Parity and Sliding Sign in Endometriosis-associated Pain and Infertility: Two Cross-sectional Studies

by

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In **Reproductive and Developmental Sciences**

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Abstract

Symptomatic women with endometriosis may present with chronic pelvic pain (CPP) and infertility. Endometriosis leads to CPP through chronic inflammation, continuous peripheral nerve stimulation, and enhancement of central sensitization. The relationship between pregnancy and endometriosis is complex. Pregnancy has been proposed as a possible risk for developing CPP. However, amenorrhea has been thought to be protective against endometriosis. For fertility, endometriosis causes infertility mainly through distortion of reproductive anatomy with endometrioma and pelvic adhesions. Although endometrioma can be diagnosed with transvaginal ultrasound and sliding sign can evaluate adhesions in the posterior uterine compartment, the only way to estimate the pregnancy rate is by calculating the endometriosis fertility index (EFI). EFI calculation during laparoscopy provides a score between 0 and 10 (10 is associated with the best fertility prognosis while a score of 0 associated with the poorest fertility prognosis).

In this thesis, I conducted two cross-sectional studies using a prospectively collected registry. In the first study, I compared the severity of pelvic pain between three groups of women: a group of nulligravid women (n=686), a group of parous women (n=371), and a group of women with a history of miscarriage or abortion (n=129). I found a higher number of women in the parous group had severe CPP. The nulligravid group had a higher rate of severe dysmenorrhea. Ordinal regression with backward elimination methods showed a strong association between parity and severe CPP (AOR= 1.448, 95%CI=1.092–1.918, *P*=0.010).

In the second study, I divided infertile endometriosis patients into two groups based on the sliding sign results. The sliding sign is considered negative when the sliding motion is not observed between the colon and cervix or uterus. I found that participants with a negative sliding sign (n=26) had significantly lower total EFI scores and a lower score for each surgical factor

than patients with positive sliding sign (n=60). Logistic regression showed that an EFI score of < 7 can be predicted using the negative sliding sign and EFI historical factors, with a high sensitivity of 87.9% and specificity of 81.1%; the area under the curve was 0.93 (95% CI = 0.88–0.98).

Lay Summary

Endometriosis means finding cells, which usually form the uterus lining, in abnormal locations. It affects women in their reproductive years, causing pain in the pelvic area and infertility. Endometriosis may cause nervous system changes leading to pain sensitivity. Similar nervous system changes have been observed in women who experienced pregnancy. Endometriosis also can prevent natural fertility through adhesions that alter the reproductive tract. To date, the only way to estimate the chance of natural conception is through surgical evaluation of the reproductive organs. My thesis included two research studies. The first study investigated the relationship between previous pregnancy and the severity of pelvic pain. I found that pregnancy was associated with greater severity of chronic pelvic pain. In the second study, I found that dynamic ultrasound imaging for adhesions could potentially replace surgery to estimate the likelihood of natural pregnancy.

Preface

Data of the research project presented in this thesis were part of the Endometriosis Pelvic Pain Interdisciplinary Cohort (EPPIC) database. EPPIC is a prospective registry conducted at British Columbia Women's Centre for Pelvic Pain and Endometriosis since December 2013. The registry was approved by the University of British Columbia (UBC) ethics committee (Approval number: H16-00264). The clinical trials registration number is NCT02911090 (Clinicaltrials.org). I participated in the data entry by updating pathology results and entering the transvaginal ultrasound results for some patients.

This thesis included two cohort studies. In both studies, the original research idea was from Dr. Mohamed Bedaiwy and I design the studies under his supervision. I preformed the statistical analysis with guidance from Dr. Sarka Lisonkova and Dr. Mohamed Bedaiwy. Finally, preparing a preliminary draft of this thesis was entirely done by me, and it was further edited based on suggestions from my committee members.

Part of chapter 3 was presented at the annual meeting for the American Society of Reproductive Medicine 2018.

Chapter 2 and chapter 3 will be submitted for publication.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

AFC = antral follicle count

AFS= American Fertility Society

AMH = anti-Müllerian hormone

AOR = adjusted odd ratio

ASRM = American Society for Reproductive Medicine

BMI = body mass index

CI = confidence interval

CNS = central nervous system

COX = cyclooxygenase

CPP = chronic pelvic pain

DIE = deep infiltrating endometriosis

DNA = deoxyribonucleic acid

D & C = dilatation and curettage

EFI = endometriosis fertility index

EHP = endometriosis health profile

EPPIC = Endometriosis Pelvic Pain Interdisciplinary Cohort

fMRI = functional magnetic resonance imaging

GAD = generalized anxiety disorder

GNRH = gonadotropine releasing hormone

HSD17B2 = 17-beta hydroxysteroid dehydrogenase type 2

IBS = irritable bowel syndrome

IDEA = International Deep Endometriosis Analysis

IL = interleukin

IUI = intra-uterine insemination

IVF = in-vitro fertilization

IQR = interquartile range

LF = least function

LLQ = left lower quadrant

MRI = magnetic resonance imaging

NGF = nerve growth factors

NK = natural killer cells

NPV = negative predictive value

NRS = numeric rating scale

NSAIDs = non-steroidal anti-inflammatory drugs

OR = odd ratio

PBS = painful bladder syndrome

PCS = pain catastrophizing scale

PG = prostaglandins

PGP = pelvic girdle pain

PHQ = patient's health questionnaires

POD = Pouch of Douglas

PPV=positive predictive value

PR = pregnancy rate

PR-B = progesterone receptor B

R-ASRM = Revised American Society for Reproductive Medicine

REDCap = research electronic data capture system

RLQ = right lower quadrant

SF = steroidogenic factor

TNF-α = tumor necrosis factors-α

TVS = transvaginal ultrasound

USL = uterosacral ligament

VEGF = vascular endothelial growth factors

Acknowledgements

First, and most of all, I would like to thank Dr. Mohamed Bedaiwy for giving me the opportunity to work under his supervision and for his expertise, guidance, and patience.

I am grateful to the physicians at the BC Women's Centre of Pelvic Pain and Endometriosis, Drs. Paul Yong, Catherine Allaire, and Christina Williams, and the research manager, Heather Noga, for giving me the opportunity to access EPPIC data and use it for my thesis work, and for their support and helpful suggestions.

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A special word of gratitude to the participants in EPPIC registry and all the patients at the Centre of Pelvic Pain and Endometriosis at BC Women's Hospital, who made a major contribution to this research.

I would like to thank all my colleagues at Dr. Bedaiwy's and Dr. Yong's laboratory. They have each made my time more positive and enjoyable.

Finally, I would like to acknowledge, with great appreciation, the support and love of my family – my husband, Ali Alfaraj; my parents, Khadijah and Abdulmajeed Alfaraj; my daughters, Leen and Yasmeen; and my brothers and sisters. They all kept me going, and this work would not have been possible without their generous moral and financial support.

This thesis work is dedicated to

endometriosis patients and

investigators who commit

their life to understand and

fight this disease.

Chapter 1: Introduction

1.1 Endometriosis

Endometriosis is a chronic inflammatory disease and a common gynaecological condition affecting 10% of reproductive-aged women [1, 2]. It is defined by the presence of endometrial stromal and epithelial cells, which normally form the lining of the uterus, in an ectopic location [3].

Pelvic endometriosis has three phenotypes [4]. The first is superficial peritoneal endometriosis, in which endometriotic tissue is superficial at the surface of peritoneum and pelvic structures. The second is endometrioma, in which a cyst lined with endometrial tissue exists in the ovary [5]. Finally, the third phenotype is deep infiltrating endometriosis (DIE), in which endometriotic lesions penetrate 5mm or greater below the surface of peritoneum and pelvic structures. It can exist as nodules in the cul-de-sac, uterosacral ligaments, the rectovaginal septum, the recto-sigmoid colon, or the bladder [6].

Patients may be asymptomatic or have pelvic pain and/or infertility [1, 7, 8]. Women with endometriosis may experience a variety of pelvic pain types [7], including dysmenorrhea (pain during menstrual bleeding), dyspareunia (pelvic pain associated with intercourse), dyschezia (pelvic pain related to bowel movement), dysuria (painful urination), and chronic pelvic pain (CPP), which is non-cyclical pelvic pain, not exclusively during intercourse, that is continuous or intermittent, lasting for six months or longer [9, 10].

1.2 Staging

Endometriosis was first identified by Sampson in 1921 [11]. Many classification systems have been developed since that time to explain endometriosis's effects on the reproductive

system. The first proposed system was published in 1971 by Acosta et al., which categorized endometriosis into mild, moderate, and severe stages [12] (Table 1.1).

The American Society for Reproductive Medicine (ASRM), formerly called the American Fertility Society (AFS), released the AFS endometriosis staging system in 1975, and then it was revised and republished as the revised-ASRM (r-ASRM) in 1996 [13]. The r-ASRM has a standardized form that scales endometriosis into four stages observed by a gynecologist during surgery. In stage I, the patient has minimal (superficial) lesions, with a score of 1–5. Stage II is a mild stage that scores between 6 and 15. Stage III is the moderate form with a score of 16–40. Finally, any score above 40 is considered stage IV, the severe form of endometriosis (Figure 1.1)[13].

The r-ASRM staging system consists of three parts. The first stage depends on the endometriotic lesion size and the depth of lesion invasion in the peritoneum and ovaries (endometriosis score). The second part is based on the density and amount of adhesion involving the ovaries and fallopian tubes. The third part is the degree of posterior cul-de-sac involvement; it is given a score of 40 when it is completely obliterated with adhesions, which immediately categorizes the patient into stage IV (Figure 2). The total r-ASRM score is calculated by adding the three scores together. The presence of a >3cm endometrioma on one ovary is given a score of 20 and immediately categorizes the patient into stage III; a patient with bilateral and >3cm endometriomas has a score of 40 and is categorized into stage IV. Further details regarding the r-ASRM scoring system form are in Figures 1.1 and 1.2 [13, 14]

Table 1.1. Acosta et.al Classification [12]

Classification	Characteristics
Mild	1) Scattered, fresh lesions (i.e., implants not associated with scarring or retraction of the peritoneum) in the anterior or posterior cul-de-sac or pelvic peritoneum. 2) Rare surface implant on ovary, with no endometrioma, without surface scarring and retraction, and without periovarian adhesions. 3) No peritubular adhesions.
Moderate	1) Endometriosis involving one or both ovaries, with several surface lesions, and with scaring and retraction or small endometrioma. 2) Minimal periovarian adhesions associated with ovarian lesions described. 3) Minimal peritubular adhesions associated with ovarian lesions described. 4) Superficial implants in the anterior and/or posterior cul-de-sac with scarring and retraction. Some adhesions, but not sigmoid invasion.
Severe	1) Endometriosis involving one or both ovaries with endometrioma >2x2cm (usually both) 2) One or both ovaries bound down by adhesions associated with endometriosis, with or without tubal adhesion to ovaries. 3) One or both tubes bound down or obstructed with endometriosis; associated adhesions or lesions. 4) Obliteration of the cul-de-sac from adhesions or lesions associated with endometriosis. 5) Thickening of the uterosacral ligaments and cul-de-sac lesions from invasive endometriosis with obliteration of the cul-de-sac. 6) Significant bowel or urinary tract involvement.

AMERICAN SOCIETY FOR REPRODUCTIVE MEDICINE
REVISED CLASSIFICATION OF ENDOMETRIOSIS

Patient's Name _____ Date _____

Stage I (Minimal) - 1-5
Stage II (Mild) - 6-15
Stage III (Moderate) - 16-40
Stage IV (Severe) - >40
Total _____

Laparoscopy _____ Laparotomy _____ Photography _____
Recommended Treatment _____
_____
Prognosis _____

PERITONEUM	**ENDOMETRIOSIS**	<1cm	1-3cm	>3cm
	Superficial	1	2	4
	Deep	2	4	6
OVARY	R Superficial	1	2	4
	Deep	4	16	20
	L Superficial	1	2	4
	Deep	4	16	20
	POSTERIOR CULDESAC OBLITERATION	Partial	Complete	
		4	40	
OVARY	**ADHESIONS**	<1/3 Enclosure	1/3-2/3 Enclosure	>2/3 Enclosure
	R Filmy	1	2	4
	Dense	4	8	16
	L Filmy	1	2	4
	Dense	4	8	16
TUBE	R Filmy	1	2	4
	Dense	4*	8*	16
	L Filmy	1	2	4
	Dense	4*	8*	16

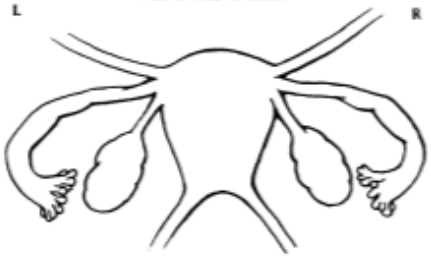
*If the fimbriated end of the fallopian tube is completely enclosed, change the point assignment to 16.

Denote appearance of superficial implant types as red [(R), red, red-pink, flamelike, vesicular blobs, clear vesicles], white [(W), opacifications, peritoneal defects, yellow-brown], or black [(B) black, hemosiderin deposits, blue]. Denote percent of total described as R___%, W___% and B___%. Total should equal 100%.

