

Are you currently pregnant? YES / NO. If YES how many weeks? _____

Bladder section ***Q 1-14*** ***Score*** ____/ *42* = _____

Urinary frequency How many times do you pass urine in the day? 0 up to 7 1 between 8-10 2 between 11-15 3 more than 15	**Nocturia** How many times do you get up at night to pass urine? 0 0-1 1 2 2 3 3 more than 3 times	**Nocturnal enuresis** Do you wet the bed before you wake up? 0 never 1 occasionally - less than 1/week 2 frequently –once or more/week 3 always – every night
Urgency Do you need to rush/hurry to pass urine when you get the urge? 0 never 1 occasionally – < 1/week 2 frequently -≥ 1/week 3 daily	**Urge incontinence** Does urine leak when you rush/hurry to the toilet/Can you make it in time? 0 never 1 occasionally – < 1/week 2 frequently -≥ 1/week 3 daily	**Stress incontinence** Do you leak with coughing, sneezing, laughing, exercising? 0 never 1 occasionally – < 1/week 2 frequently -≥ 1/week 3 daily
Weak stream Is your urinary stream/flow weak/prolonged/slow? 0 never 1 occasionally – < 1/week 2 frequently -≥ 1/week 3 daily	**Incomplete bladder emptying** Do you have a feeling of incomplete bladder emptying? 0 never 1 occasionally – < 1/week 2 frequently -≥ 1/week 3 daily	**Strain to empty** Do you need to strain to empty your bladder? 0 never 1 occasionally – < 1/week 2 frequently -≥ 1/week 3 daily
Pad usage Do you have to wear pads? 0 none - never 1 as a precaution 2 with exercise/during a cold 3 daily	**Reduced fluid intake** Do you limit your fluid intake to decrease leakage? 0 never 1 before going out/socially 2 moderately 3 daily	**Recurrent UTI** Do you have frequent bladder infections? 0 no 1 1-3/year 2 4-12/year 3 > 1/month
Dysuria Do you have pain in your bladder/urethra when you empty your bladder? 0 never 1 occasionally – < 1/week 2 frequently -≥ 1/week 3 daily	**Impact on social life** Does urine leakage affect your routine activities (recreation, shopping etc.) 0 not at all 1 slightly 2 moderately 3 greatly	**How much of a bother** is your bladder problem to you? 0 no problem 1 slightly 2 moderately 3 greatly
Other symptoms (haematuria, pain etc.)		

Bowel Section ***Q15-26*** ***Score*** ____/ *36* = ____

Defaecation frequency How often do you usually open your bowels? 2 < 1/week 1 < every 3 days 0 > 3/week or daily 0 > more than 1/day	**Consistency of bowel motion** How is the consistency of your usual stool? 0 soft 0 firm 1 hard / pebbles 2 watery 1 variable	**Defaecation straining** Do you have to strain a lot to empty your bowels? 0 never 1 occasionally – < 1/week 2 frequently -≥ 1/week 3 daily
Laxative use: Do you use laxatives to empty your bowels? 0 never 1 occasionally – < 1/week 2 frequently -≥ 1/week 3 daily	**Do you feel constipated?** 0 never 1 occasionally – < 1/week 2 frequently -≥ 1/week 3 daily	**Flatus incontinence** When you get wind/flatus, can you control it or does wind leak? 0 never 1 occasionally – < 1/week 2 frequently -≥ 1/week 3 daily
Faecal urgency Do you get an overwhelming sense of urgency to empty bowels? 0 never 1 occasionally – < 1/week 2 frequently -> 1/week 3 daily	**Faecal incontinence with diarrhoea** Do you leak watery stool when you don't mean to? 0 never 1 occasionally – < 1/week 2 frequently -≥ 1/week 3 daily	**Faecal inc. with normal stool** Do you leak normal stool when you don't mean to? 0 never 1 occasionally – < 1/week 2 frequently -≥ 1/week 3 daily

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Appendix IV: Postnatal Australian Pelvic Floor Questionnaire (Page2)

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SCOPE IRELAND FEMALE PELVIC FLOOR QUESTIONNAIRE

Incomplete bowel evacuation Do have the feeling of incomplete bowel emptying? 0 never 1 occasionally – < 1/week 2 frequently -> 1/week 3 daily	**Obstructed defecation** Do you use finger pressure to help empty your bowel? 0 never 1 occasionally – < 1/week 2 frequently -≥ 1/week 3 daily	**How much of a bother** is your bowel problem to you? 0 no problem 1 slightly 2 moderately 3 greatly
Other symptoms (pain, mucous discharge, rectal prolapse etc.)		

