HYSTERECTOMY FOR ENDOMETRIOSIS WITH OR WITHOUT OVARIAN PRESERVATION IN BRITISH COLUMBIA, CANADA: A POPULATION BASED RETROSPECTIVE COHORT STUDY OF POST SURGICAL OUTCOMES

by

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Abstract

BACKGROUND: More research is needed comparing post-surgical outcomes between patients who undergo hysterectomy for endometriosis with or without ovarian conservation.

OBJECTIVE: To compare the rate of reoperation and use of other pain-related health services after hysterectomy for endometriosis, with or without ovarian conservation

METHODS: A population-based retrospective cohort study of 4489 patients aged 19-50 in British Columbia, Canada, undergoing hysterectomy for endometriosis between 2001 and 2016. Index surgeries were classified as: hysterectomy alone (conservation of both ovaries), hysterectomy with unilateral salpingoophorectomy (USO), or hysterectomy with bilateral salpingoophorectomy (BSO). Reoperation rate was the primary outcome. Secondary outcomes (measured at 3-12 months and 1-5 years after hysterectomy) included: physician visits for endometriosis and pelvic pain, prescriptions filled for opioids and hormonal suppression medications and hormone replacement therapy (HRT).

RESULTS: 89.5% of patients remained reoperation free by the end of follow-up (median of 10 years, IQR = 6.1 to 14.3 years). Patients undergoing hysterectomy alone were more likely to undergo at least one reoperation compared to those having hysterectomy with BSO (13% vs 5%, $p<0.0001$), most commonly oophorectomy and adhesiolysis. When oophorectomy as reoperation was removed in a sensitivity analysis, this difference was attenuated. Secondary outcomes including physician visits for endometriosis or pelvic pain and rates of opioid prescriptions filled were similar between groups. The rate of prescriptions filled for hormonal suppression medications was low for all groups. The rate of prescriptions filled for HRT after hysterectomy with BSO was suboptimal - 60.6% filling at least one prescription at 3-12 months after index surgery.

CONCLUSION: Patients who underwent hysterectomy with BSO had a lower reoperation rate than those who had hysterectomy with conservation of one or both ovaries. However, there was little difference between the groups for the secondary outcomes measured, suggesting that persistent pelvic pain after hysterectomy for endometriosis may not differ significantly based on ovarian conservation status. Moreover, HRT use after hysterectomy with BSO was suboptimal, which may have significant health consequences for these individuals undergoing premature surgical menopause. Therefore, strong consideration should be given to ovarian conservation at the time of hysterectomy for endometriosis.

Lay Summary

Hysterectomy (surgical removal of the uterus) is done for some people with endometriosis to improve pelvic pain. Our study looked at people who had both, one, or none of their ovaries removed at the time of their hysterectomy, and whether their pain related outcomes would be different after surgery. We found that people who had one or both ovaries removed with their hysterectomy were slightly more likely to have another surgery, mostly to remove remaining ovaries, compared to people who had both ovaries removed at the time of hysterectomy. However, other measures of persistent pain, such as doctor visits for pain or endometriosis, hormonal medication use, and opioid medication use was not different between groups, suggesting there are other factors that may be contributing to persistent pain. We also found suboptimal use of hormonal replacement therapy in people who had both ovaries removed at the time of hysterectomy.

Preface

The research project was developed under the supervision of Dr. Paul Yong and Dr. Gillian Hanley using the PopDataBC database for this retrospective cohort population based study.

The preliminary draft of the thesis was prepared by myself under the guidance of my supervisory committee. Revisions were made after review by my supervisory committee. Data extraction from the PopDataBC database was made possible with the assistance of Dr. Paramdeep Kaur and Alexandra Lukey. For each of the study aims, I led the study design, directed the extraction of data, and analyzed the outcomes. The statistical analysis was performed by Dr. Gillian Hanley, Dr. Paramdeep Kaur and Alexandra Lukey. Chapter 2 of this thesis was submitted as a manuscript for publication to the American Journal of Obstetrics and Gynecology (AJOG), which was accepted and currently is in press (as of August 30, 2022). The results were presented at the Department of Obstetrics & Gynecology Research Day in May 2022 as an oral presentation (Edmonton, AB) and at the Society of Obstetrics and Gynecology (SOGC) meeting as an oral presentation in June 2022, Quebec City, QC.

Ethics approval was provided by the Research Ethics Board (REB) of the University of British Columbia (H20-00259).

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AMH	anti-Mullerian hormone
AFC	antral follicle count
BO	bilateral oophorectomy (removal of both ovaries)
BS	bilateral salpingectomy (removal of both Fallopian tubes)
BSO	bilateral salpingo-oophorectomy (removal of both Fallopian tubes and ovaries)
CBT	cognitive behavioural therapy
CNS	central nervous system
COC	combined oral contraceptive
CVD	cardiovascular disease
FMP	final menstrual period
GnRH	gonadotropin releasing hormone
HNPCC	hereditary nonpolyposis colorectal cancer syndrome
HPO axis	hypothalamic pituitary axis
HRT	hormone replacement therapy
IBS	irritable bowel syndrome
IASP	International Association for the Study of Pain
ICD	International Classification of Disease
KT	knowledge translation
LNG-IUS	levonorgestrel intrauterine system
MSK	musculoskeletal
MSP	medical services plan
NSAIDs	non-steroidal anti-inflammatory drugs

OCP	oral contraceptive pill
PBS	painful bladder syndrome
STRAW	Stages of Reproductive Aging Workshop
UO	unilateral oophorectomy (removal of one ovary)
USO	unilateral salpingo-oophorectomy (removal of one Fallopian tube and one ovary)

Acknowledgements

I would like to dedicate this project to my husband, Thom Male, who has unconditionally supported my academic journey across the years and across provinces, who supported me during a pandemic and a lockdown with a new baby in a new home where we had no family nearby, who allowed and encouraged me to leave the house to work on this project for as many days and hours as needed whilst keeping our newborn (now toddler) alive and thriving.

I would also like to thank my supervisors, Dr. Gillian Hanley and Dr. Paul Yong, for their support, encouragement and feedback, despite circumstances that made completing a Masters incredibly difficult during this time. Thank you as well to Dr. Paramdeep Kaur and Alexandra Lukey for assisting with the data extraction, when I felt as though I would need a degree in computer science to achieve this otherwise. Thank you to my supervisory committee for the encouragement and feedback on the project and allowing this important work to be disseminated into the scientific community. This project was supported by the Canada Graduate Scholarship - Master's Award.

Chapter 1: Introduction

1.1 Overview and Classification of Endometriosis

Endometriosis is a common estrogen dependent and inflammatory chronic condition that is estimated to affect approximately 5-10% of reproductive age women (~1 million women in Canada, or 176 million women worldwide)[1] and up to 50% of women with infertility and/or chronic pelvic pain[2]. Specifically, endometriosis is the presence of tissue resembling uterine endometrial tissue located outside the uterus ("ectopic endometrium"), in contrast to normal uterine endometrium ("eutopic endometrium"). The most common location for ectopic endometriotic lesions is in the pelvis, however in rare circumstances endometriosis may affect extra-pelvic sites such as the appendix, diaphragm, and thorax[3]. The lesions themselves may be phenotypically classified into superficial peritoneal endometriosis, endometrioma and deep endometriosis[1]. Superficial peritoneal endometriosis involves lesions that have less than 5mm depth of invasion, whereas deep lesions involve more than 5mm depth of invasion[4]. The lesions may implant on the lining of the pelvis or abdomen (the peritoneum), or may invade into visceral structures such as the uterus, the bowel, the bladder, the ovaries or other organs[5]. When endometriosis invades deeply into the ovary and forms a cyst, this is known as an endometrioma[5] (Figure 1.1). Because endometriosis can present with such diverse anatomical phenotypes, physicians and surgeons have aimed to classify the disease as means of communication[5,6]. Dating back to 1985 in its original form, the Revised American Fertility Society Classification (rAFS) was developed as a tool to classify endometriosis anatomically into four stages. A score is assigned based on a points system related to the location and depth of endometriosis lesions, resulting in a classification of minimal (Stage I), mild (Stage II), moderate (Stage III) or severe (Stage IV)[4] (Figure 1.2). Interestingly, disease severity (ie rAFS stage) is not correlated with the

patient's severity of symptoms; for example, a person with minimal (Stage I) endometriosis may present with significant pain, and conversely another individual with Stage IV endometriosis may have very little or no pain[1,6]. The reason is that while rAFS staging correlates to anatomic burden of disease, the pathophysiology of symptoms such as pain involves a continuum of factors beyond anatomic changes, from peripheral to central, such as local neurogenesis, peripheral sensitization, and cross-organ and central nervous system sensitization[6]. These factors confound the relationship between anatomic stage and clinical presentation, such that the process has begun for a new, universally accepted staging system for endometriosis[7]. A more detailed discussion of endometriosis associated pain is below. The rAFS is still used today, especially to classify anatomical severity of endometriosis, a communication tool between healthcare practitioners and patients, and for surgical planning.

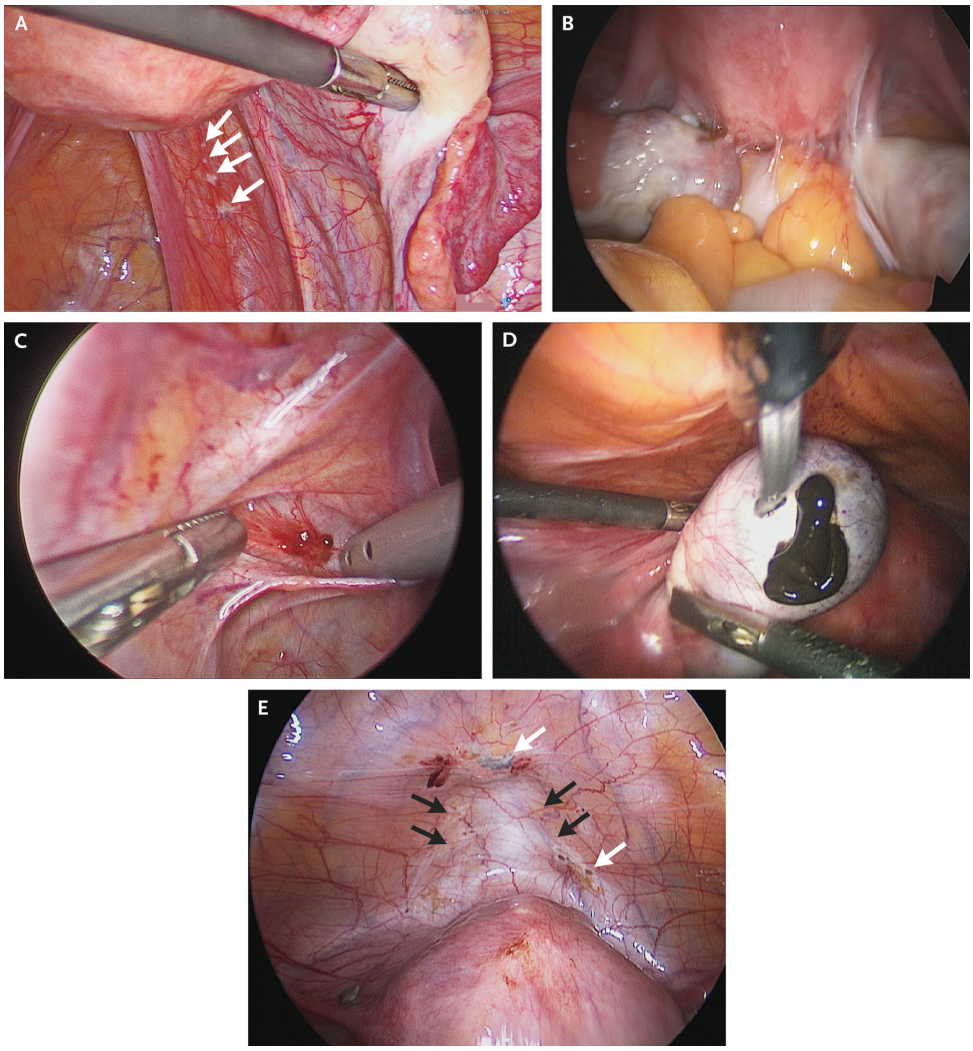


Figure 1.1 Endometriosis phenotypes. A - superficial “powder burn” endometriosis, B – deep endometriosis with obliteration of cul-de-sac, C – superficial red vascular endometriosis, D - ovarian endometrioma, E - deeply infiltrating bladder endometriosis, brown, black and red endometriosis lesions[5]

Revised American Fertility Society Classification of Endometriosis: 1985

The American Fertility Society*†

Birmingham, Alabama

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.

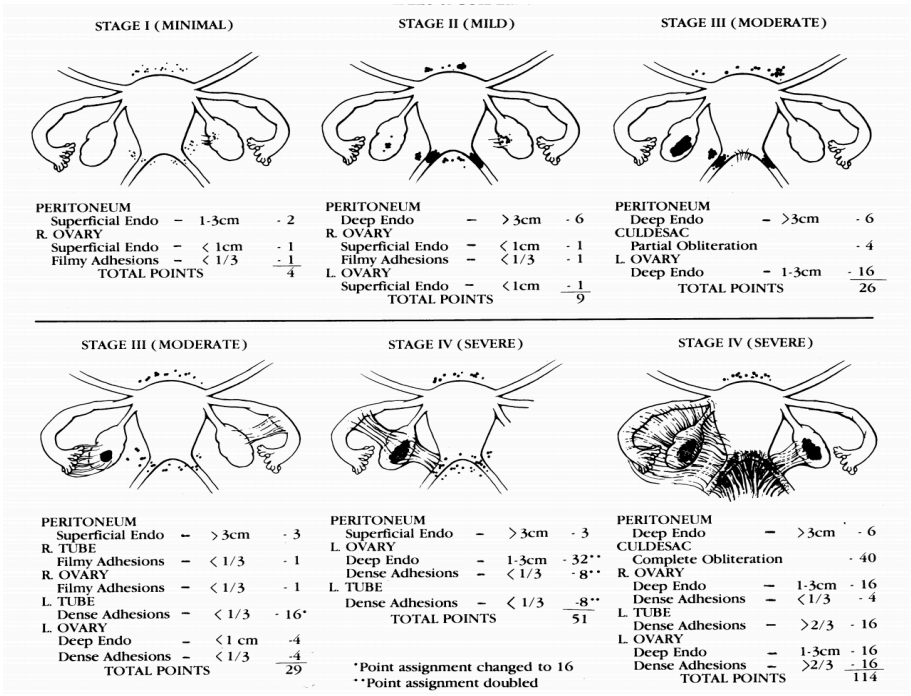


Figure 1.2 Revised American Fertility Society Classification of Endometriosis[4].