Additional Endometriosis: _____

Associated Pathology: _____

To Be Used with Normal Tubes and Ovaries



To Be Used with Abnormal Tubes and/or Ovaries

Figure 1.1. The r-ASRM scoring form [13]

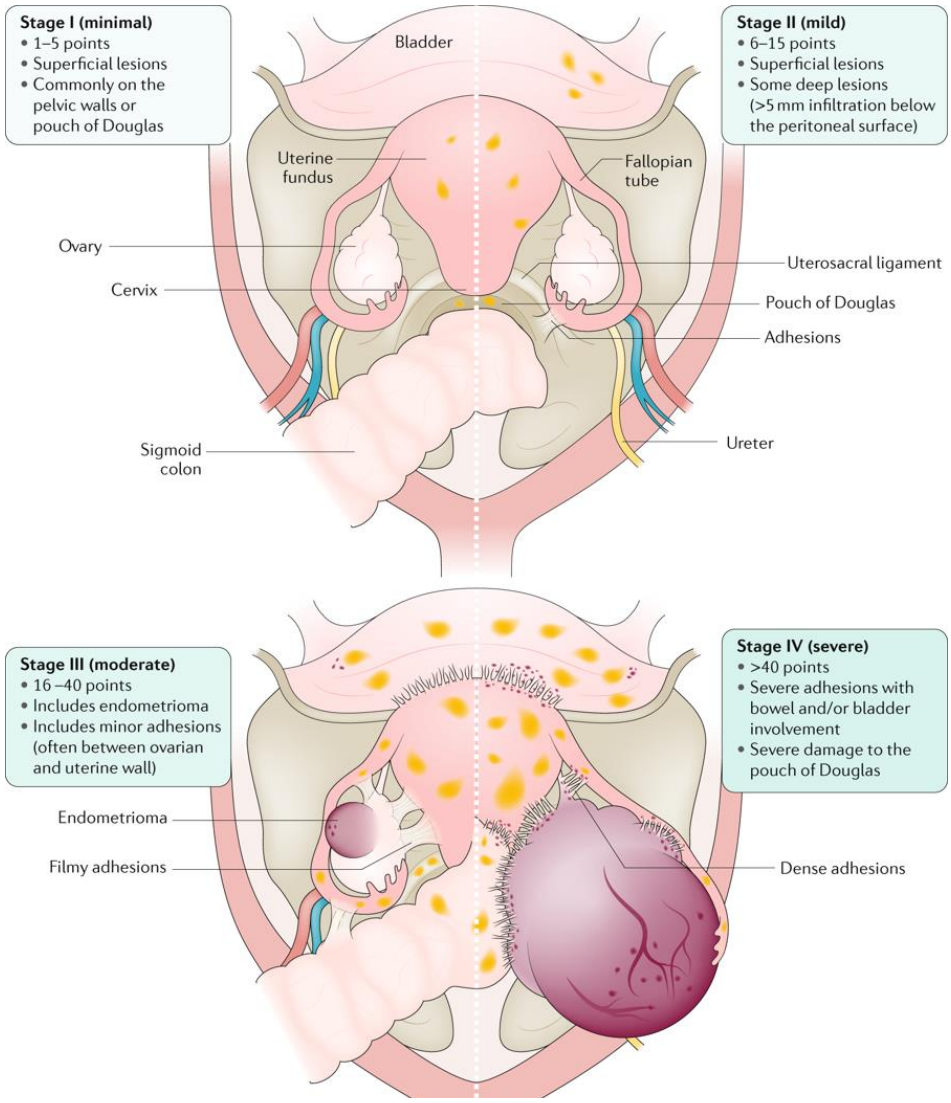


Figure 1.2. Description of the r-ASRM staging (I–IV)[14]

1.3 Diagnosis

Endometriosis is challenging to diagnose. Currently, the only way to confirm the diagnosis is through laparoscopic surgery, which is the best option for visualizing the pelvic area, obtaining a biopsy, and treating the observed lesions [15]. On average, patients take 6–10 years from the onset of symptoms to obtain the correct diagnosis [16, 17]. This delay further lowers the chance of natural conception due to age advancement, and it can negatively affect patients' well-being if pain is present. Furthermore, undergoing a diagnostic laparoscopy does not guarantee histological confirmation of endometriosis in symptomatic patients [18]. Therefore, using a non-invasive approach to diagnose endometriosis is preferable.

Transvaginal ultrasound (TVS) is considered the first-line non-invasive imaging modality to assess the pelvic cavity in women with suspected endometriosis [19]. The International Deep Endometriosis Analysis (IDEA) group proposed a 4-step approach for systematic evaluation of the pelvis in women with suspected endometriosis using TVS (Figure 1.3)[20]. This 4-step examination focuses on the visualization of significant markers of endometriosis (i.e., endometrioma, DIE, adenomyosis, or pelvic adhesions). The first step consists of examining the uterus and adnexa for any signs of endometrioma and adenomyosis. The second step includes ovarian mobility and other soft markers for endometriosis, such as site-specific tenderness and localization of free peritoneal fluid. A fixed ovary is considered an indirect marker for pelvic pathology with a near-perfect correlation between TVS results and laparoscopy [20]. The third step evaluates the Pouch of Douglas (POD) obliteration status with the sliding sign. The final step consists of diagnosing and localization of DIE in the anterior and posterior compartments.

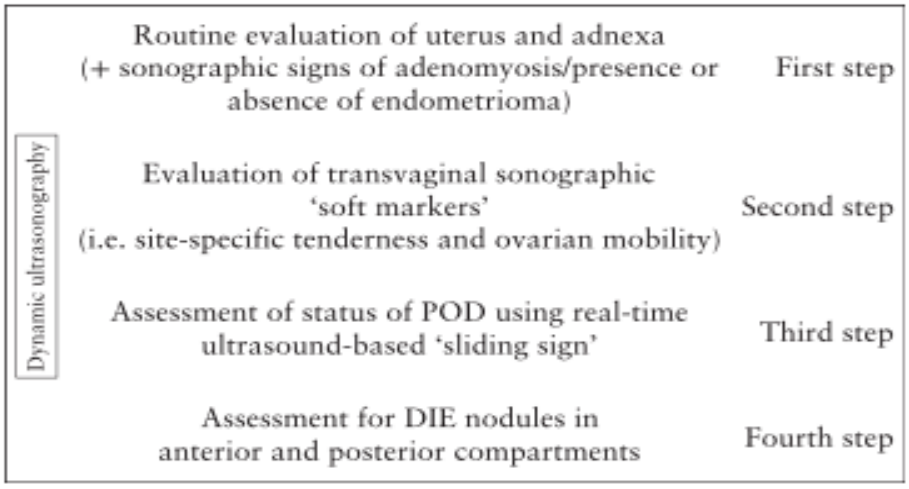


Figure 1.3. The IDEA group's 4-step approach for examining suspected endometriosis cases using TVS[20]

The sliding sign is a newly established ultrasound technique that is usually tested at two locations to predict POD obliteration. The first location is between the rectum and the cervix with the application of gentle pressure against the cervix using a transvaginal ultrasound probe to observe the anterior rectum freely slide over the posterior cervix (Figure 1.4)[20]. The other location is between the recto-sigmoid and the uterus; the examiner's left hand is applied on the lower abdominal wall to observe the recto-sigmoid freely slide over the posterior upper uterus using ultrasound. The sliding sign is considered positive when free motion is observed, and is negative when free motion is not observed [21].

Thus, the 4-step approach improves the utility of the TVS. It is a comprehensive examination of the pelvis that could minimize the need for diagnostic laparoscopy. Furthermore, it can estimate r-ASRM stages III and IV with the detection of DIE, endometrioma, and POD obliteration. However, superficial lesions still cannot be detected with any imaging techniques and the proposed peripheral biomarkers have poor sensitivity and specificity [22, 23].

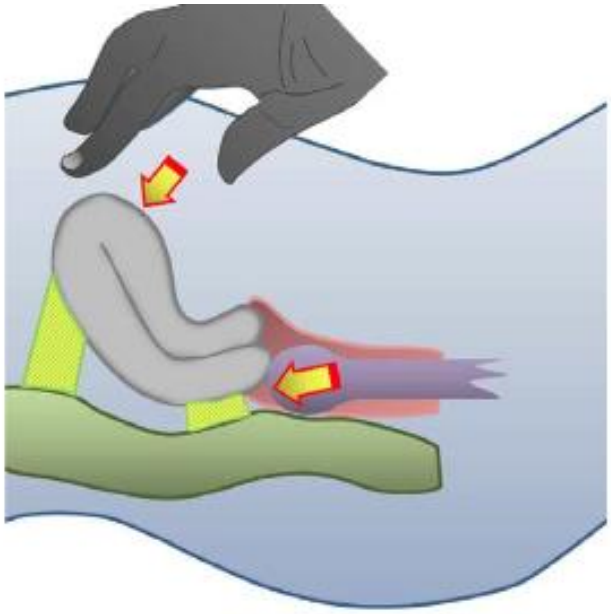


Figure 1.4. Schematic demonstrating the sliding sign examination in two locations indicated with the arrows[20]

1.4 Pathogenesis

Endometriosis will manifest if it is supported by the endocrine and immune system of genetically-susceptible women [24]. This can be summarized by discussing the proposed theories of etiology and the roles of the immune system, hormones, and genetics.

1.4.1 Theories of etiology

Many theories address the etiology of endometrial tissue existing outside the uterus in reproductive-aged women. The theory of retrograde menstruation proposed by Sampson in 1927 is a widely accepted hypothesis that explains transfer of endometrial tissue from the uterus to the pelvic cavity through the fallopian tubes [25]. Retrograde menstruation was later described as a common physiological phenomenon found in over 90% of menstruating women, but only 10%

have endometriosis [26, 27]. Viable endometrial cells are found in the peritoneal fluid of over 70% of women with and without endometriosis [28]. Thus, the presence of endometrial tissue in the pelvis does not cause the disease; rather, endometrial cells' unique survival mechanism and a favourable peritoneal environment can encourage implantation and growth in affected women. Quinn et al. proposed the denervation and reinnervation theory that considered nerve injury resulting from pelvic trauma or chronic straining as a causative factor for endometriosis and pelvic pain [29]. Another theory, the tissue injury and repair theory, also related endometriosis to pelvic trauma [30].

Other theories have been proposed to explain a few reported cases of extra-pelvic, postmenopausal, and male endometriosis. Extra-pelvic endometriosis is supported by the theory of lymphatic and blood metastasis [31, 32]. The coelomic metaplasia theory suggests that peritoneal pluripotent cells can change into endometrial cells. The theory of mullerianosis proposes the misplacement of endometrial tissue during fetal development, which explains the diagnosis of endometriosis in non-menstruating women or men receiving estrogen therapy [33, 34].

1.4.2 Dysfunctional immune system

A dysregulated peritoneal immune system promotes implantation and inflammation, but not the clearance of endometriosis [35, 36]. Natural killer (NK) cells and T-lymphocyte activity is suppressed in the peritoneal fluid of affected women [37]. Macrophages have been found to be active and in high concentration raised; however, they enhance the implantation of endometriosis by increasing the production of growth factors and cytokines, rather than phagocytosis, of the expelled endometrial cells [38-40]. Cytokines, such as tumor necrosis factors-α (TNF-α),

interleukin (IL)-6, and IL-8 are growth promotion molecules that have also been found in higher concentration in the peritoneal fluid of affected women [41-43].

Establishment of a new blood supply (angiogenesis) after implantation is an important step in the pathogenesis of endometriosis. Vascular endothelial growth factor (VEGF), a known angiogenesis protein, has been found in high concentration in the peritoneal fluid and eutopic endometrium of endometriosis patients close to menstruation (secretory phase)[44]. Furthermore, the same investigator found a higher level of VEGF in red endometriosis lesions than in black lesions; the latter is usually followed by fibrosis of the implants [44].

Prostaglandins-E_2 (PG-E_2) and F are also products of the inflammatory cascade [45]. Cyclooxygenase-2 (COX-2) is an isoenzyme that controls the synthesis of prostaglandins from arachidonic acid. It has been found to be upregulated in eutopic and ectopic endometrial tissue of endometriosis patients [46, 47]. PG-E_2 enhances estrogen synthesis through activation of steroidogenic genes [48].

1.4.3 Role of hormones in the pathophysiology of endometriosis

Estrogen and progesterone, predominantly produced by the ovaries, play major roles in endometriotic tissue growth. Endometriosis is estrogen-dependent and can independently produce estrogen through the expression of steroidogenic genes, including aromatase [49]. The aromatase enzyme catalyzes a key limiting step in the biosynthesis of estrogen [48]. Additionally, steroidogenic factor 1 (SF-1) is a transcription factor that activates steroidogenesis, and it is upregulated in endometriosis leading to increased estrogen biosynthesis [50].

Prolonged exposure to estrogen increases endometriosis risk. For example, women with endometriosis have been found to have earlier menarche, a shorter menstrual cycle, and fewer

pregnancies than women without endometriosis [51]. In contrast, decreased estrogen level in the associated with ovulation suppression has a protective effect, as to parity and lactation [52, 53]. Progesterone has anti-estrogen activity that normally limits endometrial growth via activation of 17-beta hydroxysteroid dehydrogenase type 2 (HSD17B2) which converts estrogen to it's inactive form[54]. Endometriosis produces progesterone and escapes the antiproliferative effect of progesterone through progesterone resistance [55]. Progesterone receptor B (PR-B) and the enzyme HSD17B2 are not expressed in ectopic endometrial tissue, which leads to potent estrogenic activity and weak progesterone activity [56].

1.4.4 Genetic and epigenetic factors

There is clear evidence of a familial inheritance in endometriosis [51]. A woman with a first degree relative with endometriosis has a seven to 10 times greater risk of developing endometriosis and is more likely to have a more advanced stage at the time of diagnosis [57, 58]. There is also a high rate of concordance among monozygotic twins [59]. Many genetic studies have been conducted to identify the candidate gene, resulting in 14 genetic loci linked with endometriosis [60, 61]. However, it is difficult to confirm this result since endometriosis is associated with other genetic autoimmune diseases such as asthma, hypothyroidism, systemic lupus erythematosus, and rheumatoid arthritis and other chronic diseases, such as cardiovascular diseases [62-64]. Moreover, the pattern of inheritance seems polygenic and multifactorial rather than simple Mendelian, and it likely involves epigenetic factors [65]. A higher incidence of endometriosis has been observed in some geographic areas, suggesting association with chemical pollutions linked with DNA methylation [66].

1.5 Endometriosis-associated pelvic pain

1.5.1 Pathophysiology

Pelvic pain with endometriosis has a complex pathophysiology through a wide network of events that are currently described through three interacting mechanisms of pain: inflammatory, nociceptive, and neuropathic pain [8]. The inflammatory pain is a consequence of pro-inflammatory cytokine production that mediates pain. TNF-α, IL-1, and IL-6 directly bind to nociceptive receptors in the peripheral nervous system triggering nociceptive pain [67]. PG-E_2 activates nerve endings, stimulating the release of nerve growth factors (NGF), and it also increases uterine contraction, leading to dysmenorrhea [68]. NGF is elevated in all endometriosis phenotypes [69]. It promotes neurogenesis and enhances inflammation by increasing mast cell degradation [70, 71]. Thus, it leads to the release of mast cell storage, which contains arachidonic acid and cytokines [70]. However, pelvic pain can continue after complete excision of endometriosis, which results in removal of the nociceptive stimuli [72]. This suggests the involvement of neuropathic pain, which is pain arising as consequence of a lesion or damage in the peripheral or central nervous system [8].