Prolapse section ***Q27 –31*** ***Score _____ / 15 = _____***

Prolapse sensation Do you get a sensation of tissue protrusion in your vagina/lump/bulging? 0 never 1 occasionally – < 1/week 2 frequently -≥ 1/week 3 daily	**Vaginal pressure** or **heaviness** Do you experience vag. pressure/ heaviness/dragging sensation? 0 never 1 occasionally – < 1/week 2 frequently -≥ 1/week 3 daily	**Prolapse reduction to void** Do you have to push back your prolapse in order to void? 0 never 1 occasionally – < 1/week 2 frequently -≥ 1/week 3 daily
Prolapse reduction to defaecate Do you have to push back your prolapse to empty your bowels? 0 never 1 occasionally – < 1/week 2 frequently -≥ 1/week 3 daily	**How much of a bother** is the prolapse to you? 0 no problem 1 slightly 2 moderately 3 greatly	
Other symptoms (problems sitting/walking, pain, vag. bleeding)		

Sexual function Section Q 32 – ***Score ____ / 19***

Sexually active? Are you sexually active? no < 1/week ≥ 1/week most days / daily	**If NOT, why not:** no partner partner unable vaginal dryness too painful Prolapse embarrassment Prolapse other } 19	**Sufficient lubrication** Do you have sufficient lubrication during intercourse? 1 no 0 yes
During intercourse vaginal sensation is: 3 none 3 painful 1 minimal 0 normal / pleasant	**Vaginal laxity** Do you feel that your vagina is too loose or lax? 0 never 1 occasionally 2 frequently 3 always	**Vaginal tightness/vaginismus** Do you feel that your vagina is too tight? 0 never 1 occasionally 2 frequently 3 always
Dyspareunia Do you experience pain with intercourse: 0 never 1 occasionally 2 frequently 3 always	**Dyspareunia where** Where does the pain occur no pain at the entrance of the vagina deep inside/ in the pelvis both	**Coital incontinence** Do you leak urine during sex? 0 never 1 occasionally 2 frequently 3 always
How much of a bother are these sexual issues to you? Not applicable 0 no problem at all 1 slight problem 2 moderate problem 3 great problem	**Other symptoms** (coital flatus or faecal incontinence, vaginismus etc.)	

TOTAL Pelvic floor Dysfunction SCORE:_____

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Appendix V: Study 2 results not included in the article

An increase in postnatal prevalence of PFD was detected in all 4 sections of the questionnaire.

Table A - 5.1 Prepregnancy prevalence and postnatal change of urinary symptoms

	Prepregnancy		**Increase**	**Postnatally**	
	N	**%**		**N**	**%**
Urinary Frequency	192	26,5 %		147	20,2 %
Nocturia	112	15,5 %		65	8,9 %
Nocturnal enuresis	2	0.3 %		4	0.5 %
Urgency	294	40,6 %		357	49,0 %
Urge Incontinence	88	12,2 %	**x 2.5**	215	29,5 %
Stress Incontinence	135	18,7 %	**x 2.3**	321	44,0 %
Weak Stream	164	22,7 %		171	23,5 %
Incomplete Bladder Emptying	167	23,1 %		206	28,3 %
Strain to Empty	87	12,0 %		108	14,8 %
Pad Usage	46	6,4 %	**x 2.2**	102	14,0 %
Reduced Fluid Intake	33	4,6 %		44	6,0 %
Recurrent UTI	89	12,3 %		70	9,6 %
Dysuria	71	9,8 %		58	8,0 %
Impact on Social Life	32	4,4	**x 2**	61	8,4 %
Bladder - How much of a bother	73	10,1 %	**x 2**	149	20,4 %