1.2 Pathophysiology of Endometriosis

The pathophysiology of how endometriosis originates is still not completely understood. Different potential mechanisms have been proposed but none on its own can solely explain the process of how an individual develops endometriosis. One of the most commonly cited mechanisms for endometriosis is Sampson's theory of retrograde menstruation, ie the backflow of menstrual fluid through the Fallopian tubes and into the pelvis followed by implantation of endometrial tissue onto the surfaces of the pelvis and pelvic organs[8]; however retrograde menstruation occurs in more than 90% of women with patent Fallopian tubes[9], the majority of which do not go on to develop endometriosis, suggesting that there are further factors such as genetic and immunologic influences that predispose an individual to developing endometriosis. In order for these endometrial-like cells to invade and implant into pelvic tissue, the cells must develop their own blood supply and escape the body's immune system. These cells may have an enhanced ability to escape apoptosis in women with endometriosis, and furthermore, macrophages, monocytes and natural killer cells in peritoneal fluid of women with endometriosis have been shown to have altered immune function, secreting cytokines, chemokines and prostaglandins that seem to promote the persistence of endometriosis implants, rather than protect against its development[5,10]. Rarely, endometriosis is found in extra-pelvic locations that cannot be explained by the mechanism of retrograde menstruation (ex lymph nodes, lungs, brain, limbs), and so other mechanisms for its histogenesis have been proposed including vascular/lymphatic dissemination and "coelomic metaplasia" (metaplasia is defined as the replacement of one differentiated cell type into another mature differentiated cell type - from mesothelial cells into endometrial glandular cells)[1,11,12].

Given that endometriosis is characterized by endometrial-like cells present outside the pelvis, these ectopic lesions are responsive to the monthly cycles of hormonal fluctuations that are directed by the hypothalamic-pituitary-ovarian axis, just like eutopic endometrium. Endometriosis therefore, is an estrogen dependent condition that grows and sheds in conjunction with the natural menstrual hormonal cycle. However, eutopic and ectopic endometrium do exhibit slight histologic differences. Ectopic endometrial cells have been shown to produce excess estrogen, prostaglandins, and cytokines compared to the eutopic endometrium[11]. Although not considered a malignant condition, a parallel can be drawn between endometriosis lesions and cancerous lesions, in that they both can migrate/metastasize, are invasive and have self-sustaining properties. Ectopic endometrial cells can autonomously produce their own estrogens to sustain growth and inflammation through an upregulation of aromatase and COX-2 enzymes, essentially creating a positive feedback loop of aromatase, COX-2 and estrogen production (Figure 1.3); however they are still responsive to endogenous and exogenous stimuli including hormones and other synthetic compounds[13,14]. The eutopic endometrium of individuals not affected by endometriosis is quite sensitive to progesterone. In individuals with endometriosis however, ectopic endometrial tissue is relatively resistant to progesterone, which normally has an anti-estrogenic effect on endometrial tissue. Additionally, of the two identified progesterone receptors (PR-A and PR-B), PR-A is relatively overexpressed relative to PR-B in ectopic endometrial tissue[11]. Furthermore, there is emerging evidence that even eutopic endometrium of individuals with endometriosis is more resistant to progesterone than the eutopic endometrium of individuals without endometriosis[15].

In summary, the pathogenesis of endometriosis is multifactorial, involving the anatomic mechanisms of refluxed menstrual fluid containing endometrial cells into the peritoneal cavity, which must escape normal immunomodulatory mechanisms for clearance of these cells. There is an abnormal inflammatory response in women with endometriosis, as well as hormonal mechanisms (elevated estrogen and progesterone resistance) that work to allow the persistence of ectopic endometrial implants.

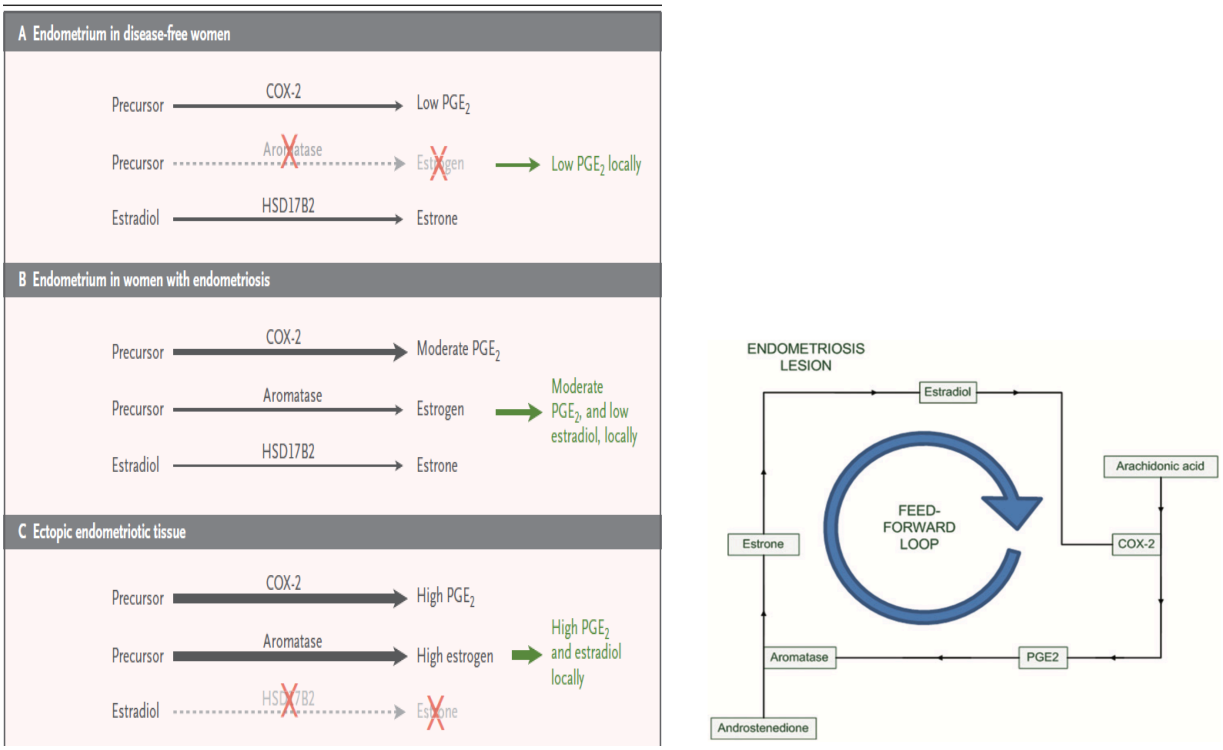


Figure 1.3 Hormonal and enzymatic alterations of ectopic endometrium[13,14].

1.3 Epidemiology of Endometriosis

Prevalence estimates of endometriosis vary according to studies, and according to whether the patients are symptomatic or asymptomatic. Given that the gold standard of diagnosing endometriosis is surgical visualization and biopsy/excision with positive histologic pathology[16],

it is difficult to appreciate the prevalence in an asymptomatic population, as these individuals may not present for medical care or ever undergo laparoscopy. Several studies looking at the prevalence of endometriosis at the time of tubal ligation (presumably asymptomatic patients), estimates the prevalence at 1-7%[2,17,18], although this is likely an underestimate[1]. In a population based cohort study of unscreened women undergoing MRI, 11% were diagnosed with endometriosis[19]. This is likely also an underestimate, as traditional non-invasive diagnostic imaging (ex ultrasound and MRI) has not been able to detect superficial (stage I/II) endometriosis to this point[20]. This population is unique, as despite the presence of endometriosis (sometimes even at advanced stages), there must be a physiological adaptation that prevents symptoms. For example, As-Sanie et al. found that in patients with endometriosis and no pain, there is a relatively increased volume of the periaqueductal gray matter in the thalamus, an area of the brain that regulates pain, which may increase descending modulation of pain signals, compared to patients with endometriosis and pelvic pain[21]. However the prevalence of endometriosis in patients experiencing infertility or pelvic pain may be as high as 50%[2]. Family history[22,23] increases an individuals risk; there is 4-8 times the baseline risk of having endometriosis if a first degree relative has the diagnosis[24]. Ethnicity may also be a risk factor, with black individuals thought to be at lower risk, and Asian populations at higher risk, compared to white individuals[25,26]. South and South East Asian women may also be at higher risk of advanced stage endometriosis compared to white populations[27]. Additional risk factors include obstructive Mullerian anomalies[28], earlier age of menarche[29], shorter cycle length[25,29], parity (lower risk with increasing parity)[25], BMI (weak inverse association)[29,30], exercise (regular exercise may decrease risk)[31], smoking (may decrease risk)[29,30], alcohol (may increase risk)[31,32]

caffeine use (may increase risk)[33], in utero exposures (diethylstilbestrol)[34] and early life exposures (being born prematurity and low birth weight)[34].

1.4 Symptoms of Endometriosis

The most common symptoms of endometriosis for which a patient will present for medical care are pelvic pain and/or infertility. In women with these symptoms, the prevalence of endometriosis may be as high as 50-60%[11]. Pain symptoms commonly include painful periods (dysmenorrhea), pain with sexual intercourse (dyspareunia), pain with bowel movements (dyschezia). Often, these symptoms are cyclical, coinciding with menses. Sometimes there is also pain outside of the menstrual cycle, which may be daily or non-cyclic. Chronic pelvic pain (defined as 6 months or more of persistent pelvic pain) is commonly attributed to endometriosis; however, not all women with endometriosis will present with pain symptoms. Interestingly, stage of endometriosis (as classified by the Revised American Fertility Society Classification (rAFS) score) does not correlate well with pain symptoms; for example, someone affected by Stage IV endometriosis may have very little pain and someone affected by Stage I endometriosis may have severe pain [5,6,35]. While the rAFS classification is useful as a descriptive tool that correlates with surgical difficulty, there have also been efforts to classify endometriosis patients based on the phenotype of their pain symptoms to be able to treat patients using medical, surgical or other approaches that will best address their pain[6].

1.5 Endometriosis Associated Pain

As described above, there is significant variability in the presentation and degree of pelvic pain associated with endometriosis, regardless of the rAFS stage assigned to the patient. Traditionally,

it has been assumed that endometriosis associated pain is predominantly related to the anatomic distortion caused by the disease[6] and that it is hormonally mediated, such that treatment is most commonly comprised of suppression of endogenous estrogen using hormonal methods, or surgery to remove endometriosis lesions and the uterus (hysterectomy) as the source of dysmenorrhea with or without removal of one or both ovaries[36]. It has been long assumed that surgical removal of both ovaries (bilateral oophorectomy) is the definitive method to decrease endogenous estrogen and to relieve endometriosis associated pelvic pain[36]. However, evolving research has demonstrated the incredible complexity of endometriosis associated pelvic pain. Patients may present with no pain or very little pain, or may present with a complex pelvic pain syndrome, or something in between, regardless of rAFS stage of endometriosis. "Nociceptive pain" occurs when there is stimulation of nociceptors at peripheral nerve endings in the tissue (either by mechanical, thermal or chemical signals), which is transmitted via these peripheral nerves to the spinal cord. There is complex interactions of excitatory and inhibitory neurons at the level of the spinal cord, which determines whether to transmit the information upward to the brain (this is known as "gate control theory"). Once the information is transmitted to the brain, it is interpreted (with various other psychological inputs playing a role), and descending signals through nerves from the brain to the spinal cord act to modulate the pain response at the level of the spinal cord[37]. Visceral pain is pain that occurs from internal organs, which is not localized as well as nociceptive pain (for example, abdominal pain could be the result of menstrual cramps, bowel cramps, appendicitis, or pancreatitis but it is difficult for an individual to pinpoint the root cause). Pain signals from visceral pain act in a similar way to nociceptive pain. Centralized pain occurs when there is amplification of pain by the central nervous system (the brain and spinal cord), with or without contribution of peripheral pain inputs[38]. This may be associated with the

experience of pain from a normally innocuous stimulus (allodynia), exacerbated response to pain from a painful stimulus (hyperalgesia)[38], altered sensation (dysaesthesia), elevated response to stimulation (hyperaesthesia) or altered/prolonged response to stimulation (hyperpathia)[37]. Central nervous system sensitization occurs when there is a heightened sensation of the central nervous system (CNS) (amplification of neural signaling) from stimuli which should not be perceived as painful. This elicits a heightened sensitivity to pain[39]. There is a psychological component to pain also, as we know that mood can alter how an individual processes and experiences pain at a biological level[40], although it is sometimes difficult to know if individuals with a predisposition to mood disorders are also more predisposed to pain syndromes, or if an individual who is in pain goes on to develop a mood disorder secondarily[38]. The presence of central nervous system sensitization may predict a suboptimal response to therapies (medical and surgical) which attempt to address only the presumed nociceptive stimulus; hence it is important to recognize CNS sensitization and apply a targeted and holistic approach[39]. In 2017, the International Association for the Study of Pain (IASP) introduced the term "nociplastic pain" defined as "pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain" which does not replace the term CNS sensitization, but rather people who have nociplastic pain are thought to have CNS sensitization as a core issue. Pain catastrophizing is the process in which there is a negative cognitive response to the anticipated or actual pain, which can have a significant impact on pain outcomes[41-43]. In the process of central sensitization there can be cross sensitization of afferent (signals going from the periphery to the CNS) or efferent (signals going from the CNS to the periphery) associated with allodynia, hyperalgesia and referred pain (pain that is perceived to be arising from a location

different from where the pain stimulus is occurring)[37] and accordingly there are frequently co-morbid pain syndromes present (musculoskeletal pain conditions, psychological factors such as anxiety, depression and pain catastrophizing) as well as cross sensitization of visceral organs leading to an increased prevalence of irritable bowel syndrome (IBS) and painful bladder syndrome (PBS)[44]. In summary, terminology surrounding chronic pain is ever evolving, making it a challenging entity to define and treat; additionally, endometriosis associated pain is very complex and heterogeneous, which requires a directed approach for management that is specific to the symptoms and syndromes unique to each patient[45], which are discussed below.