Active inflammation and neurogenesis around endometriotic lesions lower the threshold of neuron excitation (peripheral sensitization) and facilitate signal transmission to the central nervous system [73, 74]. NGF enhances the expression of neuropeptides (substance P) that increase central sensory and sympathetic fiber signal transmission, leading to hyperalgesia [70]. Prolonged peripheral sensitization and ongoing central nerve stimulation predisposes women to central sensitization [75]. Central sensitization is an amplification of pain through neuroplasticity in the central nervous system that can lead to dysfunctional pain (i.e., pain generated from the

somatosensory system itself without the healing or repair function and without the existence of lesions or disease)[76].

Central sensitization is one of the proposed mechanisms for many unexplained chronic pain conditions, such as painful bladder syndrome (PBS), irritable bowel syndrome (IBS), and myofascial pain, and it is associated with pain catastrophizing [77]. It can also explain the co-existence of these conditions in patients with CPP [78]. Another mechanism is cross sensitization, which is the convergence of pain signals originating in an organ that are sensed in a nearby structure through crossing neurones along the pain signal pathway [79].

1.5.2 Treatment of pelvic pain

Treatment of pelvic pain associated with endometriosis should be tailored to the disease severity, phenotype, and fertility plan [80]. Surgical excision is usually required in cases of large endometrioma, DIE, and pelvic adhesion when considering fertility preservation in young patients [81]. In superficial peritoneal endometriosis, empirical therapy with a combination of combined oral contraceptive pills and non-steroidal anti-inflammatory drugs (NSAIDs) could be started before obtaining a final diagnosis [82, 83]. Creating a hypoestrogenic environment, which causes amenorrhea, is the key medical treatment modality for pelvic pain with endometriosis [84]. Decreasing local estrogen production also blocks prostaglandin, which minimizes pain and inflammation [54]. Other medical treatments include progestogen oral medication, hormonal intrauterine devices, gonadotropin releasing hormone (GnRH) agonists, GnRH antagonists, aromatase inhibitors, and androgenic steroids. Given the progressive and recurring nature of the disease, all the available medical treatments are supportive rather than curative [80].

Surgical treatment in the form of total excision and ablation is usually offered after medical treatment failure or intolerance [14]. Hormonal suppressive medical therapy is usually required post-operatively to prevent recurrence [85]. To date, the only proposed definitive treatment for endometriosis with the highest reoperation-free rate (92%) in seven years follow-up is surgical menopause through hysterectomy and bilateral oophorectomy [86]. However, fertility preservation surgery is preferable in young women.

Ultimately, patients have a different response rate to different treatment modalities and failure of treatment of pelvic pain is well documented in the literature [72, 87]. Moreover, pelvic pain could be present as a part of a chronic pain syndrome, such as central sensitization and myofascial pain, without any evidence of endometriosis [77, 88]. Such chronic pain conditions required a multidisciplinary approach for focussed pain management through medical therapy, psychological support, pain education, and physical therapy [89].

1.6 Endometriosis-associated infertility

Infertility is defined as the inability to achieve a clinical pregnancy after 12-months of regular, unprotected intercourse [90]. In 2012, it was estimated that such morbidity affected 16% of Canadian couples [91]. Endometriosis is responsible for 35% of female infertility cases and 11% of in-vitro fertilization (IVF) cycles in the United States [92, 93].

1.6.1 Pathophysiology

Endometriosis affects each aspect of a woman's reproductive function (i.e., anatomical, endocrine, immunological, and sexual dysfunction) (Figure 1.5)[24]. The existence of ectopic endometrial cells around the reproductive organs leads to an inflammatory process with

subsequent adhesion [94]. As a result, at the molecular level, reactive oxygen species production can interrupt folliculogenesis and fertilization, which subsequently lowers the oocyte and embryo quality. Large endometriomas exert a pressure effect on the ovary and represent a barrier against oocyte transfer to the fimbria. Also, the alteration of estradiol, progesterone, and cytokines concentrations changes eutopic endometrial receptivity and reduces the chance of blastocyst implantation [24, 38].

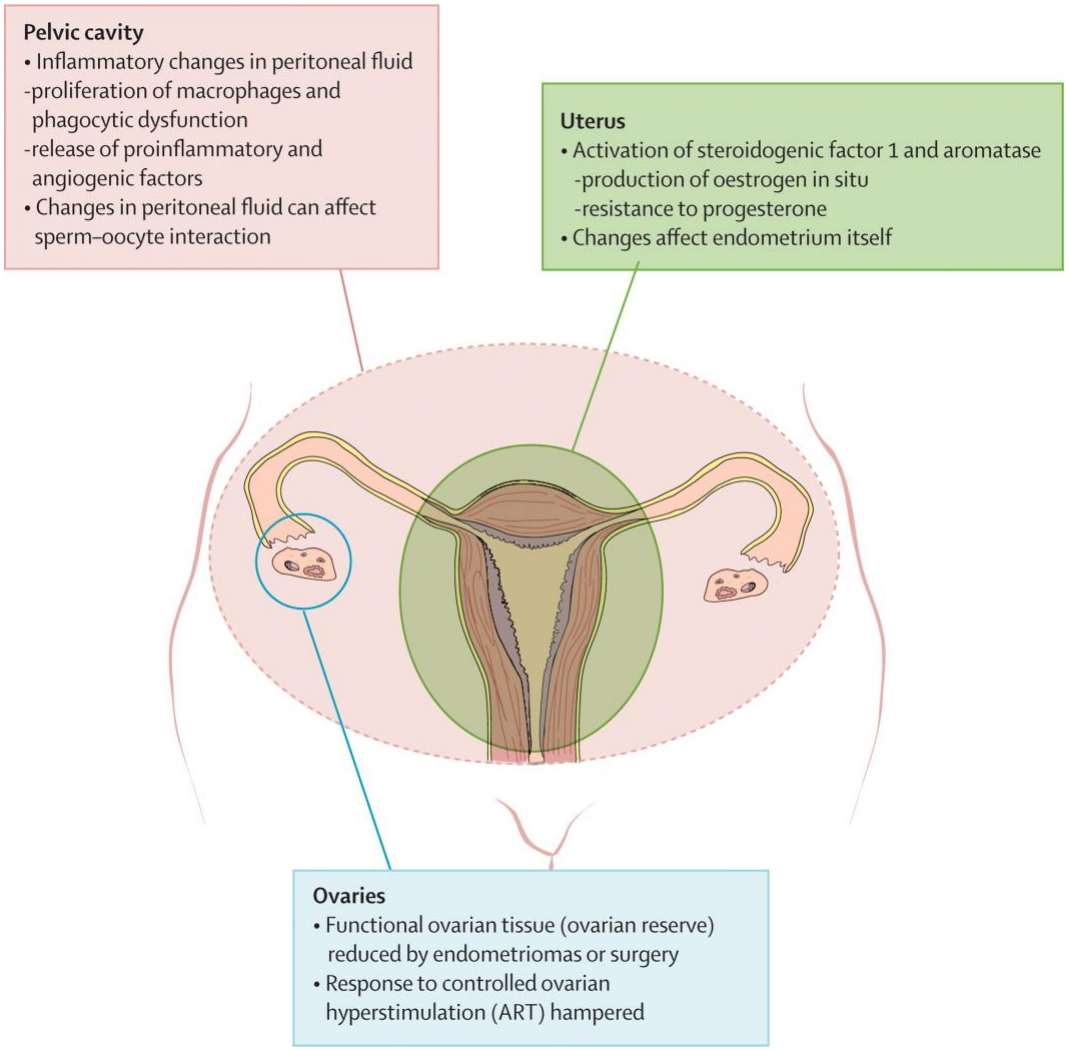


Figure 1.5. Pathophysiology of endometriosis-associated infertility [24]

To further explain the complex effect of endometriosis on the process of conception, many clinical studies have linked different stages of endometriosis to a reproductive outcome. According to the classification of Acosta et al., patients with mild lesions tend to conceive naturally without treatment, having a pregnancy rate of 52.9%. However, increased progression of the disease, which results in the anatomical distortion of the pelvic cavity, lowers the pregnancy rate (PR) to 25% and 0% in moderate and severe stages, respectively [95]. Another study investigated patients with endometriosis that excluded male and tubal infertility factors and found no significant difference in the PR after three years of follow-up for the minimal, mild, and moderate r-ASRM stages (reported as 70.5±6.1, 63.1±6.4 and 71.1±8.1, respectively), while the severe stage had a lower PR of 42.6±13.6. However, there was no significant difference between PR when stages I–II and stages III–IV where compared [96]. Thus, endometriosis is possibly related to infertility, mainly in the severe stages, with a mechanical obstruction of the reproductive tract. Additionally, other factors need to be considered in the assessment of infertility women with suspected endometriosis, such as ovarian reserve assessment through antral follicle count (AFC) or anti-Müllerian hormone (AMH) testing, tubal patency through hysterosalpingogram, and male partner's fertility through semen analysis [85].

1.6.2 Treatment of infertility with endometriosis

Infertile patients with suspected endometriosis are usually encouraged to pursue expectant management aiming for natural conception, but with exceptions. Conservative management with or without ovulation stimulation and intra-uterine insemination (IUI) is favourable in young women with good prognostic signs in terms of normal ovarian reserve, partner's semen analysis, and patent tubes [85]. Laparoscopy or IVF are the next choices after

expectant management failure, and these should be considered based on cost-effectiveness. Indeed, restoring pelvic anatomy to normalize reproductive organs' function is necessary for natural conception [95]. One study found that laparoscopic resection of stages III and IV endometriosis resulted in improvement in the crude spontaneous PR after surgery, reported as 57–69% and 52–68% for stages III and IV, respectively. That improvement was significantly higher than the PR reported after conservative management of the same stages (33% for stage III and 0% for stage IV)[95]. However, in mild and moderate endometriosis (stages I and II), surgical intervention is not cost-effective based on a pooled meta-analysis that involved two randomized control trials investigating reproductive outcomes after diagnostic or laparoscopic surgery. The laparoscopic surgery group had a higher pregnancy and live birth rate; however, 12 laparoscopic surgeries were needed to achieve one additional pregnancy [97]. This means that only one out of every 12 infertile women with stages I and II endometriosis benefited from the procedure. Based on this evidence, it is important to select the endometriosis cases that most likely benefit from surgery.

Immediate referral to IVF, rather than surgery, is recommended for women with male-factor infertility, advanced maternal age, and low ovarian reserve [85]. Additionally, other cases with low likelihood of natural conception can be considered for a post-operative IVF referral based on the surgical assessment of the pelvic endometriosis using the endometriosis fertility index (EFI)[98].

1.6.3 Endometriosis fertility index

The r-ASRM scoring system is informative when investigating endometriosis; however, it cannot predict the likelihood of natural pregnancy [15], which has led to the development of

the EFI. It is a more effective approach to counseling women with endometriosis. In 2010, Adamson and Pasta created the EFI, a staging system that predicts pregnancy rates in women with endometriosis who attempt non-IVF conception [98]. Non-IVF conceptions are defined as pregnancies that occur naturally, after ovulation induction or IUI. The EFI (Figure 1.6) is calculated during surgery by considering historical and surgical fertility prognostic (age, duration of infertility, pregnancy history, least function score (LF), as well as total and endometriosis r-ASRM scores)[98]. The highest score of 10 is associated with the best fertility prognosis while the lowest score of 0 has the poorest prognosis [98, 99].

The surgical factors contribute 50% of the EFI score, 30% from the LF score and 20% from the r-ASRM total and endometriosis scores [100]. The LF score is determined based on the surgeon's subjective evaluation of the ovaries, fimbria, and tubes' functions. A score of 0–4 is given to each of the ovaries, fimbria, and tubes bilaterally, and then the lowest score is considered to represent each side, where 4 is normal function, 0 is absence or non-functional, and 3, 2, and 1 are mild, moderate, and severe dysfunction, respectively. A sum of the lowest score from each side is calculated to report a total LF score, which is significantly better predictor of pelvic reproductive potential than the r-ASRM score. The r-ASRM total and endometriosis scores have an inverse relationship to the EFI. Patients with a complete POD obliteration would score a minimum of 40 in the total r-ASRM score, while patients with a unilateral 1-3cm endometrioma would have a minimum score of 16 in the endometriosis r-ASRM score. Patients with bilateral $\geq$ 3cm endometriomas would score at least 40 in the endometriosis score. Consequently, a cut-off point of 71 for the total r-ASRM and a score of 16 for the endometriosis r-ASRM have been selected considering the negative effects of endometrioma and complete POD obliteration on fertility [98].

ENDOMETRIOSIS FERTILITY INDEX (EFI) SURGERY FORM

LEAST FUNCTION (LF) SCORE AT CONCLUSION OF SURGERY

Score	Description		Left	Right	
4	= Normal	Fallopian Tube			
3	= Mild Dysfunction				
2	= Moderate Dysfunction	Fimbria			
1	= Severe Dysfunction				
0	= Absent or Nonfunctional	Ovary			

To calculate the LF score, add together the lowest score for the left side and the lowest score for the right side. If an ovary is absent on one side, the LF score is obtained by doubling the lowest score on the side with the ovary.

	Left		Right		LF Score
Lowest Score		+		=	

ENDOMETRIOSIS FERTILITY INDEX (EFI)

Historical Factors			Surgical Factors		
Factor	Description	Points	Factor	Description	Points
Age			LF Score		
	If age is ≤ 35 years	2		If LF Score = 7 to 8 (high score)	3
	If age is 36 to 39 years	1		If LF Score = 4 to 6 (moderate score)	2
	If age is ≥ 40 years	0		If LF Score = 1 to 3 (low score)	0
Years Infertile			AFS Endometriosis Score		
	If years infertile is ≤ 3	2		If AFS Endometriosis Lesion Score is < 16	1
	If years infertile is > 3	0		If AFS Endometriosis Lesion Score is ≥ 16	0
Prior Pregnancy			AFS Total Score		
	If there is a history of a prior pregnancy	1		If AFS total score is < 71	1
	If there is no history of prior pregnancy	0		If AFS total score is ≥ 71	0
Total Historical Factors			Total Surgical Factors		

EFI = TOTAL HISTORICAL FACTORS + TOTAL SURGICAL FACTORS:	Historical	+	Surgical	=	EFI Score

Figure 1.6. The EFI form [98]

1.6.4 EFI validation

The EFI has been validated in 11 studies, conducted in seven countries (Table 1.2). It was first internally validated using a prospective analysis of the cumulative PR of 222 women three years after surgery, showing a linear relation between the PR and EFI score[98] (Figure 1.7).