Table A - 5.2 Prepregnancy prevalence and postnatal change of faecal symptoms

	Pre-Pregnancy			Postnatally	
	N	%		N	%
Defaecation Frequency	126	17,5	%	95	13,0 %
Consistency of Bowel Motion	374	51,9	%	369	50,6 %
Defaecation Straining	428	59,2	%	447	61,4 %
Laxative Use	56	7,7	%	53	7,3 %
Do You Feel Constipated	378	52,4	%	343	47,1 %
Flatus incontinence	276	38,3	%	330	45,3 %
Faecal Urgency	345	47,9	%	395	54,2 %
Faecal Incontinence with diarrhoea	31	4,3	%	57	7,8 %
Faecal Incontinence with normal stool	5	0.7	%	12	1,6 %
Incomplete Bowel Evacuation	308	42,6	%	307	42,4 %
Obstructed Defaecation	42	5,8	%	44	6,1 %
Bowel - How much of a bother	194	26,9	%	173	23,9 %

Table A - 5.3 Prepregnancy prevalence and postnatal change of sexual symptoms

	Prepregnancy		Increase	Postnatally	
	N	%		N	%
Sexually active < 1/week	218	29,9 %		6	0.8 %
Sexually active >= 1/week	412	56,4 %		321	44,0 %
Sexually active most days/daily	66	9,0 %		321	44,0 %
Sexually active / No	21	2,9 %		38	5,2 %
Sufficient lubrication	127	17,7 %		173	24,4 %
Abnormal vaginal sensation during intercourse	89	12,4 %	x 1.7	150	21,1 %
Vaginal Laxity	35	4,9 %	x 4.2	148	20,6 %
Vaginal tightness/vaginismus	187	26,2 %		209	29,1 %
Dyspareunia	230	32,1 %	x 1.3	305	42,7 %
Coital Incontinence	11	1,5 %	x 3.2	35	4,9 %
Sexual Function - How much of a bother	67	9,3 %	x 2.5	168	23,5 %

Table A - 5.4 Prepregnancy prevalence and postnatal change of prolapse symptoms

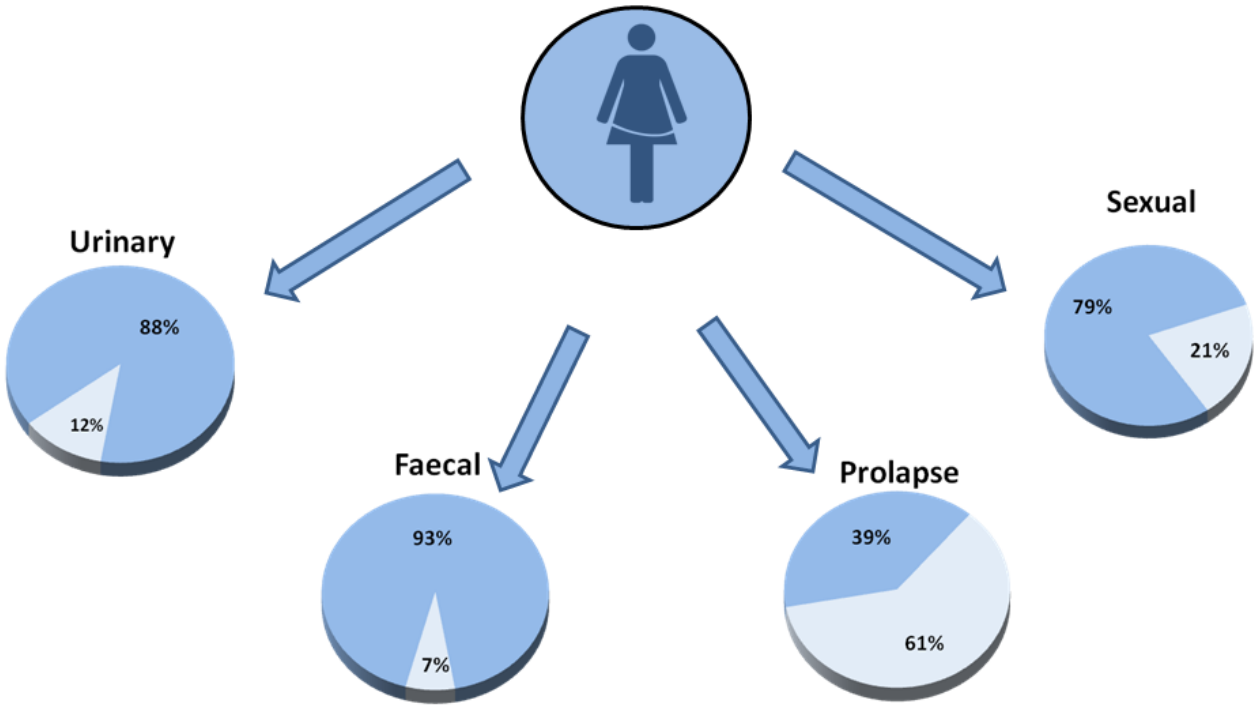
	Prepregnancy		Increase	Postnatally	
	N	%		N	%
Prolapse sensation	**8**	**1,1 %**	**x 6**	**47**	**6,5 %**
Vaginal Pressure or heaviness	**24**	**3,3 %**	**x 3.5**	**81**	**11,2 %**
Prolapse reduction to void	**3**	**0.4 %**	**x 4.5**	**13**	**1,8 %**
Prolapse reduction to defaecate	**11**	**1,5 %**		**15**	**2,1 %**
Prolapse - How much of a bother	**7**	**1,0 %**	**x 4.0**	**29**	**4,0 %**