1.6 Management of Endometriosis

Treatment of endometriosis is multimodal, including medical management (non-hormonal and hormonal) and surgical management[46,47]. Non-hormonal analgesics include non-steroidal anti-inflammatory drugs (NSAIDs) and occasionally opioid analgesics. There is certainly also a role for an approach to pain outside of medication and surgery, including cognitive behavioral therapy (CBT), mind-body and psychological approaches to pain, and including an interdisciplinary approach to pain, particularly when there is a complex pain syndrome present[45,48].

The International Association for the Study of Pain recognizes opioid therapy for short term management of acute pain, but not for the treatment of chronic, non-cancer pain[49] as there is risk for addiction, morbidity and mortality associated with chronic opioid use. Nonetheless, some patients will use opioid medications intermittently or continuously for chronic pain syndromes.

Hormonal suppression medications aim to inhibit the hypothalamic-pituitary-ovarian (HPO) hormonal axis which drives the production of endogenous estrogen by the ovaries as well as the menstrual cycle, thereby suppressing ovulation, suppressing menstruation (as ovulation pain and dysmenorrhea are often pain sensitizing events in people with endometriosis) and inhibiting the stimulation of ectopic endometriosis deposits by endogenous estrogen[11,36,47,50]. This can be achieved with various categories of hormonal medications including combined oral contraceptive pills (COCs) which contain both estrogen and progestin, as well as combined transdermal methods (including the contraceptive patch) and vaginal ring), progestin only medications (oral or levonorgestrel intrauterine system (LNG-IUS), androgens (Danazol) or GnRH agonists or antagonists. The choice of which medication to use is multifactorial. The currently available options for medical management have similar levels of effectiveness in achieving these goals[50,51]. Combined oral contraceptives have long been considered the first line hormonal therapy, but there has also been good safety and efficacy data for progestin only methods[50]. LNG-IUS (a small T-shaped device inserted into the uterus, which releases a steady dose of progestin – levonorgestrel) is also very effective in the treatment of heavy menstrual bleeding and painful menses (dysmenorrhea) and has been shown in randomized trials to be similar in efficacy to progestins and GnRH analogues in treatment of symptomatic endometriosis[52-54]. GnRH analogues are generally considered second line options[36], as there are associated menopause-like side effects, risk of decreasing bone mineral density (which may be offset by the addition of add-back hormone replacement therapy), and are also quite costly[5]. Danazol is an anti-estrogen used in the treatment of endometriosis, however it is associated with androgenic side effects and is not used as commonly in the present day for the treatment of endometriosis[55]; however vaginal danazol is occasionally used, which may limit its systemic

absorption and associated side effects[56]. The choice on which medication to use depends on the patient's choice, and potential for efficacy given an individual's medical and surgical history, balanced with the potential for side effects, medication risk profiles and costs, which vary between categories of hormonal medications[50]. There is also a risk of symptom recurrence with discontinuation[47]. Alternative medical treatments of endometriosis are an area of ongoing research including selective estrogen receptor modulators (SERMs), selective progestin receptor modulators (SPRMs), aromatase inhibitors, immunomodulators and antiangiogenic agents[46], although these are not used very commonly in clinic practice at this time and require further safety and efficacy data in human studies.

Surgery to improve endometriosis related pelvic pain is another treatment option, although not every person with suspected endometriosis requires surgery. Surgery for endometriosis is generally considered second line after a trial of medical management[36], with the exception of scenarios that require surgery more urgently such as suspected malignancy, very large endometriomas which have ruptured or are at high risk of rupture, or complications related to deeply infiltrative endometriosis, such as obstruction or severe compromise of the bowel or genitourinary system[57]. However, if medical therapy is not tolerated, has failed, or is contraindicated, or if a patient desires fertility and does not wish to take contraceptive medication (hormonal therapies for endometriosis inhibit ovulation and therefore are considered contraceptive), then surgical management is considered[36]. Surgery can be divided into excision or ablation of endometriosis lesions (i.e fertility-sparing); and/or hysterectomy (removal of the uterus), with or without unilateral or bilateral oophorectomy (removal of one or both ovaries) which is performed if an individual has completed childbearing[45]. Ideally, at the time of hysterectomy, excision or ablation of lesions would be done concurrently. While in theory,

excision should be superior to ablation, in particular to treat deep lesions or lesions near visceral or vascular structures, there remains clinical equipoise from the few randomized controlled trials comparing these two types of surgical treatment[36,58]. In general, surgery for endometriosis has been shown to improve endometriosis related pain in some, but not all women[16], however, more high quality studies are needed, as a recent Cochrane review evaluating only 1 RCT evaluating the effect of laparoscopic surgical treatment vs diagnostic laparoscopy alone found that there was not sufficient evidence to conclude that laparoscopic surgical treatment improves patients' pain scores compared to diagnostic laparoscopy alone[58]. Currently the European Society of Human Reproduction and Embryology (ESHRE) supports endometriosis surgical excision or ablation of superficial endometriosis for the treatment of endometriosis associated pain[16], as does the Society of Obstetricians and Gynecologists of Canada (SOGC), ideally after a trial of medical management of endometriosis associated pain[36]. Fertility sparing surgery for endometriosis (excision of endometriosis without hysterectomy) may improve pain, but may not be as effective as hysterectomy with excision of endometriosis, given that menstruation and dysmenorrhea will persist after fertility sparing surgery[59].

Although medical and surgical management are considered the mainstays of treatment for endometriosis, it is important to phenotype the pain that each patient experiences, as patients experiencing centralized pain and those with multiple co-morbid pain conditions (for example, irritable bowel syndrome, painful bladder syndrome, musculoskeletal pain conditions) are more likely to experience an incomplete response to traditional management, or experience recurrence of their pain[6,44]. These patients are best served by an interdisciplinary team approach to chronic pain with specific interventions such as pharmacotherapies, pain education, physical therapy psychological adjunctive treatments[44].

1.6.1 Hormonal suppression medication after hysterectomy for endometriosis with ovarian conservation

For women who undergo hysterectomy with ovarian conservation for endometriosis, they will continue to have monthly hormonal cycles including production of ovarian hormones, and ovulation which is associated with ovarian cyst formation. It is physiologically plausible that this could contribute to persistent pelvic pain, either by hormonal stimulation of residual endometriosis, or ovulation related pain. It is possible to suppress the hypothalamic pituitary ovarian hormonal axis through the use of combined estrogen/progestogen oral contraceptive pills or combined transdermal options (patch and ring), progesterone only medications, or other drugs approved in the treatment of endometriosis such as GnRH agonists or antagonists[36]. Many women undergoing hysterectomy for endometriosis desire to not take hormonal medications after surgery, as most have used hormonal agents to control pelvic pain and abnormal bleeding for many years, as surgery for endometriosis is typically considered only after failure of medical management[36]. It is difficult to counsel patients on what the chance will be of them needing to take hormonal medications after surgery as this has not been well studied in this population.

1.6.2 Hysterectomy with bilateral salpingoophorectomy as treatment for endometriosis

Hysterectomy is the second most common surgical procedure on women of reproductive age in the United States after Caesarian section, with a reported 60-68% undergoing unilateral or bilateral oophorectomy at the time of laparoscopic or abdominal hysterectomy according to a 2005 nationwide study and 61-71% in a 2014 study[60,61], although rates appear to be slowly declining in both Canada and USA, with 40-44% of women undergoing BSO at the time of

hysterectomy between 2008-2011 in a Canadian study[62]. In a Canadian study of patients who underwent hysterectomy between 2016 and 2018, 28% of patients had hysterectomy with BSO; 10% were for endometriosis, and 8% of BSO's were found to be "unnecessary", not including those done for endometriosis[63]. The presence of endometriosis is a known predictor for BSO to be performed[64,65].

Although removal of both ovaries (bilateral salpingoophorectomy; BSO) is considered the most permanent method of removing endogenous estrogen, and thus removing the hormonal stimulation of endometriosis, BSO is associated with a number of risks that must be weighed against the potential benefit. While it is plausible that the removal of reproductive hormones through BSO, and therefore the removal of stimulation of endometriosis by estrogen, could reduce endometriosis associated pain, actual pain related outcomes have not been well studied, which is the reason for pursuing this study.

Nanoum et al (1995) conducted a retrospective study of only 138 patients with a diagnosis of endometriosis; 29 with hysterectomy and ovarian conservation, and 109 with hysterectomy and BSO. They found a higher recurrence of pain in the group with hysterectomy with ovarian conservation (RR 6.1) and a higher rate of reoperation (RR 8.1) compared to the group with hysterectomy and BSO. This study has been criticized however for having a small sample number and that it is unclear if endometriosis was excised at the time of surgery, particularly because 60% of their study sample had severe (Stage III-IV) endometriosis[66].

Shakiba et al (2008) conducted in a single centre retrospective study and found that women with hysterectomy and BSO had reoperation rates at 2, 5 and 7 years of 4.0%, 8.3% and 8.3% respectively, compared to women with hysterectomy and ovarian preservation who had reoperation rates at 2, 5, and 7 years of 4.3%, 13.4% and 23% respectively. However, when

stratified by age, in women between 30 and 39, removal of the ovaries did not significantly improve reoperation rate [67], suggesting there may be other variables affecting the reoperation rate apart from oophorectomy status.

Bougie et al (2021) conducted a population based retrospective cohort study of women in Ontario, Canada aged 18-50 who underwent surgery for endometriosis, including 21,609 women who underwent hysterectomy without BSO and 8378 women underwent hysterectomy with BSO[68]. The follow up period was a median of 10 years post hysterectomy. The risk of repeat surgery was low for those who underwent a hysterectomy: 1.9% for those who underwent a hysterectomy with ovarian preservation and 0.4% for hysterectomy with BSO; however, reoperations required an associated diagnosis of endometriosis, which may have resulted in missed reoperations across all study groups, as endometriosis is not always visualized or diagnosed at the time of repeat surgery performed for persistent pelvic pain (example, oophorectomy or lysis of adhesions without endometriosis present).

The American College of Obstetricians and Gynecologists (ACOG) recommends that ovaries be left intact in women who are not at elevated genetic risk of ovarian cancer[69], as there is growing evidence for adverse health outcomes in women who undergo premature menopause[60]. In women who undergo BSO prior to the age of 45, the associated abrupt drop in reproductive hormones (particularly estrogens and androgens) has been shown to be associated with an increased risk of cardiovascular disease (CVD), osteoporosis, earlier onset of cognitive impairment/dementia and all cause mortality[70,71].

1.7 Menopause

1.7.1 Definition of natural menopause

Menopause is often quite oversimplified and thought of simply as the absence of menstrual periods for at least one year. However, natural menopause is a gradual transition in the years leading up to and in the years that follow the final menstrual period (FMP). There are multiple changes that occur at a physiological and biochemical level, and in addition to this, changes to one's health and quality of life over the short and long term. In 2001, the Stages of Reproductive Aging Workshop (STRAW) proposed a staging system, which have since been revised into the STRAW+10 staging system which serves as a clinical tool for patients and clinicians to assess the needs of patients and in healthcare decision making, and also allows for more effective communication and classification in a research setting[72]. The FMP marks Stage 0, whereas the "negative" stages include periods of a woman's life where she is not amenorrheic but physiological changes are occurring. Stage -3 represents the late reproductive stage, subdivided into -3b where menstrual cycles are regular, but anti-mullerian hormone (AMH) levels decrease and antral follicle counts (AFC) decrease, indicating decreasing fecundability (ability to achieve a pregnancy). Changes to cycle length (ex shorter cycles) and a rising follicle stimulating hormone (FSH) level characterize Stage -3a. In Stage -2 (early menopausal transition), menstrual cycle length is more variable, as well as elevated FSH and lower AMH levels and lower AFC. Stage -1 (late menopausal transition) is the presence of amenorrhea for 60 days or more, where ovulation is not occurring regularly. FSH continues to rise (>25 IU/L). This stage may last from 1-3 years and vasomotor symptoms, such as hot flashes, are likely to occur during this time. Early postmenopause (Stages +1a, +1b and 1+c) are consistent with continued elevation in FSH and a decline in estradiol for approximately 2 years after the final menstrual

period. Stage +1a is the point at which there has been 12 months of amenorrhea (the traditional clinical definition of natural menopause). In Stage +1b, there continues to be rapid increase in FSH and decline in estradiol, and +1a and +1b together often take about 2 years, during which vasomotor symotoms are common. In Stage +1c, high FSH and low estradiol levels continue to stabilize, for approximately 3-6 years. Late menopause (Stage +2) is characterized by a greater concern for somatic aging and menopause related health concerns, and symptoms such as vaginal dryness and urogenital atrophy are more common.

On average, the age of natural menopause is 51 years (when using the definition of 12 months of amenorrhea)[73]. Menopause that occurs before the age of 45 is called early menopause, which occurs in approximately 5% of the population. If menopause occurs before the age of 40, this is considered premature menopause, which occurs in approximately 1% of the population[74].