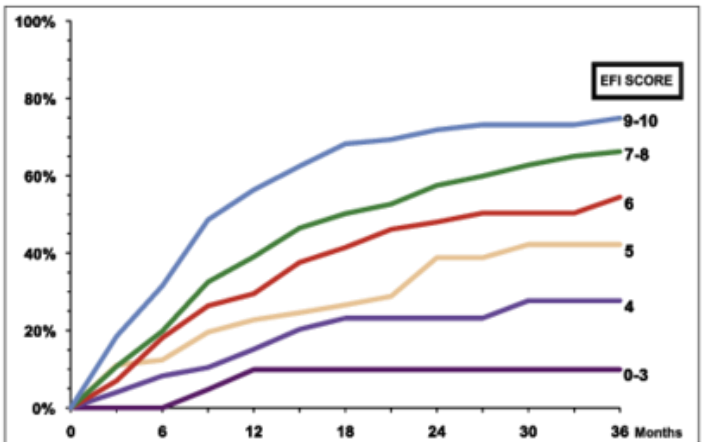


Figure 1.7. Estimated PR by EFI score in the internal validation study[98]

The EFI validation in 10 other studies showed a high predictive power of non-IVF and IVF outcomes in infertile populations and added supportive evidence to improve the utility of EFI (Table 1.2). EFI is a robust tool and superior to the r-ASRM staging system in predicting PR and counseling patients about the best fertility plan after surgery [98]. Surgical factors are superior to the historical factors in predicting the EFI total scores, which mandates surgery to calculate EFI. The LF score is the most important predictor of the EFI score, regardless of the variations between the subjective evaluations of surgeons [98, 101, 102]. Six studies suggested a threshold between 5.5 and 7.5 for immediate IVF referral [101-106].

Table 1.2. EFI validation studies

	Author/ Year	Country	Duration	Follow-up	N	EFI cut-off
Internal Validation Study						
1	**Adamson and Pasta[98], 2010**	**US**	**1984–2009**	**3y**	**222**	**--**
EFI	0-3	4	5	6	7-8	9-10
None-IVF PR	15	30	42	55	65	75
External Retrospective Validation Study						
2	**Wei[107], 2011**	**China**	**2005-2010**	**3y**	**350**	**--**
EFI	5	6	7	8	9	10
None-IVF PR	49.8	43.9	41.6	62.5	69.8	81.1
3	**Tomassetti[102], 2013**	**Belgium**	**2006-2010**	**1y**	**233**	**6**
EFI	1-3	4	5	6	7-8	9-10
None-IVF PR	18	21	20	23	45	65
4	**Zeng[108], 2014**	**China**	**3y**	**3y**	**194**	**--**
EFI	0-3	4-7	8-10			
None-IVF-PR	8.3	41.2	60.0			
5	**Garavaglia[103], 2015**	**Italy**	**2010-2013**	**2y**	**104**	**5.5**
EFI	0-3	4	5	6	7-8	9-10
None- IVF PR	0	0	21.3±11	59.3±19.3	53±9.8	86.7±12
6	**Boujenah[104], 2015**	**France**	**2004-2012**	**1.5y**	**417**	**7.05**
EFI	0-2	3-4	4-6	7-8	9-10	
None-IVF PR	0	5	35.3	42.68	57.8	
7	**Zhang[105], 2018**	**China**	**2008-2012**	**3y**	**1097**	**7.5**
EFI	2	3	4	5	6	7	8	9	10
None-IVF PR	14.3	8.3	20.9	19.1	33.3	43.9	49.6	53.5	70.3
8	**Maheux-Lacroix S[109], 2017**	**Australia**	**2001-2016**	**5y**	**235**	**--**
EFI	0-2	3-4	5-6	7-8	9-10	
None- IVF Live birth rate	0	21±10	34±6	63±7	91±10	
IVF-Live birth rate	38	53	49	59	71	
9	**Wang[101], 2013**	**China**	**2008-2012**	**--**	**199**	**6**
EFI	≤5	≥6				
IVF-PR	39.2	64.3				
External Prospective Validation Study						
10	**Hobo[100], 2017**	**Japan**	**2011-2012**	**9m**	**133**	**7**
EFI	≤7	≥8				
None-IVF PR	31.9	52.5				
11	**Boujenah[110], 2017**	**France**	**2013-2016**	**2y**	**196**	**--**
EFI	≤4	5-6	≥7			
None-IVF PR	--	30.5	48.2			
IVF PR	50	60.6	80.3			

1.7 Objectives and hypotheses

1.7.1 Study 1: The interrelationship between parity and the severity of chronic pelvic pain: a cross sectional study

Objective

To assess pelvic pain severity in women with and without previous pregnancy.

Hypotheses:

- History of previous pregnancy and birth (parity) is associated with decreased severity of chronic pelvic pain (CPP).
- The group with pregnancy ending with miscarriage or abortion is associated with more severe CPP than the parity group.

Primary outcome: Severity of CPP in the last three months on a numeric rating scale from 0 to 10 (10 categorized as the worst pain imaginable; categorized into no/mild (0–3), moderate (4–6), and severe (7–10)).

Secondary outcomes: Severity of other sexual and non-sexual pain (i.e., superficial dyspareunia, deep dyspareunia, dysmenorrhea, back pain, and dyschezia).

Participant Selection

Inclusion criteria

- Participants who had a complete assessment by a gynecologist in the Pelvic Pain Clinic from December 2013 to June 2017.
- Participants in EPPIC with active consent.
- Women between 18 and 45 years old.

Exclusion Criteria

- Participants who had withdrawn consent.

- Participants with self-reported infertility.
- Participants missing the CPP severity score and parity information.

1.7.2 Study 2: Negative sliding sign predicts low endometriosis fertility index during dynamic ultrasonography

Objective

To assess the utility of dynamic ultrasound in triaging patients with low EFI.

Hypothesis:

- Dynamic ultrasonography can predict EFI and can decrease the need for laparoscopy.

Primary outcome: To assess the ability of a negative sliding sign to predict an EFI score of less than 7.

Participant Selection

Inclusion Criteria

- Participants who were ≤ 40 years old and enrolled in EPPIC from December 2013 to June 2017.
- Participants who had EFI calculated during surgery.
- Participants who had preoperative dynamic ultrasound performed at the Pelvic Pain Clinic.

Exclusion Criteria

- Participants who had withdrawn consent.

Chapter 2: The interrelationship between parity and the severity of chronic pelvic pain: A cross sectional study

2.1 Introduction

Chronic pelvic pain (CPP) is challenging to treat due to its complex pathophysiology, and this results in a low quality of life for the individual patient and a societal burden [111, 112]. CPP is defined as continuous or intermittent pelvic pain lasting for three to six months or longer that is non-cyclical and does not exclusively occur during intercourse [9, 10]. Depending on the CPP pattern, patients might receive one of these different diagnoses: endometriosis, painful bladder syndrome (PBS), irritable bowel syndrome (IBS), or nerve and musculo-skeletal factors [9]. Endometriosis, defined as the presence of endometrial-like tissue in an ectopic location, is considered a leading cause for cyclic and noncyclic pelvic pain and infertility in reproductive-aged women [8]. Diagnosis of endometriosis, in the absence of significant markers, such as DIE or endometrioma, requires laparoscopy and a histological confirmation of the suspected lesions [15]. Endometriotic lesions activate neurogenesis, which could be the origin of changes in central system neuroplasticity, leading to amplification of pain signals (central sensitization)[75]. Central sensitization could continue after endometriosis excision and could exist without endometriosis [76]. PBS, also called interstitial cystitis, is defined as bladder pain in the absence of organic causes [113]. IBS is a symptoms complex includes pain and discomfort in the abdomen and changes in bowel movement patterns. It is diagnosed by medical history using the Rome criteria [114]. Myofascial pain is pain originating from a musculoskeletal site due to muscle trauma causing hyperactive nerve firing. It can be diagnosed by finding tender trigger points in the muscle bundles or referred pain in another anatomical site within the nerve pathway [111]. These pelvic pain conditions frequently coexisted, and patients mostly have a

combination of different pain patterns, which makes it difficult to provide a specific diagnosis and a clear management plan. Such patients are likely centrally sensitized and have a low pain threshold, which renders their pain more unbearable and results in a low quality of life [77]. The unbearable pain is also a reason for referring CPP patients for diagnostic laparoscopy with a high expectation of finding an organic cause, such as endometriosis.

Unfortunately, there is a substantial number of symptomatic women who have negative laparoscopy results, even with a high suspicion of endometriosis. In a prospective cross-sectional study, 1418 participants underwent laparoscopic surgery for endometriosis symptoms or sterilization, and the rate of laparoscopic diagnosis of endometriosis in symptomatic patients was 54.3%, while 41.5% of symptomatic patients had a negative laparoscopy. Additionally, endometriosis was found in 35.1% of the patients who underwent surgery for sterilization [115]. It is unknown whether endometriosis was the original lesion that initiate the symptoms or whether it was an incidental finding during the laparoscopy.

The likelihood of diagnosing endometriosis during laparoscopy is linked to menstruation characteristics and reproductive history, such as early age of menarche, short cycles, and nulliparity. Nulliparity increases exposure to menstruation and increases estradiol levels, which increase endometriosis risk [51]. In contrast, pregnancy is a physiological period of progesterone dominance and amenorrhea, which could lower endometriosis risk. However, parity is considered a form of pelvic trauma, whether it concludes with birth through vaginal or caesarean delivery or miscarriage [29]. According to the denervation and renervation theory, pelvic trauma may change the pelvic innervation, leading to central sensitization represented in a chronic pain syndrome frequently seen in reproductive-aged women [29].

Further understanding of the relationships between parity, the severity of CPP, and endometriosis is required. We hypothesized that the severity of CPP was greater among nulligravid women and lower among parous women.

In this cohort, in a tertiary referral center with a high proportion of women with endometriosis (>50%)[89], we compared the severity of different pelvic pain characteristics in nulligravid women, parous women, and women who had a miscarriage or an abortion.

2.2 Materials and Methods

This study analyzed cross-sectional data from the Endometriosis Pelvic Pain Interdisciplinary Cohort (EPPIC), a prospective cohort that began in December 2013 at a tertiary referral center for women with pelvic pain at the British Columbia Women's Hospital, Canada [89, 116]. The study was approved by the University of British Columbia Research Ethics Board (Approval number: H16-00264).

Consenting participants in EPPIC were asked to complete a baseline questionnaire reviewing demographic characteristics and medical history, such as age, ethnicity, smoking history, alcohol consumption, self-reported pelvic pain severity in the past three months (0–10 numeric rating scale (NRS)), ~~history of pelvic surgery for endometriosis,~~ and menstrual characteristics (such as age of menarche, duration of flow, and amount of flow). The baseline information included validated questionnaires to assess depression (Patients Health Questionnaires (PHQ)-9)[117], anxiety (Generalized Anxiety Disorder (GAD)-7)[118], pain catastrophizing (Pain Catastrophizing Scale (PCS)[119], and quality of life using the Endometriosis Health Profile (EHP-30)[120]. Comorbid conditions such as IBS and PBS were

diagnosed using Rome III criteria and the American Urological Association or the International Continence Society criteria, respectively [121, 122].

Physical examination

When patients presented at the clinic, they underwent a complete clinical assessment and physical examination by a gynecologist. Single digital palpation was used to assess tenderness at specific locations, recorded as tender or not tender. Those specific locations were the pelvic floor (levator ani muscles), bladder (anterior vaginal wall), cervix, uterus, cul-de-sac, and uterosacral ligament (USL). For the analysis, tenderness of the bladder and pelvic floor were coded as a single variable (yes/no). Likewise, tenderness of the cervix and uterus were coded as a single variable [123, 124]. Tenderness of the lower abdominal wall was assessed in three locations: right lower quadrant (RLQ), left lower quadrant (LLQ), and suprapubic area, this was followed by the Carnett test (asking the patient to raise her head to contract her abdominal muscles). A positive result of the Carnett test occurred if pain of the abdominal wall pain in any of the three locations was worse than the initial palpation of the abdominal wall muscles, and this suggested pain of a myofascial origin [125]. Pelvic girdle pain (PGP) was tested in the right and left sides using active straight leg raises, the Faber test, and the posterior pelvic pain provocation (P4) test, in addition to palpating the dorsal sacroiliac ligaments and the symphysis pubis for tenderness. PGP was considered to be present when patients reported tenderness with palpation of either location or reported pain with any of the tests, and it was considered negative if no tenderness was reported in any location [126].

Body mass index (BMI) and the current use of hormonal suppression were assessed at the time of the physical examination. DIE was diagnosed by palpating the nodule in the POD [127].

Transvaginal ultrasound was used to diagnose endometrioma [128] and adenomyosis [129] (all binary, yes/no variables).

Surgery and pathology data

Surgical data were collected by a gynecologist for the women who required surgery. Surgical data were entered prospectively into an online research electronic data capture system on the day of surgery by the center's gynecologists (REDCap)[130]. Surgical data included endometriosis r-ASRM staging and POD obliteration status, as well as histological confirmation of endometriosis from pathology results.

Patient selection

The inclusion criteria were 1) enrollment in EPPIC with active consent from December 2013 to June 2017; 2) a complete initial assessment by a gynecologist in the Pelvic Pain Clinic; and 3) women between 18 and 45 years. The three comparison groups included 1) participants who had never been pregnant (nulligravid group), 2) participants reporting pregnancy and who had at least one live birth (parous group), and 3) participants reporting pregnancy with no live birth (miscarriage and abortion group); infertile patients were excluded because they were mostly referred for infertility management and may not have presented with pelvic pain. Participants with missing CPP severity score and parity information were excluded. We analyzed the responses to three questions from the baseline questionnaire. The first question was "Have you ever been pregnant?" The second question was "Have you ever had problems getting pregnant (infertility) when you wanted to?" The third question asked for the number of live births (Figure 2.1).