In the urinary dysfunction section the prevalence of prepregnancy symptoms remained unchanged postnatally with the exception of urinary and urge incontinence, which increased 2 - 2.5 fold. In the faecal dysfunction section nearly similar prevalence of prepregnancy and postnatal symptoms was noted. Amazingly high prevalence of some sexual symptoms like vaginal laxity or dyspareunia was noted prepregnancy. Their prevalence increased 2 to 4 fold postnatally. Prolapse symptoms were not very common in nulliparous women and, as expected, significantly increased in prevalence postnatally reaching a 3 to 6 fold increase. A noticeable increase of prevalence bother due to symptoms was noted postnatally in all sections apart from faecal dysfunction, where it remained unchanged.

Additionally it was found a very high persistence of prenatal symptoms postnatally.

Figure A - 5.1 The persistence rate of prepregnancy symptoms postnatally

(Persistent symptoms in dark)

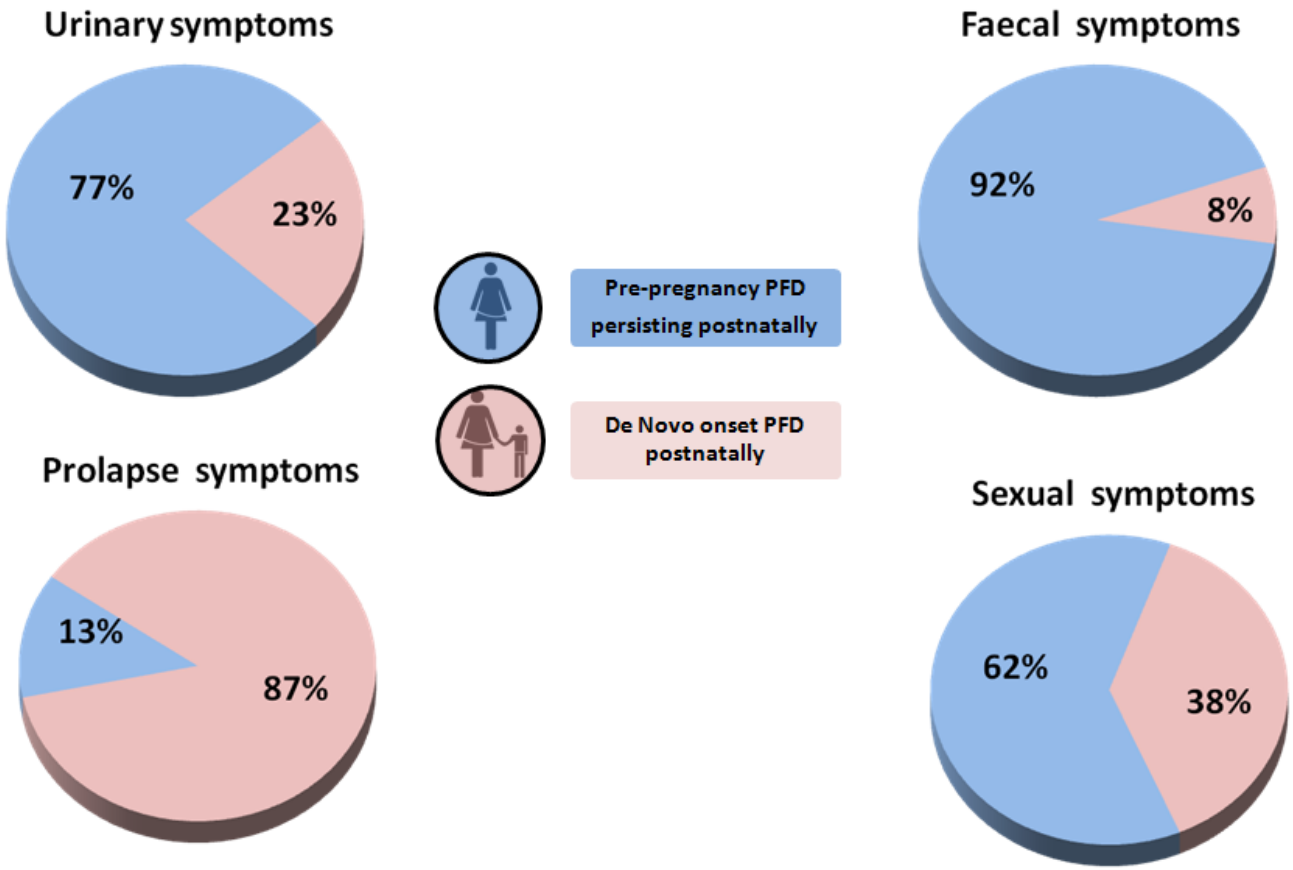


The figure above indicates the persistence of prepregnancy pathology postnatally within each section. The analysis was based here on section score. As shown in the figure, the majority of pre pregnancy PFD persisted postnatally. The only exception was prolapse dysfunction, where pathology persisted in less than half of cases.

In order to better elucidate the structure of postnatal symptoms, the total postnatal pathology was divided into two groups:

1) The Persistent Prenatal PFD (PPFD) – where symptoms were present prepregnancy and persisted postnatally.
2) DeNovo onset postnatal PFD (DN PFD) – where participants were asymptomatic prepregnancy and first noticed symptoms after delivery.

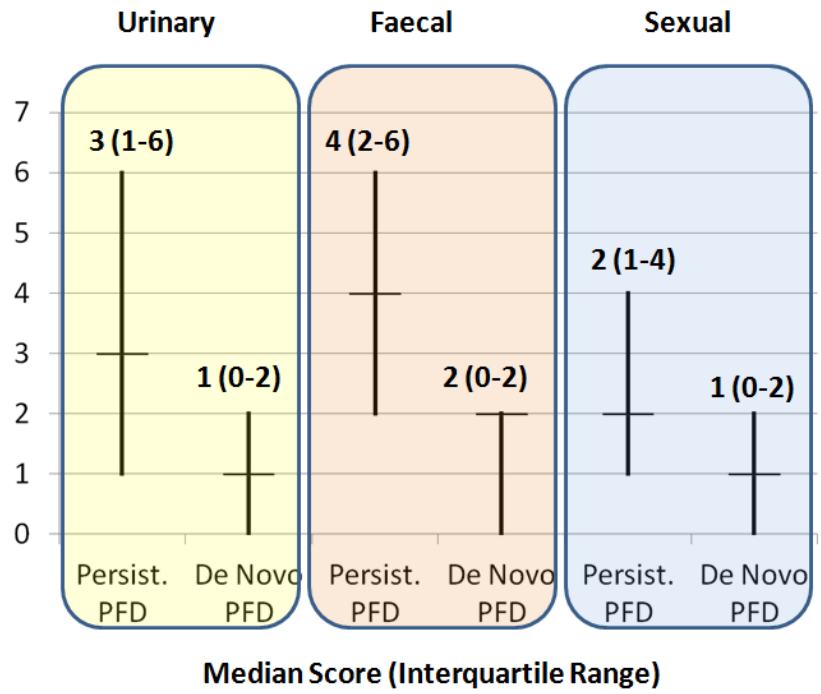
Figure A - 5.2 Relationship between PPFD and DNPFD in the structure of postnatal pathology