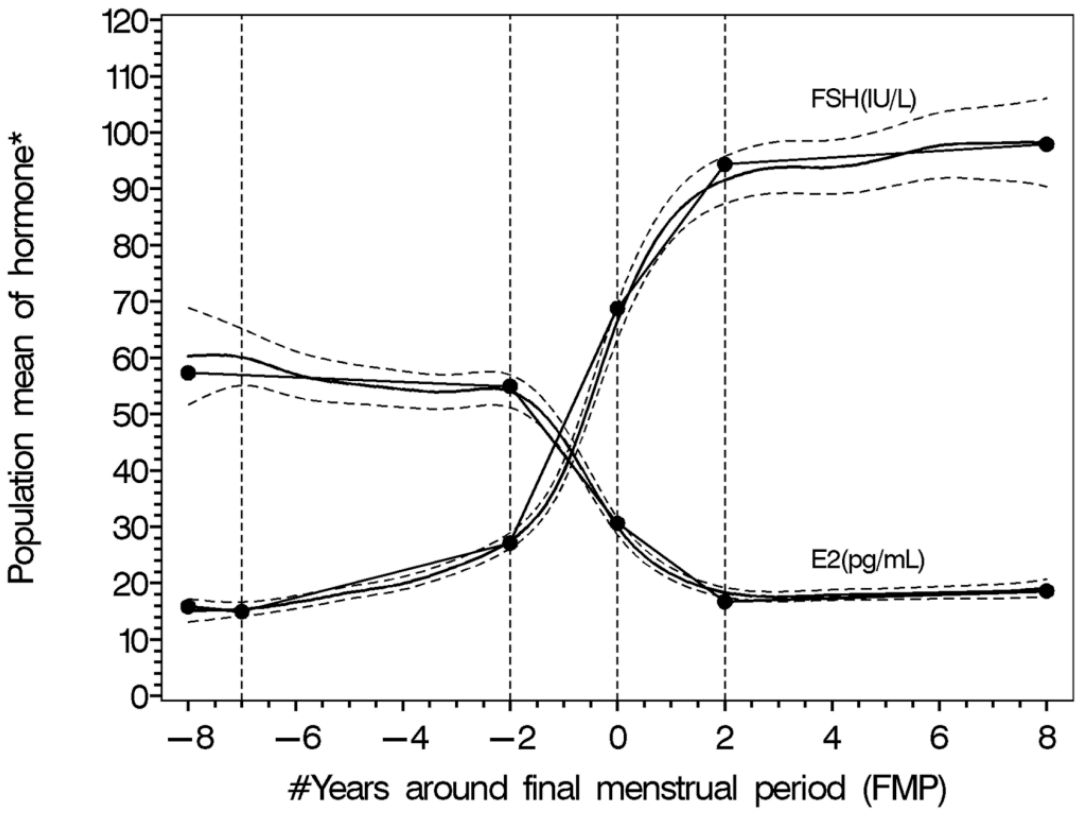


Figure 1.4 Follicle stimulating hormone and estradiol levels before and after the final menstrual period[72]

1.7.2 Short term effects of natural menopause

Symptoms of natural menopause (climacteric symptoms) are common, with 80% of women experiencing vasomotor symptoms ("hot flashes") that last for 10 years, on average, peaking around the time of the final menstrual period[75]. Although the presentation and severity of these symptoms are variable, risk factors include Black or Hispanic ethnicities, cigarette smoking, elevated BMI, anxiety and depression, and history of premenstrual symptoms[75]. Other

frequent physical and psychological symptoms include changes in mood, sleep disturbances, and changes in sexual function (desire, arousal, orgasm, dyspareunia, and vaginal lubrication)[76].

1.7.3 Short term effects of natural versus surgical menopause

Surgical menopause (ie BSO before the age of natural menopause) is a distinctly different entity than the process of natural menopause. As described above, natural menopause is a gradual and progressive process. Surgical removal of both ovaries in a premenopausal aged individual results in an abrupt loss of ovarian sex steroids including estrogens and androgens[77,78]. Research has shown not only a higher rate of climacteric symptoms (vasomotor symptoms or "hot flashes", sweating, poor memory, change in sexual desire and sexual function, sleep disturbances[78,79]) but has also showed increased rates of osteoporosis[80] in women experiencing surgical menopause, compared to natural menopause. In one study comparing sexual function between those undergoing surgical versus natural menopause, parameters of sexual function were not different between groups except for vaginal lubrication was more affected in the surgical menopause group[76] and sexual desire was lower in the surgical menopause group compared to natural menopause group in a similarly designed study[81]. In women undergoing premenopausal BSO, vasomotor symptoms, vaginal dryness and dyspareunia may be somewhat mitigated by using hormone replacement therapy (HRT), but changes to sexual desire and sexual functioning may not be fully rectified by the usage of HRT[82,83].

1.8 Hormone replacement therapy and menopause

HRT (hormone replacement therapy) is the administration of exogenous hormones (typically in oral or transdermal formulations to facilitate systemic absorption) for the purpose of

treating short and long term sequelae of menopause[77]. Estrogen is the necessary component of HRT for both alleviating hypoestrogenic symptoms of menopause and which is thought to decrease the elevated rates of morbidity and mortality described above[84]. The addition of a progestogen to an estrogen based HRT regimen is necessary in women who have a uterus to circumvent the risk of unopposed estrogen on the uterus leading to endometrial hyperplasia and malignancy (although in our study all patients have had hysterectomy). It is also recommended to add a progesterone to the HRT regimen for women without a uterus but who have residual endometriosis or deep disease present[85]. It is thought that the addition of progesterone will suppress any residual endometriosis which could contribute to a recurrence in pain or recurrence in endometriosis and possibly decrease the incidence of endometriosis related malignancies in residual foci of endometriosis that could be stimulated by exogenous estrogen, although these outcomes have not been strongly demonstrated in the literature and further large scale, high quality studies are needed[85,86]. There is also some controversy about the potential risks of giving exogenous estrogen to patients with endometriosis, due to the theoretical risk that residual endometriosis could be activated by this estrogen leading to persistent pain or increased risk of endometriosis related malignancies; however there has not actually been any study to date substantiating these claims[65], and there is known risk of harm in not taking estrogen containing HRT after premenopausal BSO, as described below.

1.9 Long term effects and consequences of premature surgical menopause

Several long term observational studies have repeatedly demonstrated the adverse effects of early menopause (before the age of 45), including increased risk of cardiovascular disease, osteoporosis, earlier cognitive changes, as well as earlier mortality, in addition to the

symptomatic morbidity of menopause as described above[77,78]. As mentioned above, surgical menopause is associated with an immediate cessation of ovarian estrogen and androgens (free and total testosterone). The decrease in androgens in natural menopause is more gradual and does not demonstrate as abrupt of a decline during natural menopause, but is more of an age related gradual decline[87]. Androgen production persists beyond menopause and are a substrate for conversion to estrogens, which may be responsible for prevention of some long term health complications associated with surgical menopause, described below[78].

1.9.1 Menopause and cardiovascular disease

Cardiovascular disease continues to be one of the leading causes of morbidity and mortality in women, particularly in those over the age of sixty five[60]. In healthy blood vessels, estrogen is involved to maintain relaxation in the smooth muscle of the blood vessel walls; a drop in estrogen leads to relative endothelial dysfunction, inflammation and immune dysfunction[88]. Evolving evidence has demonstrated that early menopause and surgical menopause are associated with elevated risks of CVD[60].

In the nurses health study[89], an increased risk of CVD was demonstrated for women who underwent BSO at all ages (HR 1.17; 95% CI 1.02-1.35), but particularly those who underwent BSO at <45 years (HR 1.26, 95% CI 1.04-1.54). The hazard ratio of BSO at age <50 without estrogen containing HRT was 1.98 (95% CI 1.18-3.32). The use of estrogen containing HRT in the early post menopausal period after BSO appeared to eliminate this risk, although the use of estrogen therapy after natural menopause did not affect the risk of CVD[90]. Additional studies have also found an association between an increased risk of CVD and premenopausal BSO including the Mayo Clinic Cohort Study of Oophorectomy and Aging[91], and a cohort of the

Swedish Health Care Registers[92]. There was conflicting data out of the Women's Health Initiative study (WHI)[93], however 78.6% of the cohort were current or past users of HRT, which may have confounded the results.

In a 2016 systematic review and meta-analysis which included 32 studies and 310,329 non-overlapping women, the authors found that in women who underwent menopause prior to the age of 45, compared to women who underwent menopause at a later age, had a 50% increased risk of overall coronary heart disease (RR 1.50; 95% CI 1.28−1.76), an 11% increased risk of fatal coronary heart disease (RR 1.11; 95% CI 1.03-1.20), a 23% increased risk of stroke (RR 1.23; 95% CI 0.98−1.53), a 19% increased risk of cardiovascular mortality (RR 1.19; 95% CI 1.08−1.31), and a 12% increased risk of all-cause mortality (RR 1.12; 95% CI 1.03-1.21)[88]. This study also performed a sensitivity analysis for type of menopause ("natural" vs "unnatural" which we presume to be surgical menopause) and found that the effect estimates for the above associations remained similar. Results were also adjusted for the use of hormone therapy, as well as age, smoking, lipid levels, hypertension and body mass index. The large scale of this study in addition to addressing surgical menopause and adjusting for the use of HRT is a major strength of this study that is often not addressed in other publications examining the long term health effects of premature menopause. In another meta-analysis of eighteen studies, a subgroup analysis on type of menopause found a more significant effect of bilateral oophorectomy on risk of cardiovascular disease, RR 2.62 (95% CI 2.05-3.35) compared to natural menopause on CVD, RR 1.14 (95% CI 0.86-1.51)[94]. In 2020, a pooled analysis of 10 studies including 203,767 women again demonstrated a higher risk of CVD with surgical menopause compared to natural menopause (HR 1.22, 95% CI 1.16-1.28) even when age at time of menopause was considered[95]. Amongst women who underwent surgical menopause before age 50, the risk of CVD was lower

in those who used HRT compared to those who did not use HRT[95].

1.9.2 Menopause and osteoporosis

Osteoporosis, decreased bone mineral density, and fractures affect postmenopausal women at a much higher rate than premenopausal women. Hip fracture can impair a person's mobility and is also associated with increased mortality[96]. Evidence suggests that bone loss after menopause is primarily related to estrogen deficiency rather than the aging process itself [60,97]. Hormone replacement therapy after natural menopause decreases the risk of osteoporosis, although evidence is lacking in prevention of fractures and bone loss. Calcium and vitamin D are recommended for women who are at an elevated risk for osteoporosis, but these agents alone are not sufficient for prevention[98]. With natural menopause, small amounts of estrogens and androgens (which are aromatized to estrogens) are released even after menopause, which appears to carry some protective benefit against osteoporosis compared to those who have undergone BSO[78]. In women undergoing premature surgical menopause (those who have undergone BSO), there is an abrupt decline in ovarian sex steroids including estrogen and androgens. Women who undergo premature menopause (before age 45) are at elevated risk for osteoporosis[99,100], and the earlier in age that menopause occurs, the higher risk of bone loss and risk of fracture[60]. In one study, having had a BSO before age 45 was associated with a 3.64 fold increased risk of fracture over the follow up period[101]. Current or previous use of hormone replacement therapy was found to be protective against fracture risk in the same cohort. In an observational study of >80,000 women, women who discontinued HRT were 55% more likely to undergo hip fracture at 6.5 years after discontinuation, and the longer duration of HRT cessation was linearly associated with a lower bone mineral density, however the protective effect of HRT on hip fracture

disappeared within 2 years of ceasing HRT use, which calls into question the long term benefit of use. This study included women who were over 60 and postmenopausal, however did not define whether participants underwent natural or surgical menopause, which makes results difficult to extrapolate to premenopausal women who undergo premature surgical menopause. In another study of postmenopausal women who had undergone BSO, there was an increased risk of osteoporotic fractures both at the hip and in other less common areas for fractures[102].

1.9.3 Menopause and cognition

There has been growing evidence illustrating that estrogen plays a protective role in brain health, particularly in cases of premature menopause or primary ovarian insufficiency. The Mayo Clinic Cohort of Oophorectomy and Aging group prospectively followed a large cohort of women for more than 25 years and found a higher risk of cognitive impairment or dementia in women who underwent premature surgical menopause compared to those who did not (HR, 1.46; 95% CI, 1.13–1.90)[103]. In another study looking at a longitudinal cohort of 1,884 women, earlier age at surgical menopause was found to be associated with more rapid decline in global cognition as well as increased Alzhemier's disease neuropathology. HRT delivered within 5 years of surgical menopause when used for at least 10 years, was associated with a reduced decline in global function[103]. These changes were not observed in women who underwent natural menopause[104]. There is a theory of "healthy cell bias" and "critical time window", whereby estrogen is thought to play a role in maintaining health of neurons, but only those cells that are currently healthy, which reinforces the findings of estrogen benefiting cognitive function when HRT is used within a few years of menopause. For cells that are already damaged, starting estrogen replacement late after menopause can actually be detrimental[78]. In a subset analysis of

the Women's Health Initiative, giving women HRT after age 65 was actually associated with an increased risk of dementia and cognitive decline[105].

1.9.4 Premature surgical menopause and all cause mortality

It has repeatedly demonstrated that there exists a higher rate of all cause mortality in individuals who undergo premenopausal BSO (premature surgical menopause)[90,106-110]. The risk appears to be greatest when BSO is performed before age 50 and for those who never used estrogen containing HRT (HR 1.41, 95% CI 1.04-1.92)[90,108]. The only large prospective study that did not demonstrate increased mortality with BSO compared to ovarian conservation was in the Women's Health Initiative (WHI) study; however, the results should be interpreted cautiously, as the average age of enrollment into the study was 63, the average length of follow up was 7.6 years, and 78.6% of participants had used HRT at some point in their lives. Older age, shorter follow up, and frequency of HRT use may contribute to the finding that all cause mortality in those who had undergone BSO was not different than those who had ovarian conservation[93]. In summary, the vast majority of well designed and well powered studies support the notion that all cause mortality is higher with premature surgical menopause, particularly when BSO is performed before the age of 50. Modeling of the data suggests there may even be some overall mortality benefit to conservation of the ovaries up to the age of 65[111].

1.9.5 Evidence regarding use of HRT in women with premature menopause

The increase in morbidity and mortality of premenopausal surgical menopause may be partially offset by the usage of post operative hormone replacement therapy (HRT)[84,107], however

this has not been well studied, and most of the existing literature is examines HRT use in and around the onset of natural menopause rather than following surgical menopause. Furthermore, HRT in the literature is often not defined as estrogen only or estrogen plus progestin and so there may be varying risk/benefit profiles in the studies that are not accounted for.

Parker et al (2005) published a study aimed to determine the strategy to achieve maximum survival (measured as survival up to 80 years) in women undergoing oophorectomy or ovarian conservation at the time of benign gynecologic surgery, who were at average risk for ovarian cancer, and found that BSO with addback estrogen containing HRT was associated with 62.15% survival by age 80, comparable to those who had ovarian conservation (62.75% survival), but survival rates were lowest for BSO without addback HRT (53.88%)[78,111].