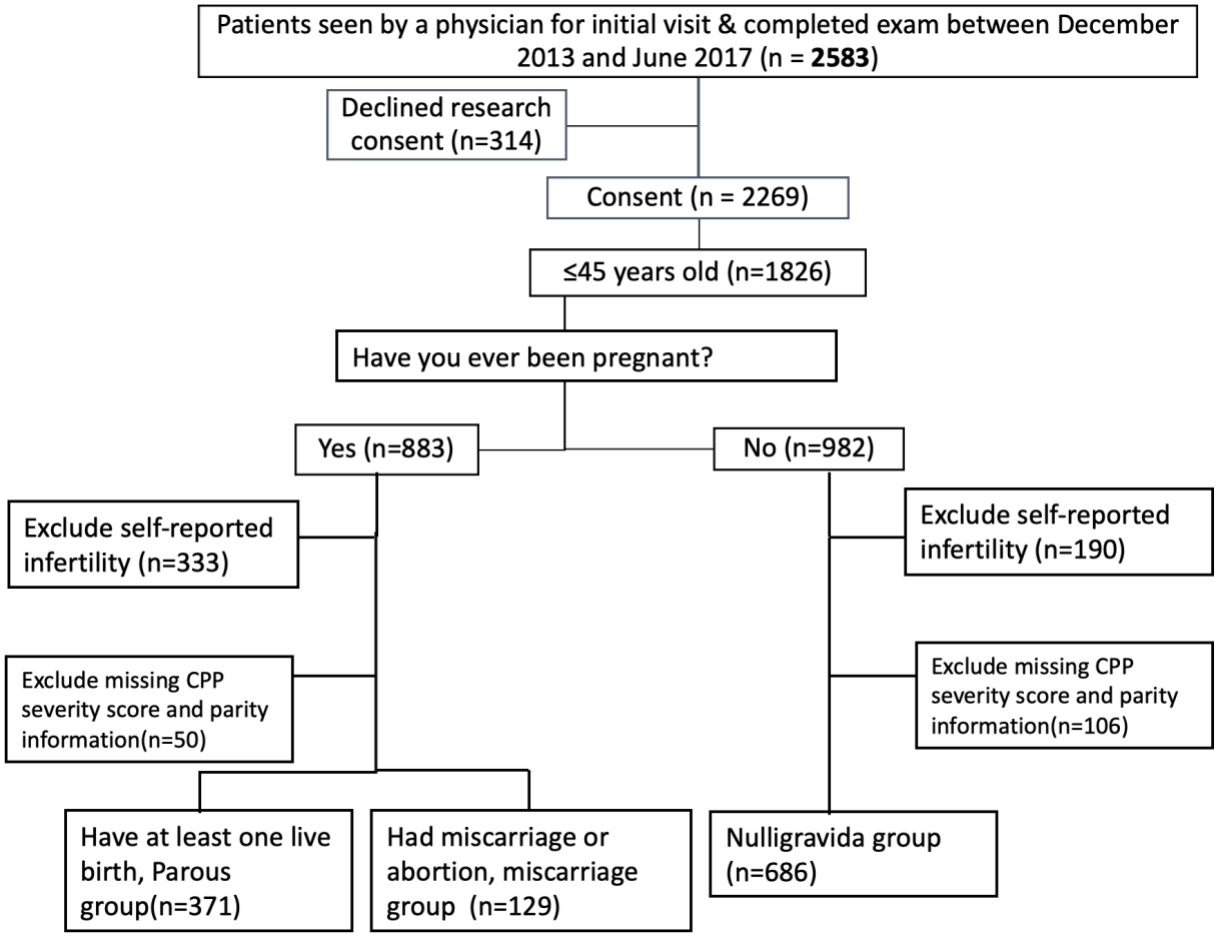


Figure 2.1. Participant selection flow chart

Outcome measures

Primary outcome was the severity of CPP in the last three months on the NRS scale from zero to 10 (zero meaning no pain and 10 meaning the worst pain imaginable). Secondary outcomes included severity of other pelvic pain characteristics (i.e., dysmenorrhea, superficial dyspareunia, deep dyspareunia, and dyschezia) and back pain. In the questionnaire, patients were asked if they had any pelvic pain characteristics and were asked to rate that pain from 0 to 10. For the analysis, pain severity was divided into three categories: a none–mild category with a

score of 0 to 3, a moderate pain category with a score between 4 and 6, and a severe pain category with a score between 7 and 10.

Statistical analysis

We first conducted bivariate analyses to assess any significant differences in the outcomes between the three groups and differenced with respect to other covariates. Chi-square tests with Bonferroni adjustment or Fisher exact tests were used to compare categorical variables. Chi-square results were reported as proportions and overall *P* values. The Kruskal-Wallis test was used to compare the medians and interquartile ranges (IQR) of the continuous variables. In the second step of the analysis, we conducted ordinal regression to adjust for covariates from the literature or with significant differences in the bivariate analyses considering the maintenance of the sample size ($P < 0.05$). The outcome for analysis was the severity of CPP. Pain severity was modelled as an ordinal variable of none to mild, moderate, and severe pain. The regression model was performed using a sequential backward elimination method. Regression results were reported as adjusted odd ratios (AOR), 95% confidence intervals (CI), and *P* values. All analyses were performed using SPSS (IBM Corp., Armonk, NY).

2.3 Results

A total of 1186 participants was included in the analysis. There were 686 participants in the nulligravid group, 371 participants in the parous group, and 129 participants in the miscarriage/abortion group.

Bivariate analysis results

Demographic and menstrual characteristics

The nulligravid group were more likely to be younger and more likely to be using hormonal suppression than the other groups. There was a lower proportion of smokers in the nulligravid group and a lower proportion of consumers of alcohol in the parous group. There was a higher rate of obesity in the parous group. Participants in the miscarriage/abortion group were significantly younger than the parous group (Table 2.1). Approximately half (47.7%) of parous women and 56.6% of women in the miscarriage/abortion reported pain onset before their first pregnancy. There was no difference in the menstrual characteristics between the three groups (Appendix A).

Table 2.1. Descriptive statistics of the parous, nulliparous, and miscarriage groups

	Total	**Nulligravida**	**Parous**	**Miscarriage/ Abortion**	***P value***
N	1186	686	371	129	
Age†	32(26–37)	**28(25–33)***	**38(344–1)***	**31(27–35)***	**<0.001**
BMI		n (%)	n (%)	n (%)	
Underweight (>18.5)	64	43(6.4)	**10(2.7)***	11(8.8)	**0.009**
Normal (18.5–24.9)	634	382(56.6)	188(51.2)	64(51.2)	
Overweight (25–29.9)	253	142(21)	84(22.9)	27(21.6)	
Obese (≥30)	216	108(16)	**85(23.2)***	23(18.4)	
Ethnicity					
Caucasian	896	507(73.9)	282(76)	107(82.9)	0.088
Others	290	179(26.1)	89(24)	22(17.1)	
Smoking					
Yes	199	**75(11.3) ***	87(23.5)	37(28.7)	**<0.001**
No	963	**587(88.7)***	284(76.5)	92(71.3)	
Alcohol					
Yes	739	432(65.3)	**212(57.1)***	95(73.6)	**0.001**
No	423	230(34.7)	**159(42.9)***	34(26.4)	
Current use of hormonal suppression					
Yes	423	**302(54.9)***	81(32)	40(36.4)	**<0.001**
No	490	**248(45.1)***	172(68)	70(63.6)	
Pain started before your first pregnancy					
Yes		--	177(47.7)	73(56.6)	0.102
No		--	194(52.3)	56(43.4)	

† median(IQR)
*****Significantly different group

Clinical variables and validated questionnaires

The miscarriage/abortion group had a higher PHQ-9 score than the other groups and a higher EHP-30 score than the nulligravid group. The parous group had a higher EHP-30 score than the nulligravid group and a lower GAD-7 than the other groups. There was no difference in the PCS score and the incidence of IBS and PBS among the three groups (Table 2.2).

Table 2.2. Clinical variables and validated questionnaires

	Total	**Nulligravida**	**Parous**	**Miscarriage/ Abortion**	***P Value***
IBS		**n(%)**	**n(%)**	**n(%)**	
Yes	304	163(23.8)	103(27.8)	38(29.5)	0.209
No	882	523(76.2)	268(72.2)	91(70.5)	
PBS					
Yes	288	155(22.6)	95(25.6)	38(29.5)	0.193
No	898	531(77.4)	276(74.4)	91(70.5)	
PHQ-9†	8(4-13)	8(4–13)	7(3–13)	**9(6–16)***	**0.036**
GAD-7†	6(3-11)	8(4–13)	**5(2–9.5)***	9(6–16)	**0.002**
PCS †	20(10-30)	20(10–30)	19(9–30)	20(12–34)	0.648
EHP-30†	52.3(38.6-52.3)	**52.3(36.4–68.2)***	**56.8(39.8–71.6)***	54.5(42.6-68.2)	**0.014**

IBS = irritable bowel syndrome
PBS = painful bladder syndrome
PHQ-9 = patient's health questionnaire-9
GAD-7 = generalized anxiety disorder-7
PCS = pain catastrophizing scale
EHP-30 = endometriosis health profile-30
† median(IQR)
*****Significantly different group

Pelvic examination and transvaginal ultrasound results

There was a significantly higher incidence of adenomyosis in the parous group than the nulligravid group (Table 2.3), with no significant difference in the incidence of endometrioma and DIE. The three groups had similar results for pain mapping, the Carnett test, and the PGP examination, except for cul-de-sac tenderness, which was more prevalence in the nulligravid group than the parous (Table 2.4).

Table 2.3. Rates of endometrioma, DIE, and adenomyosis between the three study groups.

	Total	**Nulligravida**	**Parous**	**Miscarriage /Abortion**	***P* Value**
Endometrioma					
Yes	104	64(9.3)	28(7.5)	12(9.3)	0.604
No	1082	622(90.7)	343(92.5)	117(90.7)	
DIE					
Yes	72	43(7.9)	23(7.7)	6(5.5)	0.690
No	882	504(92.1)	257(92.3)	103(94.5)	
Adenomyosis					
Yes	95	**33(4.8)***	**49(13.2)***	13(10.1)	**<0.001**
No	1091	**653(95.2)***	**322(86.8)***	116(89.9)	

DIE = deep infiltrating endometriosis
*Significantly different group

Table 2.4. Results of pain mapping in the three study groups

	Total	Nulligravida	Parous	Miscarriage/ Abortion	*P* Value
Bladder and pelvic floor		**n(%)**	**n(%)**	**n(%)**	
Yes	561	315(45.9)	187(50.4)	59(45.7)	0.325
No	625	371(54.1)	184(49.6)	70(54.3)	
Cervix and uterus					
Yes	281	160(23.3)	91(24.5)	30(23.3)	0.901
No	905	526(76.7)	280(75.5)	99(76.7)	
Cul-de-sac					
Yes	545	**340(49.6)***	**154(41.5)***	51(39.5)	**0.013**
No	641	**346(50.4)***	**217(58.5)***	78(60.5)	
Lower abdomen tenderness					
Yes	768	436(63.6)	243(65.5)	89(69)	0.464
No	418	250(36.4)	128(34.5)	40(31)	
Carnett test					
Positive	303	175(43.6)	99(46.5)	29(34.9)	0.197
Negative	394	226(56.4)	114(53.5)	54(65.1)	
Pelvic girdle pain					
Positive	505	280(43.9)	173(49.4)	52(44.8)	0.242
Negative	599	358(56.1)	177(50.6)	64(55.2)	

*Significantly different group

Pelvic pain severity

Bivariate analyses showed that a higher proportion of parous women had severe CPP and back pain than the nulligravid group, while the nulligravid group was more likely to have severe dysmenorrhea than the other groups (Table 2.5). Being in the parous group was associated with severe CPP (odds ratio (OR))=1.6, 95%CI=1.226–2.086, Table 2.6).

Table 2.5. The severity of pelvic pain for the three study groups

	Total	**Nulligravida**	**Parous**	**Miscarriage/ Abortion**	***P* Value**
CPP					
None–mild	104	70(10.2)	23(6.2)	11(8.5)	**0.006**
Moderate	320	**204(29.7)***	**83(22.4)***	33(25.6)	
Severe	762	**412(60.1)***	**265(71.4) ***	85(65.9)	
Superficial dyspareunia					
None–mild	558	293(46.2)	195(53)	70(55.6)	0.168
Moderate	265	160(25.2)	79(21.5)	26(20.6)	
Severe	305	181(28.5)	94(25.5)	30(23.8)	
Deep dyspareunia					
None–mild	218	118(18.6)	67(18.4)	33(26.2)	0.184
Moderate	253	153(24.2)	75(20.5)	25(19.8)	
Severe	653	362(57.2)	223(61.1)	68(54)	
Dysmenorrhea					
None–mild	190	**90(15.6)***	**80(26.2)***	20(16.4)	**0.003**
Moderate	209	126(21.9)	61(20)	22(18)	
Severe	604	**360(62.5)***	**164(53.8)***	80(65.6)	
Back pain					
None–mild	122	79(13.6)	29(9.4)	14(12.4)	**0.003**
Moderate	405	**252(43.3)***	**104(33.7)***	49(43.4)	
Severe	477	**251(43.1)***	**176(57)***	50(44.2)	
Dyschezia					
None–mild	447	272(39.7)	130(35)	45(34.9)	0.288
Moderate	336	196(28.6)	100(29.8)	40(31)	
Severe	403	218(31.8)	141(38)	44(34.1)	

*****Significantly different group

Table 2.6. The different severities of CPP and the odds ratio of being in one of the study groups

	Nulligravida	**Parous**		**Miscarriage/Abortion**	
		OR (95%CI)	*P value*	OR (95%CI)	*P value*
CPP None–mild versus moderate	1**	1.233(.729-2.088)	0.515	0.972(.473-2.00)	1
CPP moderate versus severe	1**	1.523(1.138-2.037)	**0.004**	1.092(.714-1.671)	0.749
CPP severe versus other pain scores (None–mild and moderate)	1**	1.6(1.226-2.086)	**0.001**	1.084(.738-1.594)	0.699

******Reference category

Multivariable analysis

In the ordinal regression, parity associated with severe CPP (AOR=1.448, 95%CI=1.092–1.918, *P*=0.010) was independent of having severe back pain, high BMI, or a higher score of PCS (Table 2.7). Original regression result without backward elimination are provided in Appendix B.

Table 2.7. Backward elimination factors associated with the severity of CPP

	***P* value**	**AOR^**	**95%CI**
Parity	**0.010**	1.448	1.092–1.918
BMI	**0.003**	1.035	1.011–1.058
Severe back pain	**<0.001**	2.502	1.895–3.304
PCS	**<0.001**	1.042	1.031–1.053

Surgical findings and histological confirmation of endometriosis

In total, 487 participants had surgery. Nulligravid women were more likely to have pathology resembling endometriosis during surgery and more likely to have histologic confirmation of endometriosis (Table 2.8).