A predominance of PPFD postnatal symptoms over DNPFD was discovered in all sections apart from prolapse section.

The severity of postnatal symptoms was compared between the two groups.

Figure A - 5.3 Comparison of severity of PPFD and DNPFD symptoms



It was established that he median section severity score was higher in the PPFD Group comparing to DN PFD. Prolapse section was not included in analysis due to very low prevalence of symptoms in the prepregnancy group

Similarly the bothersome incidence was 2-3 folds higher in the PPFD group (apart from the bowel section), as well as the grade of bothersome was overall higher in the PPFD pathology, where more participants complained of grade 2 and 3 bothersome due to the presence of symptoms.

Table A - 5.5 Comparison of bother prevalence and grade

Bother grade	Bothered * prenatally	Bothered * postnatally	Postnatal Denovo bothersome *	Postnatal Persistent bothersome *
	Urinary dysfunction			
1	63(86%)	123(83%)	94(90%)	27(64%)
2	8(11%)	23(15%)	9(9%)	13(31%)
3	2(3%)	3(2%)	1(1%)	2(5%)
Tot. Bothered**	73(10%)	149(20%)	104 (70%)	42(58%)
	Faecal dysfunction			
1	148(76%)	135(78%)	62(83%)	71(74%)
2	36(19%)	31(18%)	11(15%)	20(21%)
3	10(5%)	7(4%)	2(3%)	5(5%)
Tot. Bothered**	194(27%)	173(24%)	75(43%)	96(51%)
	Prolapse dysfunction			
1	4(57%)	18(62%)	15(63%)	1(33%)
2	3(43%)	6(21%)	4(17%)	2(67%)
3	0	5(17%)	5(21%)	0
Tot. Bothered**	7(1%)	29(4%)	24(83%%)	3(50%)
	Sexual dysfunction			
1	51(76%)	126(75%)	102(78%)	21(62%)
2	13(19%)	31(18%)	21(16%)	10(29%)
3	3(4%)	11(7%)	8(6%)	3(9%)
Tot. Bothered**	67(9%)	168(24%)	131(78%)	34(51%)

* Out of total bothered in the group

** Out of total symptomatic PFD

Appendix VI: Medical conditions associated with POP and PFD

	Medical conditions associated with POP and PFD
1	Joint hypermobility (Double jointed)
2	Varicose vein disease
3	Stretch marks / stria of the skin
4	Uterine prolapse / womb collapse
5	Bladder prolapse / collapse
6	Bowel prolapse / collapse
7	Stress Urinary Incontinence
8	Urge Urinary Incontinence
9	Obstructed Defaecation (Incomplete bowel emptying)
10	Chronic Obstructive Pulmonary Disease (COPD)
11	Asthma
12	Bronchectatic disease
13	Chronic cough
14	Mitral valve prolapse
15	Presence of various hernias
16	Operation for hernias
17	Spine disks dislodgment (Vertebral hernia)
18	Polycystic Ovary Syndrome (PCO)
19	Hyperinsulinemia
20	Diabetes Mellitus Type 1
21	Diabetes Mellitus Type 2
22	Diabetes Mellitus unknown type
23	Ehlers-Danlos syndrome
24	Marfan's syndrome
25	Achard syndrome
26	Osteogenesis Imperfecta
27	Homocystinuria
28	Systemic lupus erythematosus (SLE or lupus)
29	Rheumatoid arthritis (RA)
30	Polymyositis
31	Dermatomyositis
32	Systemic sclerosis (scleroderma)
33	Sjogren's syndrome
34	Mixed connective tissue disease
35	Dupuytren's contracture

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