In fact, there is evidence of benefit from a retrospective cohort study of 10,533 postmenopausal Danish nurses, 504 of which had oophorectomy before the age of natural menopause. The study found a higher incidence of ischemic heart disease among women with oophorectomy before age 40 (HR 8.7; 95% CI 2.0-38.1) compared to oophorectomy after age 45, which was more significant risk than those undergoing natural menopause before age 40 (HR 2.2; 95%CI 1.0-4.9) compared to natural menopause after age 45. When analyzing self-reported users of HRT vs non-users of HRT among women with oophorectomy before age 45, the rate of ischemic heart disease among non-users was 3 fold higher[112].

In summary, there is good evidence to support the use of HRT in women who have undergone premature surgical menopause menopausal to attenuate some, or all, of the risks of ischemic heart disease and associated consequences[95,113]. The evidence for the effect of HRT on bone and brain health of women who have undergone premature surgical menopause is lacking

as most research in this area is on women who undergo natural rather than surgical menopause; however there is physiological plausibility to support the use of HRT in those who have undergone premature surgical menopause as well. Further research in this area is warranted. Moreover, the usage of HRT after BSO in premenopausal women has been shown to be suboptimal; only 72% of premenopausal women undergoing hysterectomy with BSO for endometriosis fill at least one prescription postoperatively in a retrospective cohort study by Jang et al[65].

1.10 Endometriosis, ovarian cancer and BSO

Although there are some genetic syndromes (ex BRCA1/2 mutations, Lynch Syndrome) that increase an individual's risk of ovarian cancer, the baseline risk of ovarian cancer in the general female population is approximately 1.4%[60]. The presence of endometriosis is thought to increase an individual's risk of specific histotypes of ovarian cancer – clear cell and endometrioid, by a relative risk of about two to three fold, the risk seeming to increase particularly when there is an early diagnosis, long standing endometriosis, older age at diagnosis and ovarian endometriosis present[114-118]. There also may also be a slightly increased risk of a third histotype, low-grade serous ovarian carcinoma[114,118]. These endometriosis-associated cancers tend to be less aggressive and present at an earlier stage than the more common high grade serous ovarian cancer. Premenopausal risk-reducing BSO is recommended for those with a hereditary predisposition to ovarian cancer, as it has been shown to reduce ovarian cancer risk and all-cause mortality[119] and it will result in a reduction in risk for ovarian cancer overall[120]. However, BSO for prevention of ovarian cancers in average risk women is not currently recommended due to

the known morbidities and elevated all-cause mortality associated with this procedure, especially if done prior to menopause[60,69]. In fact, tubal ligation alone (without salpingectomy) is also protective against all types of ovarian cancer including invasive serous, endometrioid, clear cell and mucinous[121]. In a prospective study of 1.1 million women in the UK over 13.8 years of follow up and observing 8035 cases of ovarian cancer, tubal ligation was associated with half the risk of clear cell (RR 0.54, 95% CI 0.43-0.69) and endometrioid ovarian cancer risk (RR 0.55, 95% CI 0.39-0.77)[122]. Risk reducing bilateral salpingectomy has been shown to reduce the risk of ovarian cancer also, as evidence emerges that high grade serous ovarian cancer is actually derived from the epithelial cells of the Fallopian tubes[123]. Hysterectomy alone may also decrease an individual's risk of ovarian cancer by up to 34%[60]. In one Swedish nationwide study with over 64,000 women enrolled, those women who underwent hysterectomy before or at the time of endometriosis diagnosis did not demonstrate an increased risk of ovarian cancer[117]. Further research is needed into the protective effects against endometriosis-related ovarian cancers, such as hormonal suppression of endometriosis, tubal ligation or salpingectomy, hysterectomy, excision of ectopic endometriosis lesions as well as oophorectomy.

1.11 Purpose

While there are many areas that require further research with respect to treatment of endometriosis, an area that would immediately inform clinical practice is understanding what happens to a patient's pain if one or both ovaries are conserved at the time of hysterectomy for endometriosis, compared to removal of both ovaries (BSO). Given the known morbidities of BSO in premenopausal women, if there is no significant improvement of pain related outcomes

after BSO at the time of hysterectomy for endometriosis, compared to conservation of one or both ovaries, then empiric BSO should be avoided.

Overall objective: To examine pain-related health utilization outcomes after hysterectomy for endometriosis, by comparing three groups based on oophorectomy status: those with concurrent removal of both ovaries, those with concurrent removal of one ovary, and those with preservation of both ovaries.

Specific aims:

Aim 1: To assess the primary outcome of re-operation, as well as secondary outcomes of physician visits and usage of pain medications, in the three groups based on oophorectomy status.

Aim 2: To study the rates of hormonal therapy use, both hormonal suppressive treatment and hormone replacement therapy (HRT), in the three groups based on oophorectomy status

Hypotheses:

Hypothesis 1**:** There will be lower rates of re-operation in the group with removal of both ovaries, but no differences in other measures of health care utilization (physician visits for endometriosis or pelvic pain, and opioid medication use) between the three groups based on oophorectomy status.

Hypothesis 2: There will be low rates of use of both hormonal suppressive medications in patients with hysterectomy and conservation of one or both ovaries, and suboptimal use of HRT after hysterectomy with BSO for endometriosis.

Chapter 2: Reoperation rates and pain-related health services usage following hysterectomy for endometriosis in women with or without ovarian conservation in British Columbia, Canada

2.1 Introduction

Endometriosis is a common chronic disease that affects approximately 10% of reproductive age women (~1 million women in Canada), and can lead to painful menstrual cramps, painful sexual activity, and chronic pelvic pain. Traditionally, endometriosis is treated by suppressing endogenous estrogen with hormonal medications, or with fertility sparing surgery, or with hysterectomy (removal of the uterus and cervix) accompanied by conservation of both ovaries or removal of one (unilateral salpingo-oophorectomy; USO) or both ovaries (bilateral salpingo-oophorectomy; BSO)[45,46]. Ideally, at the time of hysterectomy, excision or ablation of endometriosis lesions would be performed concurrently, as the presence of residual endometriosis lesions is a risk factor for symptom recurrence[85,124].

Given that endometriosis lesions are stimulated by endogenous estrogen produced by the ovaries, removal of both ovaries (bilateral oophorectomy (BSO) is sometimes performed as a permanent form of hormonal suppression, which is believed to reduce the risk of persistent pelvic pain[36] and previous research has suggested a reduced rate of reoperation with BSO compared to ovarian conservation of one or both ovaries[66-68]. However, there is morbidity associated with BSO such as increased risk of cardiovascular events, osteoporosis, earlier cognitive changes and symptoms of surgical menopause [125]. Additionally, there has not been sufficient research examining pain-related outcomes after hysterectomy with BSO for endometriosis compared to hysterectomy with ovarian conservation. Pelvic pain is a complex entity whose etiology is often not singular, and frequently includes non-hormonal mechanisms

such as musculoskeletal and central nervous system pain contributors as well as cross sensitization of visceral structures, making co-morbid pain contributors such as irritable bowel syndrome (IBS) and painful bladder syndrome (PBS) common[6,44]. Psychological morbidities such as anxiety, depression and pain catastrophizing are also frequently present[45]. Because pain is so complex, it is very important to understand the different layers of each patient's pain and treat them appropriately; for example, utilizing an interdisciplinary team with pain education, physical therapy, and addressing mental health, therapies which are often overlooked.

BSO has classically been the "definitive management" for patients with significant pain who have failed other medical and/or surgical management[36,126]; however, however, little research has examined outcomes actually related to pain (including pain related health services use) to determine if these patients are actually benefiting from BSO from a pain perspective and existing studies focus solely on reoperation rates. Thus, a more comprehensive look at multiple outcomes following surgery is warranted to truly understand whether hysterectomy with BSO improves outcomes compared to hysterectomy alone. Our study aims to examine pain-related health services use after hysterectomy for endometriosis with both ovaries conserved, compared to hysterectomy with USO and hysterectomy with BSO. We hypothesized that while reoperation rates may be higher with ovarian conservation, this higher reoperation rate may be driven by repeat surgery to remove ovaries simply because there are ovaries to remove, and that other pain-related health services use (e.g. physician visits and opioid usage) would be similar between the groups. We also examined use of hormonal suppression medications and hormone replacement therapy (HRT) use after hysterectomy for endometriosis.

2.2 Methods

We conducted a population-based retrospective cohort study of all patients who underwent a hysterectomy for endometriosis in the province of British Columbia, Canada (population 4.6 million) between 2001 and 2016. Approvals were granted by the relevant data stewards and Population Data BC permitted access to the Discharge Abstract Database[127], which contains records of all hospital stays and day surgeries in the province (including up to 25 ICD 10 diagnostic codes and 20 procedure codes for each hospitalization). Herein we identified our cohort and linked these data with the Medical Services Plan (MSP) data[128] (which includes information on all visits to fee-for-service health care providers in British Columbia), vital statistics data[129] (which records the date and cause of all deaths in the province), the BC Consolidation file (which records information on registration for the provincial health insurance program), and the BC PharmaNet[130] (which includes every prescription medication dispensed in an outpatient setting in British Columbia, regardless of the insurance status of the person filling the prescription). The BC Cancer Registry data set[131] (which includes information on all cancer diagnoses in BC residents) was accessed to identify and exclude patients with a history of gynecologic malignancy from our cohort. Ethics was approved by the University of British Columbia's Behavioural Research Ethics Board. All inferences, opinions, and conclusions are those of the authors and do not reflect the opinions or policies of the Data Stewards.

Cohort: The total cohort of patients included everyone who underwent hysterectomy between April 1, 2001 and Dec 31, 2016, for the primary indication of endometriosis (ICD-10-CM-N80.X), or a primary indication of chronic pelvic pain (ICD-10-CM R10.2 or R10.3) with a secondary diagnosis of endometriosis. Patients were excluded from further analysis for the

following reasons: 1) age greater than 50 or less than 19, 2) history of any gynecologic malignancy, 3) history of bilateral salpingo-oophorectomy (BSO) or bilateral oophorectomy (BO) or USO (unilateral salpingo-oophorectomy) or UO (unilateral oophorectomy) in the 15 years prior to the index surgery, or 4) not enrolled in medical services plan (MSP) the year of index surgery (Figure 2.1).

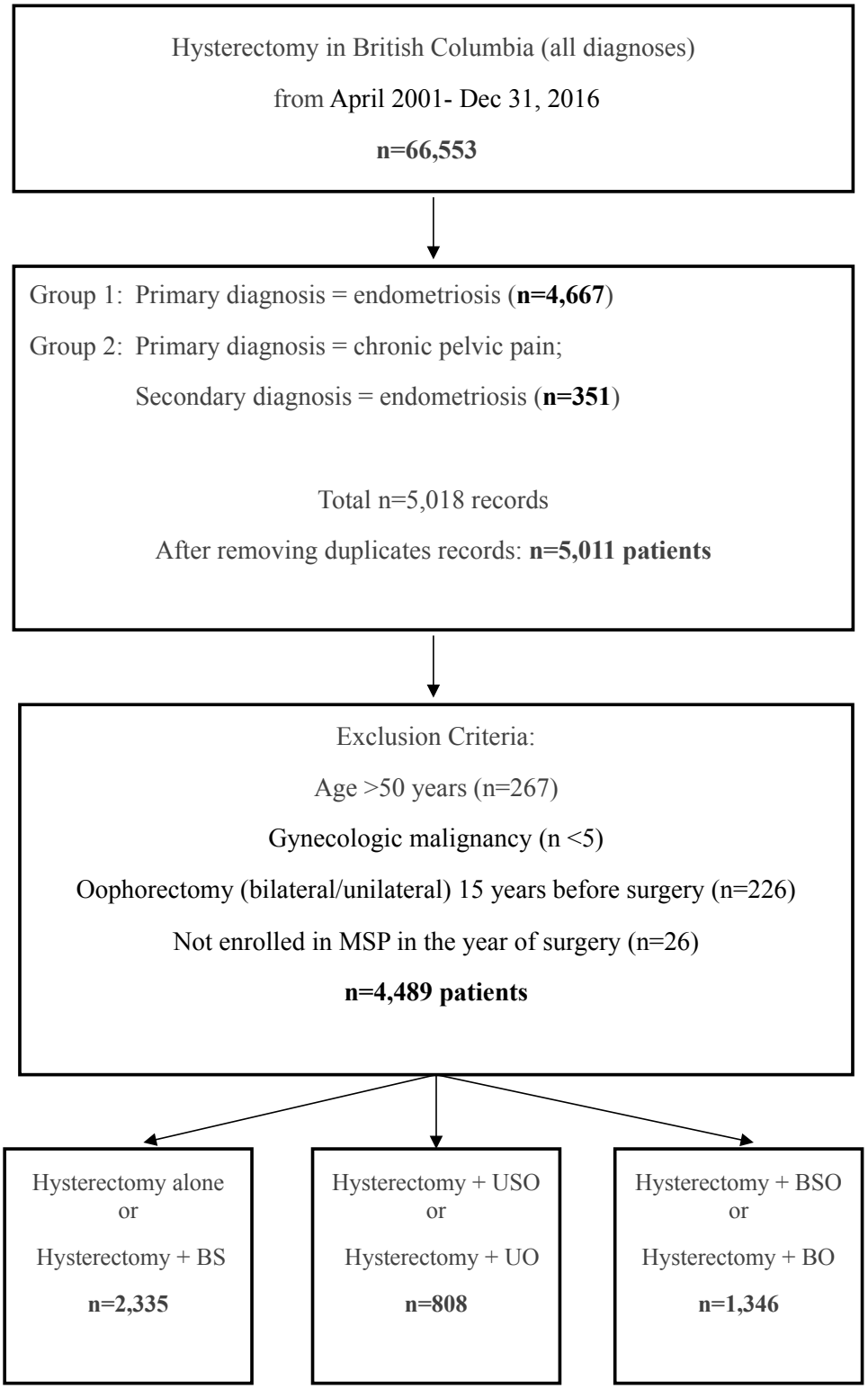


Figure 2.1 Inclusion and Exclusion Criteria Flowchart

Exposure: Our exposure of interest was the inclusion of USO/UO or BSO/BO with the hysterectomy. Using relevant Canadian Classification of Health Intervention (CCI) codes (Table 2.1), patients were further categorized. Each procedure has a unique code; for example, hysterectomy and BSO would be separately coded for a patient undergoing a single surgery. We categorized patients into the following cohorts: 1) hysterectomy alone or hysterectomy with BS (bilateral salpingectomy) (patients with two intact ovaries after index surgery), 2) hysterectomy with USO or UO (patients with one intact ovary after index surgery), or 3) hysterectomy with BSO or BO (patients with no intact ovaries after index surgery) (Figure 1).