Table 2.8. Surgical findings and histological confirmation of endometriosis in the three study groups

	Total	**Nulligravida**	**Parous**	**Miscarriage/ Abortion**	**P value**
N	487	269	171	47	
Pathology observed during surgery					
Yes	453	**257(95.5)***	**151(88.3)***	45(95.7)	**0.011**
No	34	**12(4.5)***	**20(11.7)***	2(4.3)	
R-ASRM					
I	190	113(51.8)	59(52.2)	18(48.6)	0.582
II	75	38(17.4)	28(24.8)	9(24.3)	
III	40	28(12.8)	9(8)	3(8.1)	
IV	63	39(17.9)	17(15)	7(18.9)	
POD obliteration					
Yes	73	42(18.9)	22(18.6)	9(23.1)	0.814
No	306	180(81.1)	96(81.4)	30(76.9)	
Histologic confirmation					
Yes	336	**203(79.3)***	**100(60.6)***	33(71.7)	**<0.001**
No	131	**53(20.7)***	**65(39.4)***	13(28.3)	

***Significantly different group

2.4 Discussion

Our study compared the severity of CPP and other pelvic pain types in three groups of women referred to a tertiary care center specializing in chronic pelvic pain and endometriosis management. Our cohort consisted of a group of nulligravid women, a group of parous women, and a third group who had experienced a miscarriage or an abortion. We found a significant association between severe CPP and parity independent of other confounding variables.

The study used a large sample size and standardized data from a prospective registry (EPPIC); it included a comprehensive pelvic examination and pain mapping, endometriosis staging, and histologic confirmation of endometriosis. The main limitation was that the EPPIC registry was not designed to answer our specific research question, so our analysis did not include possible confounding variables, such as duration of pelvic pain, lactation history, time since last birth, history of difficult vaginal delivery, and what proportion of miscarriages/abortions required dilatation and curettage (D & C). Therefore, the independent, strong relationship between severe CPP and parity needs further investigation in future studies.

Pregnancy is associated with changes in women's physiology and neuroendocrine functions that could last long after the postpartum period. Parity and pregnancy termination are considered risk factors for developing adenomyosis [131, 132]. Adenomyosis results from the invasion of endometrial tissue into the myometrium [129]. It may cause CPP with primary symptoms of dysmenorrhea and menorrhagia [133]. There is a high rate of concordance of adenomyosis and endometriosis[134]. Nevertheless, parity increases adenomyosis risk, but lowers endometriosis risk[132, 135]. In this cohort, there was an overall high rate of finding pathology resembling endometriosis during surgery and histologic investigation. However, there was a higher rate of endometriosis observed during surgery and histologic confirmation in the

nulligravid group than the parous group. This observation could be related to the protective effect of amenorrhea during pregnancy and breastfeeding, which may lower the risk of endometriosis [52, 53]. We have also observed a higher incidence of adenomyosis during transvaginal ultrasound assessment in parous women compared to the nulligravid women.

Pregnancy is also associated with changes in pelvic bones and lumbosacral vertebrae, resulting in chronic lower back pain and PGP, which could be a risk for developing pelvic pain[126]. Obesity also enhances the severity of back pain and may contribute to the severity of CPP [136, 137]. In this study, we observed that parous women had a higher rate of obesity (P=0.003), greater severity of lower back pain (<0.001), and a higher incidence of PGP, although this was not statistically significant. Additionally, difficult labour is associated with injury of the levator ani muscles [138]. A myofascial defect of the levator ani muscles was observed in the magnetic resonance imaging (MRI) of 20 out of 26 parous women with unexplained CPP [139]. Quinn suggested the denervation and reinnervation theory that related injury to pelvic structures to the risk of developing central sensitization [29]. Pregnancy is associated with stretching of the uterus and uterosacral ligament to accommodate the growing fetus and the placenta. In adaptation to the expansion in uterine size and distention of the abdominal and pelvic cavities, blood vessels are elongated through an active angiogenesis, but the nerves fibers are not elongated [140]. This may cause injury to the autonomic nerve fibers leading to loss of nerve supply (denervation). An episode of denervation is associated with muscle weakness and loss of sensation in support of the physiological changes during pregnancy and labour. Injury to pelvic structures can also result from difficult vaginal delivery, pelvic surgery (including caesarean section), D & C, or from prolonged straining with chronic constipation [29]. Following the injury, as part of tissue repair, an arbitrary reinnervation occurs, forming dense nerve fibers and

diffused peripheral branching, especially for nerves that supply muscles [141]. The result is an alteration of peripheral nerve function leading to neuropathic pain with peripheral sensitization and unusual referred pain [141, 142]. Prolonged excitation of the central nervous system (CNS) could lead to central sensitization [143]. Evidence to support the theory of the denervation and reinnervation is lacking. In this study, about half of the participants in the parous and miscarriage/abortion group experienced pelvic pain before their first pregnancy, however, the severity of this pain was not assessed before pregnancy. Therefore, a conclusion about the relationship between parity and pain sensitization cannot be established from our results.

Furthermore, neuroscientists have found that pregnancy is associated with a decrease in the volume of brain gray matter, which can last for two years postpartum. It is unknown if that effect can last longer because participants of the study were followed for only two years [144]. Interestingly, similar findings have been described in CPP patients with or without endometriosis, but not in endometriosis patients without CPP [145]. It is unknown whether endometriosis is the source of active neurogenesis and changes in brain function or whether it is a co-enhancer.

In a 1-year follow-up study that investigated factors contributing to the persistence of the severity of CPP, age had an inverse association with CPP severity [89]. This could be due to pain acceptance and coping strategies, which could take time to establish, reflecting an improved attitude towards pain and general quality of life improvement in older women [146]. However, in this study, a higher proportion of parous women had severe CPP and worse quality of life, regardless of their older age.

There was a higher rate of smoking in the parous women. Smoking is known to contribute to chronic pain, including CPP, either directly through enhancing inflammation,

autonomic nerve injury, and nicotine interaction with nociceptive receptors, or indirectly through musculoskeletal pain following a chronic cough [147, 148].

In this cohort, adjusting for confounding variables resulted in four factors (parity, severe back pain, higher BMI, and PCS score) having an independent association with the severity of CPP. In agreement with previously published studies from EPPIC, higher BMI and pain catastrophizing strongly associated with CPP severity in an initial visit [116]. Moreover, pain catastrophizing was a marker of pain persistence notwithstanding multidisciplinary management [89].

Dysmenorrhea is the most relevant pelvic pain pattern for endometriosis [9, 149]. During menstruation, micro-bleeding of the endometriotic implants activates local inflammation and initiates pelvic pain [150]. Additionally, nulliparity is a risk factor for developing dysmenorrhea [151]. In the current cohort, the parous group was less likely to have severe dysmenorrhea than the other two groups, while the nulligravid group had the highest rate of self-reported severe dysmenorrhea.

Our observations provide an insight into the importance of understanding the different patterns and severity of pelvic pain among reproductive aged women. Endometriosis is an important disease to consider in cases of unexplained, chronic, and severe pelvic pain. However, other factors, such as adenomyosis need to be investigated. Further validation of our results is required, and further study should consider the theory of the denervation process during pregnancy.

Chapter 3: Negative sliding sign predicts low endometriosis fertility index during dynamic ultrasonography

3.1 Introduction

Endometriosis is a challenging gynecological condition responsible for 30% of female infertility cases and 11% of in vitro fertilization (IVF) cycles in the United States [92, 152]. It can affect every aspect of a woman's reproductive function, whether at the molecular or the anatomical level [24]. The endometriosis fertility index (EFI) is the most current effective approach for formulating treatment plans for infertile patients with endometriosis and for predicting the pregnancy rate (PR) of patients attempting spontaneous conception or intrauterine insemination[153]. It has been validated in 11 studies, showing a high predictive power for non-IVF or IVF outcomes in infertile endometriosis patients [101-109, 153, 154]. The highest score of 10 is associated with the best fertility prognosis, and the lowest score of 0 has the poorest fertility prognosis. Patients assigned a low EFI score can, therefore, be referred immediately for IVF if they wish to conceive without delay; patients with a high EFI score can be expectantly managed for up to 12 months, allowing for natural conception [24, 99]

The EFI is calculated during surgery by considering historical and surgical fertility prognostic factors as defined by age, duration of infertility, pregnancy history, least function (LF) score, and total and endometriosis revised American Society of Reproductive Medicine (r-ASRM) scores. Historical factors account for 50% of the EFI score [106], with nulliparity, increasing age, and duration of infertility resulting in a lower EFI score. Surgical factors, calculated using the LF score (30%) and the r-ASRM endometriosis and total r-ASRM scores (20%), account for the other 50% of the EFI score [106]. Although the LF score is subjective, relying on the surgeon's evaluation of the function of the ovaries, tubes, and fimbria, it is

considered a reliable measurement [102]. A cut-off of 71 for the total r-ASRM and a score of 16 for the endometriosis r-ASRM have been selected by considering the negative effect of large endometrioma and complete POD obliteration on fertility [153]. Currently, the r-ASRM stage and EFI score can only be determined surgically; however, newly established imaging techniques offer a promising alternative. Endometrioma and POD obliteration with adhesion can be detected with a high degree of accuracy using transvaginal ultrasound (TVS). Endometriomas appear as regular cystic lesions containing materials with a ground glass appearance [128] and are diagnosed with 90% sensitivity and 96% specificity through a routine TVS [155, 156]. Moreover, dynamic imaging can assess the sliding movement between the uterus or cervix against the colon to determine the extent of adhesion in the posterior uterine compartment [157] The negative sliding sign can predict POD obliteration with 93% accuracy, with a sensitivity of 83.3%, and a specificity of 97.1% [157].

The objectives of our study were to investigate the relationship between the sliding sign and the EFI in endometriosis patients and to explore the utility of the sliding sign to identify patients with an EFI score <7 and consequently a low chance of non-IVF conception.

3.2 Materials and methods

Patient selection

This study analyzed data from the Endometriosis Pelvic Pain Interdisciplinary Cohort (EPPIC), a prospective endometriosis registry (clinicaltrials.gov, NCT02911090) established in December 2013 at a tertiary referral center for endometriosis and pelvic pain in British Columbia, Canada. The registry was approved by the University of British Columbia Research Ethics Board and the BC Women's Hospital and Health Centre (H16-00264). Data for the EPPIC

registry is managed by the Research Electronic Data Capture (REDCap) data management platform at BC Children's Research Institute [130].

EPPIC contains a large dataset of women with endometriosis and/or pelvic pain, and details of its procedures have been previously published [89, 116]. After providing informed consent, participants were asked to complete an online baseline questionnaire, which included information about their demographic characteristics, pain assessment, and past medical and surgical history. When new or re-referred patients presented to the pelvic pain clinic, they had a physical examination and a TVS performed by an endometriosis specialist. If patients required surgery, surgical data, including staging, were entered prospectively by a gynecologist.

Inclusion criteria

In this study, we included consenting participants enrolled between December 2013 and June 2017 who matched the following inclusion criteria: 1) seen by a gynecologist in the pelvic pain clinic; 2) were ≤ 40 years old at the time of enrollment; 3) had EFI calculated via laparoscopy; 4) had sliding sign testing at the pelvic pain clinic (Figure 1).

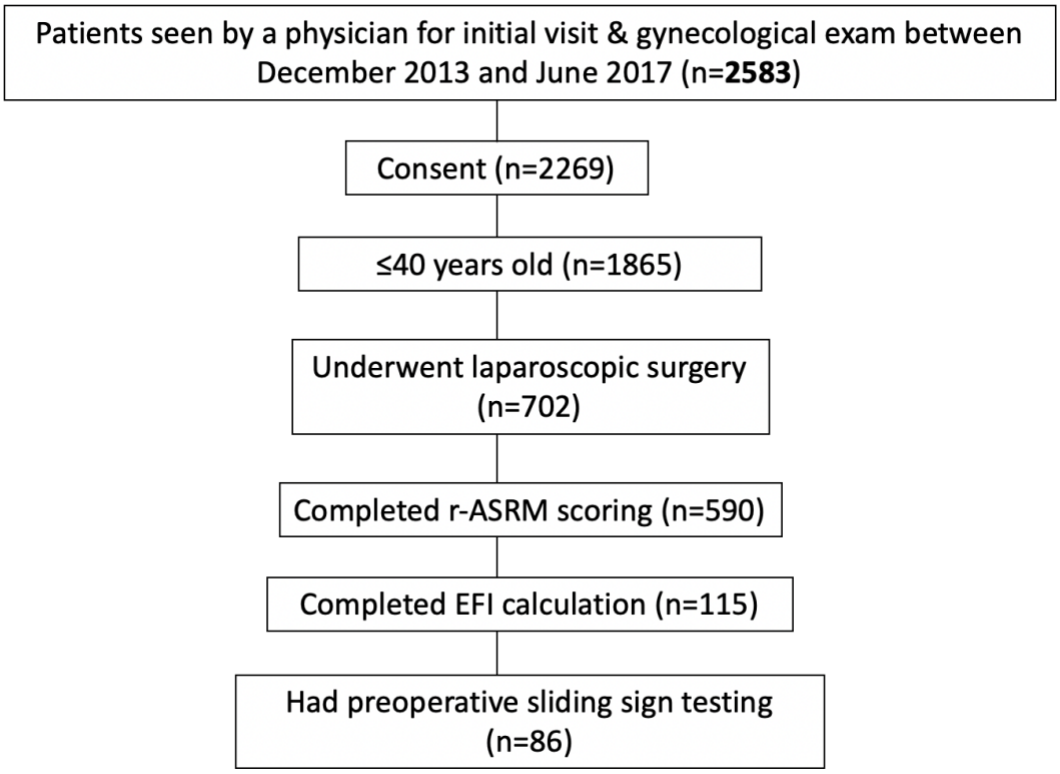


Figure 3.1. Participant selection flow chart

Gynecological assessment

In the pelvic pain clinic, a routine gynecological examination for endometriosis patients included palpating for DIE nodules of the POD, sliding sign assessment, and visualization of endometrioma by TVS. Sliding sign testing requires real-time dynamic imaging of uterine movement. This is part of the evaluation of POD obliteration status and pelvic adhesions, and it was performed at the pelvic pain clinic by gynecologists with more than five years of experience with dynamic ultrasonography. The sliding sign was tested in two locations: 1) between the rectum and cervix, where gentle pressure was applied on the cervix using the transvaginal ultrasound probe to observe the anterior rectum freely sliding over the posterior cervix; and 2) between the recto-sigmoid and the uterus, where the gynecologist applied pressure using a hand

on the lower abdominal wall to observe the recto-sigmoid freely sliding over the posterior upper uterus. The sliding sign is considered positive when free movement is observed in both locations (posterior cervix and posterior upper uterus). The sliding sign is considered negative when the colon is not seen to slide on the uterus or cervix.