Primary outcome: Our primary outcome of interest was reoperation over the study period (median 10.0 years). We defined a list of procedures using relevant CCI codes that constituted reoperation for the endometriosis patients included in our cohort (Table 2.1) and identified ICD-9-CM and ICD-10-CM diagnoses associated with these procedures (Table 2.2). An associated diagnosis of endometriosis was not required at the time of reoperation, given endometriosis lesions may or may not be present at reoperation. To account for the fact that those with retained ovaries may be at increased risk of a reoperation simply because they have ovaries to remove, a sensitivity analysis was performed excluding patients who had oophorectomy as a reoperation from the cohort of all patients who had any reoperation. We also examined whether there were meaningful differences in the diagnostic codes associated with reoperation across the three hysterectomy groups.

Table 2.1 Canadian Classification of Health Interventions (CCI) surgical procedure codes

CCI code	**Description**	**Assumption of common endometriosis procedure**
1.RM.89	Hysterectomy	Hysterectomy (abdominal, vaginal, laparoscopic)
2.RM.70.X	Inspection, uterus and surrounding structures	Diagnostic laparoscopy
2.OT.70	Inspection, uterus and surrounding structures	Diagnostic laparoscopy
2.RM.71.X and 2.OT.71	Biopsy of uterus and surrounding structures, biopsy of abdominal cavity	Biopsy of abdominal cavity
1.OT.72	Adhesiolysis, abdominal	Adhesiolysis/lysis of adhesions
1.RD.72	Adhesiolysis, tubal	Adhesiolysis/lysis of adhesions surrounding Fallopian tube
1.RM.87.X	Excision, partial uterus and surrounding structures including excision of aberrant endometrial tissue	Excision of endometriosis
1.RM.59.X	Ablation/cautery of endometriosis	Ablation/cautery of endometriosis
1.RB.87.X	Excision partial, ovary	Ovarian cystectomy
1.RB.72	Manual rupture and drainage of ovarian cyst	Drainage of ovarian cyst
1.RB.89.X	Excision total, ovary	Oophorectomy
1.RF.89.X, 1.RD.89.X	Salpingoophorectomy	Salpingoophorectomy
1.RF.87.X	Excision partial, fallopian tube	Salpingectomy
1.RF.89.X	Excision total, fallopian tube	Salpingectomy
1.RN.87.X	Trachelectomy	Total trachelectomy
1.RN.89.X	Partial trachelectomy	Partial trachelectomy
1.BF.59	Uterine nerve ablation, uterosacral nerve ablation	Presacral neurectomy, uterosacral nerve ablation

Table 2.2 International Diagnostic Codes (ICD) 9 and 10

International Disease Classification 10 (ICD10)	
N80	Endometriosis
N80.0, N80.1, N80.2, N80.3, N80.4, N80.5, N80.6, N80.8, N80.9	N80.0 Endometriosis of uterus N80.1 Endometriosis of ovary N80.2 Endometriosis of fallopian tube N80.3 Endometriosis of pelvic peritoneum N80.4 Endometriosis of rectovaginal septum and vagina N80.5 Endometriosis of intestine N80.6 Endometriosis in cutaneous scar N80.8 Other endometriosis N80.9 Endometriosis, unspecified
R10.2	Pelvic and Perineal Pain
R10.3	Pain localized to other parts of lower abdomen
D26	Benign neoplasm of the cervix uteri, corpus uteri, or other part of the uterus
D27	Benign neoplasm of the ovary
D28.7	Benign neoplasm of other and unspecified female genital organs
N83.2	Other and unspecified ovarian cysts
International Disease Classification 9 (ICD9)	
617	Endometriosis
625	Pain and other symptoms associated with female genital organs
625.0, 625.1, 625.2, 625.4, 625.5, 625.8, 625.9	Dyspareunia, Vaginismus, Mittleschmerz, Premenstrual tension syndromes, Pelvic congestion syndrome, Other, Unspecified
789.0	Other symptoms involving abdomen and pelvis – abdominal pain

Secondary outcomes: To obtain a more complete picture of endometriosis and pelvic pain-related health services across our three groups, we also examined other endometriosis and pelvic pain-related outcomes in the postoperative period. For all outcomes, we imposed a three-month washout period after discharge from the index hysterectomy to exclude routine postoperative follow-up visits and immediate surgical complications. Secondary outcomes were investigated at two different time periods: 1) 3-12 months post-discharge for the index hysterectomy, and 2) 1 to 5 years post-discharge for the index hysterectomy. The secondary outcomes included 1) ambulatory visits to a physician, with an associated diagnostic code of endometriosis (ICD-10-CM N80.X) or pelvic pain (ICD-10-CM R10.2 or R10.3), and 2) filling a prescription for analgesia, including opioids, as well as the number of days supplied of the prescription level analgesia in each of our relevant time periods.

We also performed a corollary analysis of hormone prescriptions filled after hysterectomy for endometriosis, including hormonal suppressive medications commonly used to treat endometriosis (oral contraceptive pills (OCP) and other medications to treat endometriosis such as progestins and GnRH agonists/antagonists), as well as usage of HRT. A list of generic names of OCP and endometriosis medications is found in Table 2.3.

Table 2.3 Generic drug names of hormone replacement therapy, combined estrogen/progestin contraceptives and endometriosis hormonal suppression medications

	Oral and Transdermal Hormonal Replacement Therapy	
	Estrogen Component	**Progestin Component**
1	Estradiol	
2	Estradiol	Drospirenone
3	Estradiol	Levonorgestrel
4	Estradiol	Norethindrone acetate
5	Estradiol	Micronized progesterone
6	Conjugated estrogen	Micronized progesterone acetate
7	Conjugated estrogen	
8	Ethinyl estradiol	Norethindrone acetate
9		Medroxyprogesterone acetate
10		Progesterone
11		Micronized progesterone
12	Estradiol (transdermal)	
13	Estradiol (transdermal)	Norethindrone acetate (transdermal)
14	Ethinyl estradiol (transdermal)	Norelgestromin (transdermal)

	Oral, Transdermal and Transvaginal Combined Estrogen/Progestin Contraceptives	
	Estrogen Component	**Progestin Component**
1	Ethinyl estradiol	Desogestrel
2	Ethinyl estradiol	Cyproterone
3	Ethinyl estradiol	Drospirenone
4	Ethinyl estradiol	Ethynodiol diacetate
5	Ethinyl estradiol	Levonorgestrel
6	Ethinyl estradiol	Norethindrone acetate
7	Ethinyl estradiol	Norelgestromin
8	Ethinyl estradiol	Norethindrone
9	Ethinyl estradiol	Norgestimate
10	Ethinyl estradiol	Etonogestrel

*Levonorgestrel IUD not included as our cohort have all had hysterectomy
*Etonogestrel implant not included as this device not approved in Canada during follow up period of our study

	Progestins, GnRH agonists and antagonists used in the treatment of endometriosis
1	Dienogest
2	Norethindrone
3	Norethindrone acetate
4	Medroxyprogesterone acetate
5	Danazol
6	Leuprolide acetate
7	Goserelin
8	Nafarelin
9	Buserelin

*Elagolix not included as this medication not approved in Canada during follow up period of our study

Statistical analysis: For the primary outcome, we analyzed reoperation as time to event data. Kaplan-Meier curves were created, and Cox proportional hazards models were fitted to model time to reoperation. We censored patients upon death or upon withdrawal from the province's universal health insurance, as this likely reflects a move out of the province. We first present crude hazard ratios. Then we adjusted for patient age at the index surgery, income, year of index surgery, previous surgeries for endometriosis (prior to the index surgery) and route of index surgery (i.e. open, laparoscopic, vaginal, etc). After fitting the models, we assessed the proportional hazards assumptions using the Schoenfeld residuals for non-zero slope. We found no evidence that this assumption was violated. All p-values are 2-sided. Statistical significance was defined as $P<0.05$ for all analyses.

For secondary outcomes, we conducted descriptive analyses. We report proportions of each group with a secondary outcome in each of the two relevant time periods and compare the three hysterectomy groups using standardized mean differences. A difference between the groups was considered clinically important if the standardized difference was greater than 0.1[132].

2.3 Results:

During the study period (April 1, 2001 to Dec 31, 2016), 4489 patients underwent hysterectomy for endometriosis and/or chronic pelvic pain. Of these patients, 2335 (52.0%) had hysterectomy alone (or hysterectomy with bilateral salpingectomy [BS]), 808 (18.0%) had hysterectomy with unilateral salpingoophorectomy (USO) or unilateral oophorectomy (UO), and

1346 (30.0%) had hysterectomy with bilateral salpingoophorectomy (BSO) or bilateral oophorectomy (BO) (Figure 2.1).

Table 2.4 presents baseline characteristics across the three hysterectomy groups. Compared to hysterectomy alone, hysterectomy USO/UO and hysterectomy BSO/BO groups had a higher mean age at the time of index surgery (39.5 years vs 40.3 years ($p<0.001$) vs 42.2 years ($p<0.001$)). Compared to hysterectomy alone, hysterectomy USO/UO and hysterectomy BSO/BO groups were more likely to have had surgery using an open/abdominal approach (51.1% vs 76.9% ($p<0.0001$%) vs 81.1% ($p<0.001$%). A greater proportion of index surgeries were performed between 2001-2005 (43.4%) compared to 2006-2010 (28.1%) and 2011-2016 (28.6%). Compared to hysterectomy alone, hysterectomy USO/UO and hysterectomy BSO/BO groups were more likely to have had a previous surgery (excluding prior unilateral or bilateral oophorectomy) for endometriosis (26.5% vs 37.9% ($p<0.0001$) vs 40.8% ($p<0.0001$)). Length of follow-up and household income were similar across the three groups.

Table 2.4 Characteristics of the cohort according to whether the hysterectomy included USO/UO or BSO/BO

	Total	Group A (Hyst Alone or Hyst+BS)	Group B (Hyst + USO or Hys+UO)	P value (A vs. B)	Group C (Hyst + BSO or Hyst+BO)	P value (A vs. C)
	n=4489	n=2335	n=808		n=1346	
Age (at time of index surgery, years) Mean (SD)*	40.4 (5.6)	39.5 (5.7)	40.3 (5.3)		42.2 (5.2)	
	Min: 19.6	Min: 22.6	Min: 21.8		Min: 19.7	
	Max: 50	Max: 50	Max: 49.9		Max: 50	
Median Age (IQR)	41.2 (36.7 to 44.9)	40.0 (35.4 to 44.1)	41.0 (36.7 to 44.1)	**0.001**	43.4 (39.3 to 46.2)	**<0.0001**
Age category (at time of index surgery), years				**<0.001**		**<0.0001**
19-29	213 (4.7)	150 (6.4)	28 (3.5)		35 (2.6)	
30-39	1,683 (37.5)	1,017 (43.5)	320 (39.6)		346 (25.7)	
40-50	2,593 (57.8)	1,168 (50.0)	460 (56.9)		965 (71.7)	
Year of surgery				**<0.001**		**<0.0001**
2001-2005	1,947 (43.4)	1,055 (45.2)	312 (38.6)		580 (43.1)	
2006-2010	1,260 (28.1)	574 (24.6)	246 (30.4)		440 (32.7)	
2011-2016	1,282 (28.6)	706 (30.2)	250 (30.9)		326 (24.2)	
Mean length of follow up, years (SD)	10.0 (4.7)	10.0 (4.8)	9.6 (4.6)		10.2 (4.3)	
	Min: 0.10	Min: 0.20	Min: 0.10		Min: 0.2	
	Max: 16.7	Max: 16.7	Max: 16.7		Max: 16.7	
Median length of follow up, years (IQR) ¶	10.7 (6.1 to 14.3)	10.7 (5.7 to 14.6)	10.2 (5.5 to 13.8)	**0.01**	10.8 (7.0 to 14.1)	0.46
Household income (Quintile)				0.83		0.18
1	865 (19.3)	444 (19.0)	169 (20.9)		252 (18.7)	
2	893 (19.9)	458 (19.6)	155 (19.2)		280 (20.8)	
3	954 (21.2)	508 (21.8)	171 (21.2)		275 (20.4)	
4	912 (20.3)	461 (19.7)	165 (20.4)		286 (21.2)	
5	776 (17.3)	409 (17.5)	131 (16.2)		236 (17.5)	
Missing	89 (2.0)	55 (2.4)	17 (2.1)		17 (1.3)	
Route of index surgery				**<0.0001**		**<0.0001**
Total laparoscopic or laparoscopic assisted vaginal	887 (19.8)	506 (21.7)	155 (19.2)		226 (16.8)	
Abdominal/open	2,906 (64.7)	1,193 (51.1)	621 (76.9)		1,092 (81.1)	
Vaginal	696 (15.5)	636 (27.2)	32 (4.0)		28 (2.1)	

	Group A Total n=4489	Group B (Hyst Alone or Hyst+BS) n=2335	P value (Hyst + USO or Hys+UO) n=808	Group C (A vs. B)	 (Hyst + BSO or Hyst+BO) n=1346	
Previous surgery for endometriosis				**<0.0001**		**<0.0001**
Yes	1,473 (32.8)	618 (26.5)	306 (37.9)		549 (40.8)	
No	3,016 (67.2)	1,717 (73.5)	502 (62.1)		797 (59.2)	
Loss to follow-up	49 (1.1)	29 (1.2)	9 (1.1)	0.77	11 (0.8)	0.23

Primary outcome: The proportion of patients undergoing at least one reoperation was low, with nearly 90% of people in the cohort not having undergone a reoperation by the end of follow-up (Table 2.5). The rates of reoperation were 13%, 12.2% and 5.3% for hysterectomy alone, hysterectomy USO/UO and hysterectomy BSO/BO, respectively (Table 2.5). Those undergoing hysterectomy alone were more likely to have had at least one reoperation compared to those with hysterectomy with BSO/BO ($p<0.0001$), however, they were no more likely than those with hysterectomy with USO/UO to have had at least one reoperation ($p=0.57$). There was no statistically significant difference in the number of reoperations between the three cohorts for people who underwent at least one reoperation. Time to the first reoperation between the three cohorts was also not statistically significantly different (median 2.2 years, IQR 1.2-4.8) (Table 2.5). The most common reoperations were adhesiolysis (5.1% of hysterectomy alone, 4.6**%** of hysterectomy with USO/UO, and 2.5% of hysterectomy with BSO/BO), followed by oophorectomy (4.7% of hysterectomy alone, 6.9% of hysterectomy with USO/UO, and 1% of hysterectomy with BSO/BO). Other procedures were low in frequency (<2%) (Table 2.7). Patients undergoing hysterectomy with USO and subsequent reoperation were more likely to include the diagnostic code of endometrioma associated with reoperation (21.2% vs 14.1% in hysterectomy alone group) (Table 2.5).