Endometriosis fertility index

The EFI was determined only in infertile patients with complete r-ASRM scoring information. EFI and r-ASRM scores were prospectively collected for EPPIC as an integral part of the registry's surgical data [13, 153]. The r-ASRM form was completed when lesions consistent with endometriosis were observed during surgery.

A review of six studies showed the optimal EFI cut-off for IVF referral is between 5.5 and 7.5 [101-106]. The calculated mean of the suggested cut-off points is 6.5. Accordingly, we chose an EFI score of 7 as a cut-off, with EFI <7 being an indication for and immediate IVF referral.

Statistical analysis

We compared two groups, women with a positive sliding sign and women with a negative sliding sign, according to the dynamic TVS results. The comparisons were made with respect to 1) demographic and clinical factors, including age, body mass index (BMI), ethnicity, smoking, and alcohol use; 2) a pelvic examination with endometriosis-specific findings (i.e., presence of endometrioma, endometrioma size and laterality, and palpation of DIE nodules) and antral follicular count (AFC); 3) r-ASRM staging (stage I–IV); and 4) each element of the EFI, such as historical factors (age divided into three groups, history of parity, and duration of

infertility) and surgical factors (LF score, total r-ASRM, and endometriosis score) in addition to the total scores (historical factors score + surgical factors score = total EFI score). Continuous variables (i.e., age, historical factors score, surgical factors score, and total EFI scores) were compared using the Mann-Whitney test, and categorical variables were compared using chi-square or Fisher exact tests. We used logistic regression to create predictive models for low EFI (<7) and to calculate the receiver operating characteristic (ROC) area under the curve (AUC). The predictive model included the historical factors score, sliding sign, DIE, and endometrioma considering size and laterality (no endometrioma, unilateral endometrioma <3cm, and unilateral or bilateral endometrioma ≥3cm). All analyses were performed using SPSS version 24 (IBM Corp., Armonk, NY); $P<0.05$ was considered statistically significant.

3.3 Results

Eighty-six patients met the inclusion criteria: 60 participants had a positive sliding sign and 26 had a negative sliding sign. Participants with a negative sliding sign were older with a higher proportion of Southeast Asian women (Table 3.1).

Table 3.1. Descriptive statistics of the positive and negative sliding sign groups

	Total	Positive sliding sign	Negative sliding sign	*P Value*
N	86	60	26	
Age, Median (IQR)	33(30-36)	**32(29-35)**	**34(32-36)**	**0.010**
BMI	n (%)	n (%)	n (%)	
Underweight (>18.5)	3(3.5)	2(3.4)	1(3.8)	0.490
Normal (18.5–24.9)	54(62.8)	37(61.6)	17(65.4)	
Overweight (25–29.9)	14(16.3)	12(20)	2(7.8)	
Obese (≥30)	15(17.4)	9(15)	6(23)	
Ethnicity				
Caucasian	47(54.7)	37(62.7)	10(38.4)	0.061
East Asian	11(12.8)	7(11.9)	4(15.4)	0.728
Southeast Asian	5(5.8)	**1(1.7)**	**4(15.4)**	**0.028**
South Asian	11(12.8)	5(8.5)	6(23)	0.081
Others	11(12.8)	9(15.2)	2(7.8)	0.492
Smoking				
Yes	7(8.4)	4(7)	3(12)	0.425
No	76(91.6)	54(93)	22(88)	
Alcohol use				
Yes	46(55.4)	36(62)	10(40)	0.092
No	37(44.6)	22(38)	15(60)	

Clinical examination findings

Endometriomas were found in 29.1% of the participants (25/86); of these women, 60% (15/25) were in the negative sliding sign group and 40% (10/25) were in the positive sliding sign group. Endometriomas in the negative sliding sign group were more likely to be ≥ 3 cm in diameter (P<0.001). Women with a negative sliding sign were more likely to have DIE (*P*<0.001). AFC testing in 53 participants showed that most women with a positive sliding sign (82%, 32/39) had a normal AFC, at least in one side, with a measurement of ≥ 5 (*P*=0.033). An equal number of negative sliding sign women were in the normal and low AFC groups (bilaterally < 5 AFC) (Table 3.2).

Table 3.2. Transvaginal ultrasonography assessment in the positive and negative sliding sign groups

Gynecological examination factors	Total	Positive sliding sign	Negative sliding sign	*P Value*
Endometrioma	n (%)	n (%)	n (%)	
None	61(70.9)	**50(83.3)**	**11(42.3)**	**<0.001**
Unilateral<3	11(12.8)	7((11.7)	4(15.4)	
Unilateral or bilateral ≥3	14(16.3)	**3(5)**	**11(42.3)**	
DIE				
Yes	16(30.2)	**5(8.4)**	**11(42.3)**	**<0.001**
No	70(69.8)	**55(91.6)**	**15(57.7)**	
AFC*				
One side ≥5	39(73.6)	**32(82)**	**7(50)**	**0.033**
<5 bilaterally	14(26.4)	**7(18)**	**7(50)**	

***** tested in 53 participants
DIE = deep infiltrating endometriosis
AFC = antral follicular count

Surgical findings

Women with a negative sliding sign had higher r-ASRM scores (Table 3.3); we found that 92% (24/26) of women in this group had stage IV endometriosis, 3.8% (1/26) had stage III, 3.8% (1/26) had stage II, and none of the women had stage I. In contrast, women with a positive sliding sign had lower r-ASRM scores; we found that 10% (6/60) of women in this group had stage IV, 23.3% (14/60) had stage III, 35% (21/60) had stage II, and 31.7% had stage I (P<0.001). Women with a negative sliding sign had lower overall EFI scores (median = 5, IQR = 4–6, versus median = 7, IQR = 5–9; P<0.001; Figure 3.2, Table 3.4). Women with negative sliding sign also had lower scores for all surgical factors, including the LF score (P<0.001), they had a higher proportion of r-ASRM endometriosis scores over 16 (P<0.001), and a higher proportion of total r-ASRM scores over 71 (P<0.001). Overall, women with a negative sliding sign had a lower median for the total surgical factor score (median = 2, IQR = 1–3 versus median=5, IQR=4–5, P<0.001). With respect to medical historical factors, women with a negative sliding sign were more likely to report duration of infertility lasting greater than three years (P=0.03). The median total historical factors score was not significantly different between negative and positive sliding sign groups.

Table 3.3. R-ASRM scoring for the positive and negative sliding sign groups

R-ASRM	Total	Positive sliding sign	Negative sliding sign	*P Value*
	n(%)	n(%)	n(%)	
I	19(22.1)	19(31.7)	0	**<0.001**
II	22(25.6)	21(35)	1(3.8)	
III	15(17.4)	14(23.3)	1(3.8)	
IV	30(34.9)	6(10)	24(92.4)	

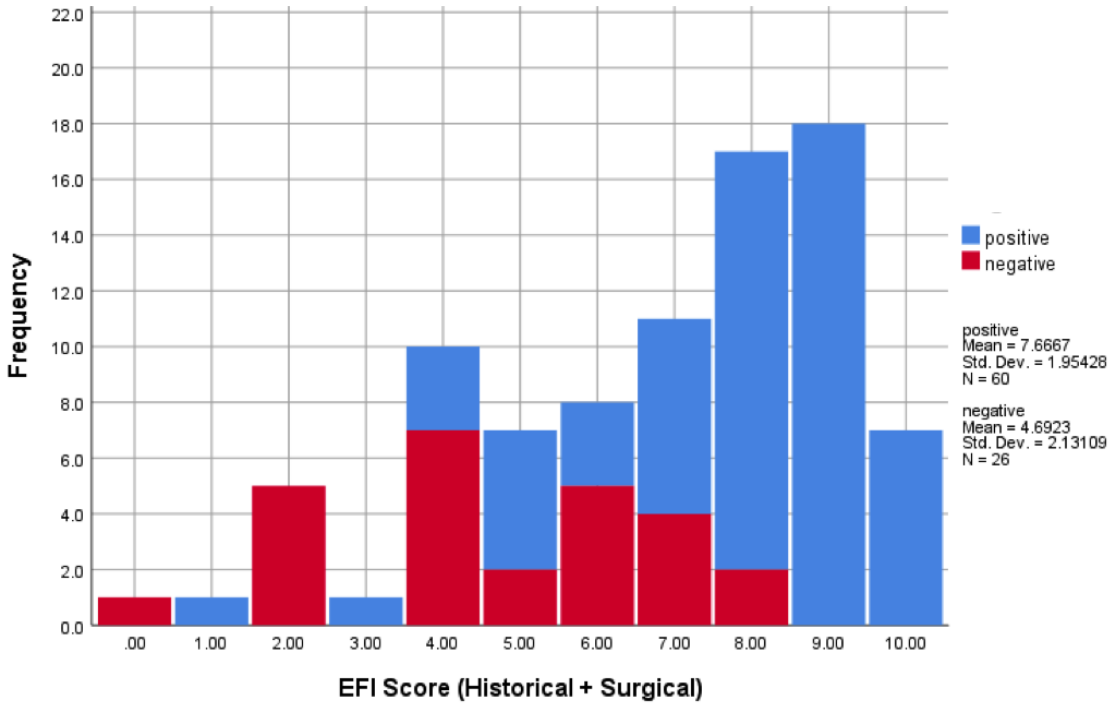


Figure 3.2. Total EFI score distribution of positive (blue) and negative (red) sliding sign participants

Table 3.4. EFI total and variable scores in the positive and negative sliding sign groups

EFI	Total	Positive sliding sign	Negative sliding sign	*P Value*
Historical factors				
Age	n (%)	n (%)	n (%)	
≤35	61(70.9)	45(75)	16(61.5)	0.389
36–39	16(18.6)	9(15)	7(27)	
≥40	9(10.5)	6(10)	3(11.5)	
Years of infertility				
>3	31(36)	**17(28.3)**	**14(53.8)**	**0.030**
≤3	55(64)	**43(71.7)**	**12(46.2)**	
Prior pregnancy				
Yes	28(32.6)	19(31.6)	9(34.6)	0.806
No	58(67.4)	41(68.3)	17(65.4)	
Historical Factors Score†	4(2–4)	4(2–4)	3.5(2–4)	0.051
Surgical factors				
Least function score	n (%)	n (%)	n (%)	
7–8	42(48.8)	**41(68.3)**	**1(3.8)**	**<0.001**
4–6	31(36)	**14(23.3)**	**17(65.4)**	
1–3	13(15.1)	**5(8.4)**	**8(30.8)**	
AFS endometriosis score				
<16	48(55.8)	**46(76.7)**	**2(7.7)**	**<0.001**
≥16	38(44.2)	**14(23.3)**	**24(92.3)**	
AFS total score				
<71	70(81.4)	**59(98.3)**	**11(42.3)**	**<0.001**
≥71	16(18.6)	**1(1.7)**	**15(57.7)**	
Surgical factors score†	4(2–5)	**5(4–5)**	**2(1–3)**	**<0.001**
EFI total score †	7(5–9)	**8(7–9)**	**5(4–6)**	**<0.001**

†median(IQR)

Predictive models

Logistic regression results are shown in Table 3.5 and Figure 3.3. Using the historical factors score alone in the predictive model resulted in AUC of 0.85 (95% CI 0.77–0.94), sensitivity of 63.6%, and specificity of 90.6%. Adding endometrioma as a predictor to the EFI historical factors score resulted in AUC of 0.87 (95% CI = 0.78–0.94), sensitivity of 69.7%, and specificity of 88.7%, while adding sliding sign to the EFI historical factors (without the endometrioma) resulted in AUC of 0.93 (95% CI = 0.878–0.983), sensitivity of 87.9%, and

specificity of 81.1%. Using DIE with endometrioma and the historical factors score resulted in AUC of 0.89 (95%CI=0.82–-0.96), sensitivity of 72.7, and specificity of 84.9. Using endometrioma and sliding sign with the EFI historical factors score resulted in AUC of 0.95 (95% CI=0.90–0.995), sensitivity of 84.8%, and specificity of 92.5%. Finally, the same results were achieved when the diagnosis of DIE was added as a predictor to the previous model (Table 3.5, Figure 3.3).