Table 2.5 Rate and frequency of reoperation and associated diagnostic codes, by whether the hysterectomy included USO/UO or BSO/BO.

	Total	**Group A (Hyst Alone or Hyst+BS)**	**Group B (Hyst+USO or Hyst+UO)**		**Group C (Hyst+BSO or Hyst+BO)**	
	(n=4,489)	**(n=2,335)**	**(n=808)**		**(n= 1,346)**	
	n (%)	**n (%)**	**n (%)**	**p value (A vs B)**	**n (%)**	**p value (A vs C)**
Patients requiring *at least 1* reoperation	474 (10.5)	304 (13.0)	99 (12.2)	0.57	71 (5.3)	**<0.0001**
Number of reoperations				0.14		0.6
1	358 (75.5)	221 (72.7)	83 (83.8)		54 (76.1)	
2	93 (19.6)	64 (21.0)	15 (15.1)		14 (19.7)	
3	14 (2.9)	12 (3.9)	≤5		≤5	
4	6 (1.3)	≤5	0		≤5	
≥5	≤5	≤5	0		0	
Number of reoperations, mean (SD)	1.3 (0.6) Min: 1 Max:5	1.4 (0.7) Min: 1 Max:5	1.2 (0.4) Min: 1 Max:3		1.3 (0.6) Min: 1 Max:4	
Time to first reoperation, Mean (SD), years	3.4 (3.1) Min: 0.01 Max: 15.5	3.3 (3.1) Min: 0.01 Max: 15.5	3.7 (3.3) Min: 0.2 Max: 13.9		3.2 (3.0) Min: 0.03 Max: 12.9	
Time to first reoperation, Median (IQR), years	2.2 (1.2 to 4.8)	2.2 (1.1 to 4.6)	2.4 (1.4 to 5.6)	0.29	2.2 (1.1 to 4.7)	0.68
Diagnostic codes associated with reoperation						
Endometriosis	139 (29.3)	94 (30.9)	23 (23.2)		22 (30.9)	
Pelvic pain	60 (12.6)	41 (13.5)	9 (9.1)		10 (14.1)	
Benign ovarian cyst	93 (19.6)	63 (20.7)	22 (22.2)		8 (11.3)	
Endometrioma	70 (14.8)	43 (14.1)	21 (21.2)		6 (8.4)	
Female pelvic peritoneal adhesions	166 (35.0)	109 (35.8)	37 (37.4)		20 (28.2)	
Postprocedural pelvic peritoneal adhesions	60 (12.6)	40 (13.1)	8 (8.1)		12 (16.9)	
Peritoneal adhesions (postprocedural/ postinfection)	56 (11.8)	35 (11.5)	12 (12.1)		9 (12.7)	
Corpus luteum cyst	40 (8.4)	20 (6.6)	14 (14.1)		6 (8.4)	
Follicular cyst of ovary	27 (5.7)	14 (4.6)	11 (11.1)		≤5	
Removal of other organ (partial/total)	25 (5.3)	16 (5.3)	≤5		≤5	

With respect to the Cox proportional hazards models, patients with hysterectomy with BSO/BO were less likely to undergo reoperation (aHR 0.42, 95% CI 0.32-0.55) than those with hysterectomy alone. There was no statistically significant difference in time to reoperation among patients who underwent hysterectomy + USO/UO (aHR 0.94 (95% CI 0.74-1.19) compared to hysterectomy alone (Table 2.6). Rates of reoperation free "survival" were high (>85%) at 5, 10, and 15 years after index surgery for all groups (Figure 2.2).

Table 2.6 Crude and adjusted hazard ratios of Cox proportional hazard regressions and 95% confidence interval for reoperation during the study follow up period.

	Main Analysis		**Sensitivity Analysis (oophorectomy patients removed)**	
	Crude Hazard ratio (95% CI)	**Adjusted Hazard ratio* (95% CI)**	**Crude Hazard ratio (95% CI)**	**Adjusted Hazard ratio* (95% CI)**
Hysterectomy +BSO/BO	0.38 (0.29-0.49)	0.42 (0.32-0.55)	0.58 (0.42-0.80)	0.63 (0.44-0.89)
Hysterectomy +USO/UO	0.94 (0.75-1.18)	0.94 (0.74-1.19)	0.67 (0.45-0.99)	0.67 (0.44-1.00)
Hysterectomy alone	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)

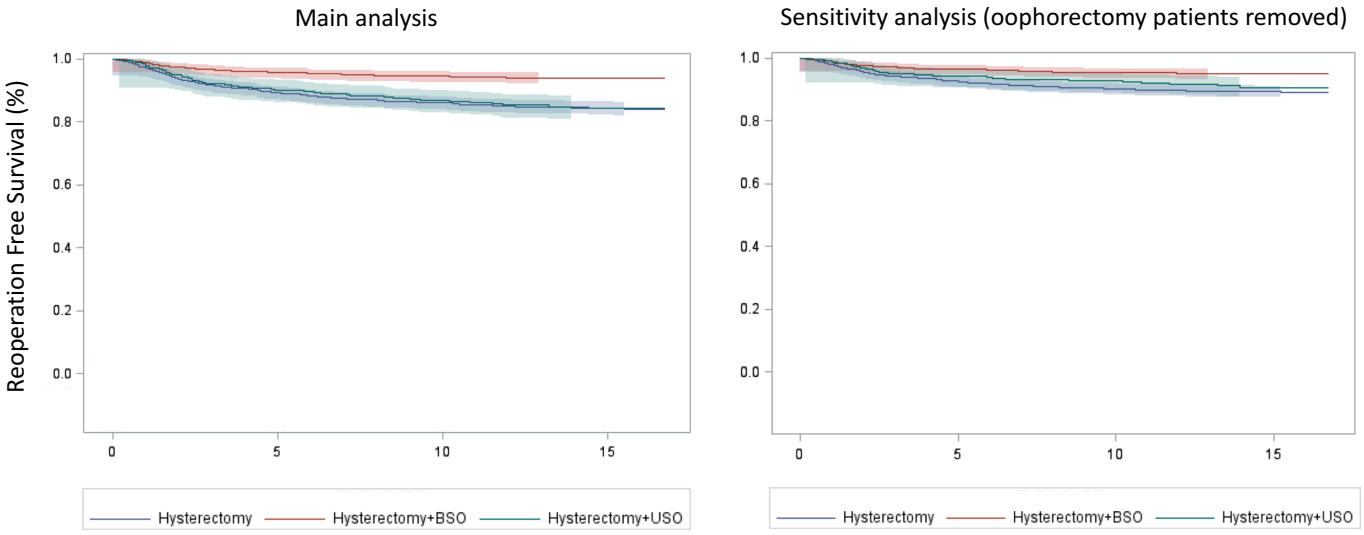
*Adjusted for age at index surgery, income, year of index surgery, previous surgery for endometriosis (prior to index surgery), route of index surgery.

We performed a sensitivity analysis, which excluded the patients undergoing oophorectomy as a reoperation. This revealed that the frequency of patients undergoing at least one non-oophorectomy-related operation was 6.3%, 4.2% and 3.4% for hysterectomy alone, hysterectomy USO/UO and hysterectomy BSO/BO, respectively (Table 2.7). After excluding oophorectomy, adhesiolysis was the most common reoperation; 3.1% in hysterectomy alone group, 2.0% in hysterectomy with USO/UO group, and 2.2% in hysterectomy with BSO/BO group. The Cox proportional hazards model demonstrated a reduced risk of reoperation for the hysterectomy with BSO/BO group (aHR 0.63, 95% CI 0.44-0.90) and hysterectomy with USO/UO group (aHR 0.665, 95% CI 0.44-1.00) compared to the hysterectomy alone group (aHR 1.00, reference) (Table 2.6). Reoperation free "survival" was high for all groups (>90%) at 5, 10, and 15 years (Figure 2.2).

Table 2.7 Reoperation by procedure type by whether the hysterectomy included USO/UO or BSO/BO

	Main analysis				Sensitivity analysis (oophorectomy removed)			
	Total (n)	**Group A (Hyst Alone Hyst+BS)**	**Group B (Hyst+USO/ Hyst+UO)**	**Group C (Hyst+BSO Hyst+BO)**	**Total**	**Group A (Hyst Alone Hyst+BS)**	**Group B (Hyst+USO/ Hyst+UO)**	**Group C (Hyst+BSO/ Hyst+BO)**
Total in cohort, n	4,489	2,335	808	1,346	4,232	2,167	740	1,325
Total requiring at least one reoperation, n (% of total)	474 (10.5)	304 (13.0)	99 (12.2)	71 (5.3)	217 (5.1)	136 (6.3)	31 (4.2)	50 (3.4)
Type of first reoperation	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Diagnostic laparoscopy only	54 (1.2)	35 (1.5)	10 (1.2)	9 (0.7)	39 (0.9)	24 (1.1)	9 (1.2)	6 (0.5)
Biopsy of abdominal cavity	19 (0.4)	13 (0.6)	≤5	≤5	9 (0.2)	7 (0.3)	≤5	≤5
Excision of endometriosis	37 (0.8)	18 (0.8)	7 (0.9)	12 (0.9)	20 (0.5)	8 (0.4)	≤5	10 (0.8)
Ablation/cautery of endometriosis	39 (0.9)	31 (1.3)	≤5	≤5	26 (0.6)	22 (1.0)	≤5	≤5
Ovarian cystectomy	34 (0.8)	25 (1.1)	≤5	≤5	22 (0.5)	16 (0.7)	≤5	≤5
Oophorectomy or salpingoophorectomy	179 (4.0)	109 (4.7)	56 (6.9)	14 (1.0)	-	-	-	-
Salpingectomy only	35 (0.8)	33 (1.4)	≤5	≤5	26 (0.6)	24 (1.1)	≤5	≤5
Total and partial trachelectomy	≤5	≤5	≤5	≤5	≤5	≤5	≤5	≤5
Presacral neurectomy or uterosacral nerve ablation	≤5	≤5	≤5	≤5	≤5	≤5	≤5	≤5
Release, ovary with fallopian tube	14 (0.3)	10 (0.4)	≤5	≤5	8 (0.2)	6 (0.3)	≤5	≤5
Adhesiolysis, abdominal or release, abdominal cavity	188 (4.2)	118 (5.1)	37 (4.6)	33 (2.5)	111 (2.6)	67 (3.1)	15 (2.0)	29 (2.2)

Figure 2.2 Reoperation free survival over follow up period after hysterectomy for endometriosis with conservation of both ovaries (blue), hysterectomy with USO/UO (green), or hysterectomy with BSO/BO (red): main analysis (left) and sensitivity analysis removing oophorectomy patients (right).



*Model adjusted for age at index surgery, income, year of index surgery, previous surgery for endometriosis (prior to index surgery), route of index surgery.

Secondary outcomes: We analyzed the proportion of patients who had at least one physician visit for endometriosis or pelvic pain at 3-12 months and 1-5 years after index surgery (Table 2.8). At 3-12 months after index surgery, the hysterectomy BSO group was *more* likely to have visited a physician for endometriosis (16.4%) than the hysterectomy alone group (12.8%; standardized difference 0.1); the hysterectomy with USO/UO group had a higher rate of physician visits (20.2%; standardized difference 0.2). At 1-5 years after index surgery, there was no difference in the number of physician visits between the hysterectomy alone group and hysterectomy with BSO/BO group (25.9% and 25.6% respectively; standardized difference 0.01). However, the hysterectomy with USO/UO group continued to have higher rates of physician visits than the hysterectomy alone group (36.8% vs 25.9% respectively, standardized difference 0.24).

Between 3-12 months after index surgery, 25.1%, 21.8% and 19.5% of patients with hysterectomy alone, hysterectomy with USO/UO and hysterectomy with BSO/BO, respectively, filled at least one opioid prescription (standardized difference of 0.13 for the comparison between hysterectomy with BSO and hysterectomy alone). At 1-5 years, 51.4%, 44.7%, and 45.4% of patients with hysterectomy alone, hysterectomy with USO/UO and hysterectomy with BSO/BO, respectively, filled at least one opioid prescription (standardized difference of 0.14 and 0.12, respectively). Among users, the number of days supplied was small and not significantly different across all cohorts – at 3-12 months after index surgery, 24/270 days (8.9%) for hysterectomy alone, 30/270 days (11.1%) for hysterectomy with USO/UO and 29/270 days (10.7%) for hysterectomy with BSO/BO. At 1-5 years after index surgery, the number of days supplied to those who filled at least one prescription continued to be low with 34/1460 days (2.3%) for hysterectomy alone, 40/1460 days (2.7%) for hysterectomy with USO/UO and

37/1460 days (2.5%) for hysterectomy with BSO/BO (Table 2.8).

Usage of OCP was low across all cohorts after index surgery, with 1.4%, 1.9% and 1.3% of women with hysterectomy alone, hysterectomy with USO/US and hysterectomy with BSO/BO, respectively, filling at least one prescription between 3-12 months after index surgery, and 2.3%, 2.6% and 1.9% filling at least one prescription between 1-5 years after index surgery. Of those filling at least one prescription, mean days of usage was also low across all cohorts (Table 3.1). With regards to usage of hormonal suppression medications other than OCP, among patients with hysterectomy alone 1.8% filled at least one prescription between 3-12 months after index surgery, 4.1% of those with hysterectomy plus USO/UO compared to 2.8% of those with hysterectomy plus BSO/BO. Of the patients who filled at least one prescription, the number of days of use between 3-12 months after index surgery were also low across all groups – 23 days (8.5% of possible 270 days) for the hysterectomy alone group, 25 days (9.2% of possible 270 days) for the hysterectomy with USO/UO group and 33 days (12.2% of possible 270 days) for the hysterectomy with BSO/BO group. (Table 2.8).