Table 3.5. Binominal logistic regression results and factors used to predict EFI<7

Factors	Sensitivity	Specificity	PPV	NPV	AUC (95%CI)
EFI Historical factors score	63.6	90.6	80.8	80	0.85 (0.77–0.94)
EFI Historical factors score +endometrioma	88.7	69.7	79.3	82.5	0.87 (0.78–0.94)
EFI Historical factors score +endometrioma +DIE	72.7	84.9	75.0	83.3	0.89 (0.82–0.96)
EFI Historical factors score + sliding sign	87.9	81.1	74.4	91.5	0.93 (0.88–0.98)
EFI Historical factors score + sliding sign + endometrioma	84.8	92.5	87.5	90.7	0.95 (0.90-1.00)
EFI Historical factors score + sliding sign + endometrioma + DIE	84.8	92.5	87.5	90.7	0.95 (0.90-1.00)

PPV=positive predictive value
NPV=negative predictive value

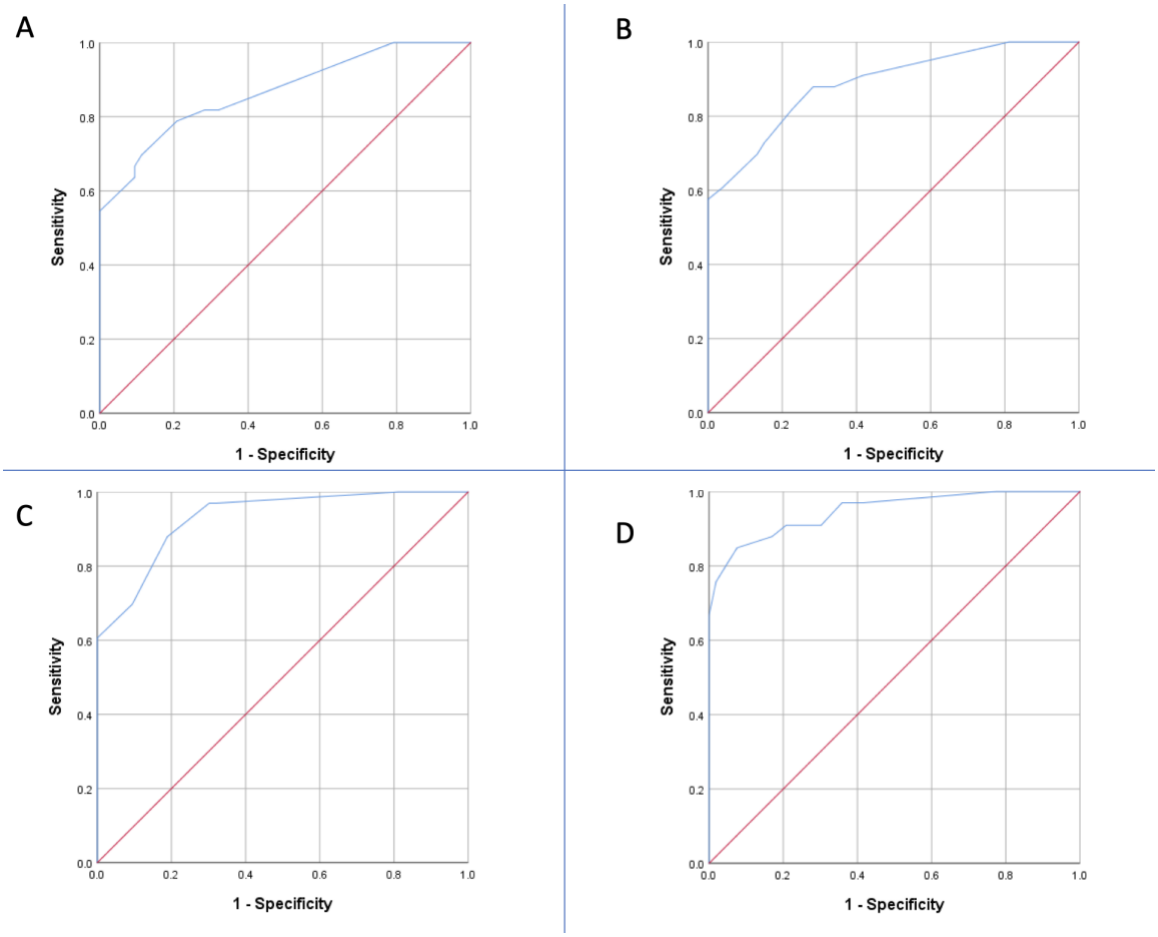


Figure 3.3. ROC curve (blue line) for EFI<7 based in the following models: A) historical factors score and endometrioma, B) historical factors score + endometrioma + DIE, C) historical factors score + sliding sign, D) historical factors score + endometrioma + sliding sign

3.4 Discussion

In this study of women with endometriosis who were referred to a tertiary center, we found that the EFI for women with a negative sliding sign was lower than for those with a positive sliding sign. Participants in the negative sliding sign group were older and more likely to have severe endometriosis and endometriomas. The negative sliding sign was associated with a lower EFI surgical factors score than the historical factors score. Results of regression analysis suggest that a negative sliding sign can be combined with simple fertility prognostic measures (the EFI historical factors score and the diagnosis of endometrioma) to predict a low EFI score,. This could provide an alternative approach to counseling infertile women with suspected endometriosis about their fertility plan without the need for laparoscopy.

One strength of our study was the use of a standardized prospectively collected data registry. Additionally, we used a validated technique (sliding sign testing) that can be conducted in a gynecologist's office without the need for a fertility trained subspecialist. The study's main limitation was the small sample size, which was a consequence of the restrictive inclusion criteria (complete EFI calculation and sliding sign testing). Furthermore, prospective replication and validation of these results through linking the sliding sign to the clinical PR is required.

Endometriosis is a progressive disease that, in the severe stage, may be associated with infertility through mechanical disruption of the reproductive organs. Increasing size of endometriotic cysts, DIE, and complete POD obliteration are markers of disease advancement [158, 159]. Thus, in older, infertile women with endometriosis, the condition is expected to be more advanced. In our study, women with a negative sliding sign had a higher median age than women with a positive sliding sign. A negative sliding sign was also associated with the diagnosis of endometriomas and DIE nodules. Reid et al. reported a higher percentage of

unilateral endometriomas, bilateral endometriomas, and rectal DIE in their negative sliding sign group than in their positive sliding sign group (34%, 27%, and 66% versus 12%, 3%, and 7%, respectively)[160]. However, their research focused on the sliding sign's prediction of DIE during laparoscopy, which showed a high specificity (90.3%) and sensitivity (73.7%). Accuracy of the sliding sign's prediction of POD obliteration status during surgery has been validated in a previous study [157]. It has also been validated in a study using our data; the sensitivity was 73.2% (95% CI=57.1%–85.8%) and the specificity was 93.9% (95% CI=89.9%–96.6%)[161]. Furthermore, in another study, the sliding sign was used to evaluate the intra-abdominal adhesion status in women who had undergone repeated caesarean section deliveries. The negative sliding sign had a sensitivity of 56% (95% CI=35–76) and specificity of 95% (95% CI=93–97) in predicting severe intra-abdominal adhesions [162].

Endometriomas hamper fertility as they exert a pressure effect on the ovary and create a barrier to oocyte retrieval at the fimbria [163]. In addition, toxic agents that can have a detrimental effect on folliculogenesis and oocyte fertilization can potentially diffuse through the wall of the endometrioma [164]. A 2008 Cochrane review indicated that the complete removal of endometriomas resulted in an increased rate of spontaneous pregnancy [165]. However, a cystectomy should be carefully considered because it may have a negative effect on ovarian reserve, especially in bilateral endometriomas [166, 167]. The relationship of DIE to infertility is controversial due to the high rate of association with other forms of the disease (endometrioma, adhesions, and adenomyosis)[168]. Surgical treatment of DIE without the association of other forms resulted in a 46.7% spontaneous PR [169]. However, Vercellini et al. reported that surgical management of DIE and expectant management resulted in similar PRs (44.9% and 46.8%, respectively)[170]. The existence of endometrioma with DIE lowers the PR with or without

surgical treatment [171]. Posterior compartment DIE is usually associated with adhesions and POD obliteration that could affect tubal function and prevent spontaneous conception [172]. In one study, surgical treatment of complete POD obliteration resulted in a viable intrauterine pregnancy in 70% of 46 women with infertility [173]. This suggests that endometriomas and/or POD obliteration have a significantly greater effect on fertility than DIE alone. In our study, using the sliding sign and the presense of endometrioma with historical factors resulted in the highest predictive power (AUC=0.95). Moreover, the sliding sign appeared to be more important than endometrioma and DIE (together) in predicting the EFI score, suggested by the higher AUC when the sliding sign and the historical factors score were used in the prediction of EFI <7 (Table 3.5, Figure 3.3).

Options for the treatment of endometriosis-associated infertility are conservative management, IVF, or surgery [24, 174]. Conservative management is reserved for young women who have the mild form of the disease, a normal ovarian reserve, and whose partners have normal semen. In other cases, IVF bypasses and surgery aims to correct the distorted pelvic anatomy. Evidence to support the superiority of either method (IVF or surgery alone) in treating infertility is lacking, and there is no consensus on whether surgery or IVF should be offered first for patients with advanced endometriosis [175]. IVF is less invasive than surgery, but advanced endometriosis reduces the chance of successful IVF according to a recent study that analysed the Society for Assisted Reproductive Technologies (SART) database [92]. Surgical excision of endometriosis improves the chance of spontaneous pregnancy[176], which has a more favorable outcome than pregnancy resulting from IVF [177]. However, increasing maternal age among infertile women and the negative effect of endometriosis on ovarian reserve should be taken into consideration when offering surgical treatment. Scheduling a surgical procedure in a specialized

endometriosis center, ensuring adequate post-operative recovery, and allowing a period of natural pregnancy in those women contribute to a reduced probability of pregnancy in a given time period. Although the EFI is a robust tool for the prediction of natural PR and IVF outcomes, it mandates surgery and cannot resolve this debate.

Our study suggests that EFI can be effectively estimated without the need for laparoscopy. In this cohort, a negative sliding sign, presence of endometrioma, and the EFI historical factors score predicted the EFI score of < 7 with a high degree of accuracy. However, these results need to be replicated in a larger study. If proven accurate, this relatively simple tool could be used to counsel patients with endometriosis about their low probability of spontaneous conception.

Chapter 4: Conclusion and Future direction

4.1 Conclusion

Endometriosis is an enigmatic, incurable, chronic, and recurrent gynecological disease, which provides a substantial challenge for investigators and the health care system [93]. One of the challenges of managing endometriosis is the potential delayed diagnosis due to the requirement for a specialist referral and the requirement for laparoscopic evaluation in some patients [16, 17]. There is a substantial rate of negative findings at laparoscopy, even in cases in which endometriosis is highly suspected, leaving those patients with unexplained symptoms and an unclear management plan[18]. There are many overlapping comorbidities that might contribute to the severity of endometriosis symptoms, and this require further understanding [77, 78]. There is a high rate of failure of medical or surgical treatment [72, 87], especially for CPP associated with central sensitization, which requires a long-term, multidisciplinary plan to improve patients' symptoms and quality of life. The only evidence-based practice, to date, to counseling patients about their predicted PR is through EFI, which requires a specialist to perform surgery on infertile patients with endometriosis [99]. Moreover, attempting to explain the non-specific symptoms, the risk, and the prognostic factors is complicated by a contradictory and a frequently low-quality evidence [93].

In this thesis, I used registry data from a specialized tertiary care center for the management of pelvic pain and endometriosis. Most of the participants who consented to join the registry were referred for management of persistent pelvic pain symptoms or prolonged periods of infertility with suspected endometriosis. I found a significant and independent association between parity and severity of CPP, independent of pain catastrophizing, obesity, and severe back pain symptoms. In addition to a worse quality of life, I found a lower rate of observing

pathology resembling endometriosis during surgery and a lower rate of histological confirmation of endometriosis in parous women than in nulligravid women. In the second part of this thesis, I found that simple diagnostic imaging (using the sliding sign and the presence of endometrioma) can be used with patients' historical prognostic fertility factors (i.e., age, previous parity, and duration of infertility) to predict an EFI score of <7.

4.2 Future direction

Both of these studies proposed a novel approach to further understand factors contributing to CPP and infertility. The findings need further validation to be applied in practice. More studies are required to explain the relationship between parity and severe CPP. For example, the relationship between the high incidence of adenomyosis in parous women or women with history of D & C needs further investigation. Additionally, the central and peripheral nervous system changes during and after pregnancy need to be closely investigated in parous women with CPP, together with sensory testing for central sensitization. Given the protective effect of pregnancy, there is a lower likelihood of finding endometriosis in those patients; pelvic trauma and the denervation process could be the causative factors for CPP, not endometriosis itself. If confirmed in future studies, this would provide a closer understanding of cases with severe CPP and normal laparoscopic findings. Damage could be at the level of the peripheral nerve ending or the central nervous system, and this cannot be diagnosed with laparoscopic surgery. The status of neurogenesis in patients with negative findings during laparoscopy can be investigated with a nerve bundle density study. Biopsies could be collected from tender locations with the guide of preoperative pain mapping. Those patients may also require functional magnetic resonance imaging (fMRI) scanning to determine gray matter

changes. Medical treatments for pathological neurogenesis associated with endometriosis are being investigated. If enhanced neurogenesis in parous women is shown to result from pelvic trauma, those patients could be candidates for such medical treatment in the future.

In the second study, I proposed using a less invasive approach (TVS and patient's history) to triage women with endometriosis and infertility who require IVF. This approach could replace EFI, which would lower the number of required surgeries. Furthermore, providing training for sliding sign testing in the secondary health care system would lower the requirement for tertiary center referral and avoid the management delay. Additionally, this less invasive approach would guide future study to investigate further characteristics of the disease associated with IVF failure, and it could provide evidence to triage patients into undergoing IVF or surgery. In the future, I would like to increase the sample size and conduct a longitudinal study to follow patients over time. It is important to validate the proposed model by linking our findings to the PR and the number of live births.

Finally, it is essential to translate these research findings for patients and health care providers. I have presented some of my findings at the annual meeting for the American Society of Reproductive Medicine in 2018; the annual celebration of hope, which is part of endometriosis awareness month and involved patients from the BC Women's CPP and endometriosis centre; and at the Annual Academic Day for the Department of Obstetrics and Gynecology at UBC. I will also submit both study papers for publication.

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Appendices

Appendix A

A.1 Menstrual characteristics of the three groups

	Total	**Nulliparous**	**Parous**	**Miscarriage/ Abortion**	***P* Value**
Age of menarche†	12(12-13)	12(12-13)	13(12-14)	12(11-13)	0.750
Days of bleeding†	5(4-7)	5(4-7)	5(5-7)	5(4-7)	0.290
Menstrual flow	**841**	**n (%)**	**n (%)**	**n (%)**	
Light	114	64(13.1)	33(13.4)	17(15.7)	0.154
Moderate	285	180(37)	69(28)	36(33.3)	
Heavy	442	243(49.9)	144(58.5)	55(50.9)	

*Significantly different group.
†Median (IQR)

Appendix B

B.1 Ordinal regression results: factors included in the analysis

Factors	*P* Value	AOR	95%CI
Parity	0.012	1.544	1.102–2.163
Miscarriage	0.292	1.260	0.820-–1.937
Age	0.489	0.992	0.971–1.014
BMI	0.004	1.035	1.011–1.059
Smoking	0.161	1.306	0.899–1.897
Alcohol	0.065	0.776	0.593–1.016
Cul-de-sac tenderness	0.530	1.086	0.840–1.404
Severe back pain	0.000	2.483	1.874–3.291
Adenomyosis	0.962	0.989	0.618–1.581
Previous surgery for endometriosis	0.723	0.950	0.715–1.262
GAD-7	0.821	0.997	0.969–1.025
PCS	0.000	1.040	1.027–1.053

Appendix C

C.1 Publications

1. Wu CQ, Albert A, **Alfaraj S**, Taskin O, Alkusayer GM, Havelock J, Yong P, Allaire C, Bedaiwy MA. Live birth rate after surgical and expectant management of endometriomas after in vitro fertilization: A systematic review, meta-analysis, and critical appraisal of current guidelines and previous meta-analyses. J Minim Invasive Gynecol. 2019 Feb 26.
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6. Bedaiwy MA, Allaire C, Yong P, **Alfaraj S**. Medical management of endometriosis in patients with chronic pelvic pain. Semin Reprod Med. 2016 Dec 21.