For HRT usage, we analyzed the percentage of patients in each cohort who filled at least one prescription with the expectation that usage would be low in those with ovarian conservation. In patients with hysterectomy and BSO, across all age groups (19-50 years old), 60.6% filled at least one prescription (39.4% never filling a prescription) between 3-12 months after index surgery, and 58.8% filling at least one prescription between 1-5 years after index surgery (41.2% filling no prescription in this timeframe). To determine ongoing usage, the number of days of prescription used per timeframe was determined. Among women undergoing hysterectomy with BSO, and filling at least one prescription, these patients filled on average 54

days worth of medication out of a maximum of 270 days (20% of possible days) 3-12 months after index surgery, and 197/1470 days (13% of possible days) between 1-5 years after index surgery (Table 3.1). Those aged 19-29 who underwent hysterectomy and BSO had slightly higher usage on average (71.4% filled at least one prescription between 3-12 months after index surgery) compared to the 40-50 cohort (57.7% filled at least one prescription between 3-12 months) but mean number of days of usage remains low and not significantly different amongst age categories (Table 2.9).

Table 2.8 Physician visits and prescription medication use after hysterectomy for endometriosis, with conservation of both, one or no ovaries

	Time after index surgery	Group A Hyst Alone/ Hyst+BS	Group B Hyst+USO/ Hyst+UO	Group C Hyst+BSO/ Hyst+BO	Standardized difference (A vs B)	Standardized difference (A vs C)
Total (19-50 years)		2335	808	1346		
Physician Visits						
At least one physician visit, N (%)	3-12 months	299 (12.8)	163 (20.2)	221 (16.4)	**0.2**	**0.1**
	1-5 years	604 (25.9)	297 (36.8)	345 (25.6)	**0.24**	0.01
Opioid Use						
Filled at least one prescription, N (%)	3-12 months	586 (25.1)	176 (21.8)	263 (19.5)	0.08	**0.13**
	1-5 years	1201 (51.4)	361 (44.7)	612 (45.4)	**0.14**	**0.12**
# of days filled among users / time period, median days (IQR)	3-12 months	24 (11, 58)	30 (17, 73)	29 (14, 88)	0.07	**0.14**
	1-5 years	34 (16, 99)	40 (20, 129)	37 (19, 109)	0.03	0.02
OCP use						
Filled at least one prescription, N (%)	3-12 months	32 (1.4)	15 (1.9)	17 (1.3)	0.04	0.01
	1-5 years	54 (2.3)	21 (2.6)	25 (1.9)	0.02	0.03
# of days filled among users / time period, median days (IQR)	3-12 months	21 (10, 28)	24 (4, 48)	50 (30, 70)	**0.17**	**1.09**
	1-5 years	36 (18, 90)	66 (31, 117)	59 (26, 223)	**0.21**	**0.52**
Endometriosis medication use						
Filled at least one prescription, N (%)	3-12 months	41 (1.8)	33 (4.1)	37 (2.8)	**0.14**	0.07
	1-5 years	78 (3.3)	49 (6.1)	44 (3.3)	**0.13**	<0.01
# of days filled among users / time period, median days (IQR)	3-12 months	23 (11, 47)	25 (11, 45)	33 (17, 47)	0.05	**0.2**
	1-5 years	42 (22, 76)	30 (16, 80)	40 (12, 135)	**0.14**	**0.25**
HRT use						
Filled at least one prescription, N (%)	3-12 months	67 (2.9)	126 (15.6	816 (60.6)	**0.45**	**1.58**
	1-5 years	196 (8.4)	207 (25.6)	792 (58.8)	**0.47**	**1.26**
# of days filled among users / time period, median days (IQR)	3-12 months	30 (16, 48)	45 (26, 73)	54 (31, 90)	**0.44**	**0.59**
	1-5 years	71 (27, 175)	134 (43, 254)	197 (84, 313.5)	**0.12**	**0.32**

Table 2.9 Use of hormone replacement therapy after hysterectomy for endometriosis, with bilateral salpingoophorectomy, by age category

		Time after index surgery	Hyst+BSO/ Hyst+BO
Total, N (19-50 years)			1346
Filled at least one prescription, N (%)			
	Total (19-50 years)	3-12 months	816 (60.6)
		1-5 years	792 (58.8)
	19-29	3-12 months	25 (71.4)
		1-5 years	24 (68.6)
	30-39	3-12 months	234 (67.6)
		1-5 years	228 (65.9)
	40-50	3-12 months	557 (57.7)
		1-5 years	540 (56.0)
# of days filled among users / time period, median days (IQR)			
	Total (19-50 years)	3-12 months	54 (31, 90)
		1-5 years	197 (84, 313.5)
	19-29	3-12 months	61 (24, 104)
		1-5 years	172 (59, 604)
	30-39	3-12 months	54 (30, 100)
		1-5 years	227 (102, 373)
	40-50	3-12 months	54 (33, 87)
		1-5 years	184 (79, 286)

2.4 Discussion:

Individuals undergoing hysterectomy for endometriosis with BSO/BO were less likely to have a reoperation compared to those with hysterectomy with ovarian conservation, although overall reoperation rates were low for all groups. Most reoperations were for oophorectomy or adhesiolysis. Our finding that those undergoing hysterectomy with BSO were less likely to undergo reoperation was consistent with previous studies in this area[66-68]. The differences were partially attenuated after sensitivity analysis (removal of oophorectomy as a reoperation). It is possible that a subset of oophorectomy reoperations were performed "empirically" in patients experiencing post-hysterectomy persistent pain, which is actually multifactorial in etiology and therefore it is uncertain the level of benefit conferred by performing BSO[44]. Although reoperation rates have been studied after hysterectomy by oophorectomy status, outcomes related to pelvic pain have not been studied to our knowledge. Additionally, oophorectomy performed in the hysterectomy alone and hysterectomy with USO/UO groups as reoperation does not necessarily reflect disease recurrence, as evidenced by low rates of "endometriosis" as diagnostic codes associated with reoperation surgeries, and our observation that excision/ablation of endometriosis as a reoperation was similar in all groups, implying that at the time of reoperation, there was no difference in the presence of residual endometriosis lesions, ie disease recurrence, across the three cohorts. These observations again support the hypothesis that some BSO reoperations are performed "empirically" as a last resort for women with persistent pelvic pain. In contrast, women who have hysterectomy with BSO as the index surgery, there are no ovaries to remove surgically or suppress medically if a patient presents with persistent pelvic pain, and the surgeon may feel that they have "nothing more to offer". Therefore, reoperation should not be used as a measure to compare these patients to those who had hysterectomy with ovarian

conservation, which is why we performed sensitivity analysis removing patients who had reoperation for oophorectomy, to make a more direct comparison in pain-related health services use between groups. In our study, post-hysterectomy physician visits were similar between the groups regardless of oophorectomy status. Use of opioids was low and similar across groups as well. These results suggest that there are no major differences in pain-related health services use after hysterectomy for endometriosis based on oophorectomy status, which we have used as a surrogate outcome for persistent pelvic pain.

Hormonal suppression medications, including OCP, may be used after hysterectomy with ovarian conservation to suppress the residual ovaries in patients with persistent pain. Because surgical management, particularly hysterectomy, is generally not considered until medical therapy has been attempted and failed or is contraindicated[36], patients undergoing hysterectomy for endometriosis often desire "definitive surgical management" and desire to not have to take hormonal medications after surgery. Therefore, there needs to be an informed discussion between the patient and the surgeon about the possible need for hormonal suppression medications after hysterectomy if the ovaries are conserved. To date, there has not been good data to inform patients the rate at which patients with ovarian conservation will require ovarian hormonal suppression after hysterectomy for endometriosis. In this study, we observed that use of hormonal suppressive medications after hysterectomy was low across all groups (<3% filling a prescription for OCP, and <6% filling any other hormonal suppression medication typically used for endometriosis within 3-12 months after index surgery), suggesting that patients with ovarian conservation are no more likely than those with BSO to require ovarian suppression after hysterectomy. This is reassuring for those undergoing hysterectomy with ovarian conservation.

Our study demonstrates low rates of patients filling even a single prescription of HRT after premenopausal BSO at the time of hysterectomy for endometriosis – 60.6% across all age groups between three months and one year after index surgery, and 58.8% between one and five years after index surgery, which is consistent with data from other studies of HRT use in premature surgical menopause[65]. We went on to explore the ongoing use of HRT across distinct time periods and found very poor rates of HRT adherence even among those who filled at least one prescription (54 out of a possible 270 days (20%) at 3-12 months and 197 days out of a maximum of 1460 days (13%) between 1-5 years after index surgery). There were not significant differences in HRT usage over time based on age category. Thus, inducing premature surgical menopause is likely conferring additional long-term health risks in the hysterectomy with BSO group that are not being adequately addressed through HRT use.

Interestingly, we found a higher use of pain-related health services, including physician visits for endometriosis or pelvic pain and the use of endometriosis hormonal suppression medications, in patients with hysterectomy plus USO/UO. This USO/UO group were more likely to have an ovarian endometrioma at reoperation, and thus these findings may reflect more severe disease at the index surgery for the USO/UO group; however, we did not have data on endometriosis stage to compare between the three groups to confirm this hypothesis. These findings suggest that there could be a higher chance of persistent pelvic pain and reoperation when ovarian endometriomas and deep endometriosis are present.

In conclusion, we found that despite a modestly lower rate of reoperation in the hysterectomy with BSO compared to the hysterectomy alone group, the number of physician visits for endometriosis or pelvic pain, ongoing opioid use, and the need for ovarian suppression with hormones were similar. It is important to note that reoperation was infrequent in all groups, with almost 90% of the cohort being reoperation free by the end of the follow-up period (median 10.0 years). Moreover, there were suboptimal rates of HRT use following hysterectomy with BSO, with only 60% filling at least one prescription within twelve months after surgery. We conclude that there should be caution when considering bilateral oophorectomy at the time of hysterectomy for endometriosis.

Chapter 3: Conclusion

3.1 Summary of key findings and implications

The objective of this thesis was to compare pain-related health utilization outcomes after hysterectomy for endometriosis, based on oophorectomy status. Re-operation rates were generally low across groups (nearly 90% did not require another operation at median 10 years follow-up), but reoperation rates were lowest in the bilateral oophorectomy groups compared to patients where one or both ovaries were conserved. However, we expected that re-operation would be lower in the BSO group, simply because all reproductive organs have been removed and a surgeon would likely be less agreeable to moving forward with another surgery even if the patient has persistent pelvic pain; therefore we examined other pain related health utilization outcomes. Regardless of oophorectomy status after hysterectomy for endometriosis, we found no clinically significant differences in the number of patients filling at least one opioid prescription after index surgery, nor in mean number of days filled, which was low overall. We also found no significant differences in the number of physician visits for endometriosis or chronic pain between hysterectomy alone and hysterectomy with BSO/BO groups. Moreover, we found that reoperation was primarily driven by oophorectomy and adhesiolysis, presumably for persistent pelvic pain after hysterectomy for endometriosis, but the effectiveness of these reoperations in relieving pelvic pain after reoperation is unclear. After performing a sensitivity analysis by removing reoperation oophorectomies and then examining reoperations in all groups, re-operation for adhesiolysis was very low (<3%) across the groups. Based on these findings, we conclude that pain-related health utilization outcomes after hysterectomy for endometriosis are similar regardless of oophorectomy status. The clinical implication of this is that despite the hysterectomy with BSO group having a statistically lower rate of reoperation (12-13% chance of

reoperation when ovaries are conserved compared to a 5% chance in reoperation with a BSO), reoperation to remove an ovary or to perform adhesiolysis does not mean that a patient's pain will resolve, which is suggested by our results in usage of pain related health utilization, and that a 7-8% increased risk of reoperation with ovarian conservation should be weighed carefully against the known morbidities associated with premenopausal surgical menopause.

One interesting observation is that we found a slightly higher rate of physician visits for the hysterectomy USO/UO group. We also found that the associated diagnostic code for endometrioma at the time of reoperation was also higher in this group, suggesting that the presence of endometrioma or deeply infiltrating endometriosis at the time of index surgery. Particularly if deep disease is not fully excised, this may be a risk factor for persistent pelvic pain and account for the increased uptake of pain related health services use in the hysterectomy with USO/UO group. However, with the current dataset, we do not have the data on the stage of endometriosis at the time of index surgery to confirm this hypothesis. Endometriosis stage would be an important variable to examine in future research on this topic to further elucidate the impact of endometriosis stage on surgical outcomes, and whether these outcomes vary by oophorectomy status.

We also found that the rate of patients who filled at least one prescription for HRT after having hysterectomy with BSO/BO was suboptimal (60.6% overall) and number of days filled in a given time period, indicating ongoing use, to be poor (20% of possible days within 3-12 months after index surgery and 13% of possible days within 1-5 years after index surgery). In patients with ovarian conservation, the number of patients filling at least one prescription as well

as rates of ongoing usage of OCP and other endometriosis hormonal medications was low. This finding could have several explanations: 1) most patients have significant pain improvement after hysterectomy and do not require the use of OCP or endometriosis hormonal medications for suppression of endogenous estrogen; 2) patients who do have persistent or recurrent pain after hysterectomy may be declining hormonal suppressive therapies, or 3) non-hormonal sources of persistent pelvic pain are being recognized and addressed by patients and clinicians.

3.2 Implications

Hysterectomy is one of the most common surgical procedures performed among reproductive aged women in Canada and in the United States[60,133], with endometriosis a common indication for hysterectomy with BSO[63]. Despite being a common procedure, there has been very little research on pain related outcomes after hysterectomy for endometriosis, apart from cohort studies examining rates of reoperation after hysterectomy with or without ovarian conservation[66-68]. However, reoperation itself is not indicative of more frequent or severe persistent pelvic pain, as women who have had hysterectomy with BSO may have persistent pelvic pain at a similar rate to those with conserved ovaries. However, some practitioners may feel as though they have "nothing left to offer" when a patient has a history of hysterectomy with BSO, as there are no gynecologic organs left to remove and may recognize that without ovaries and low systemic levels of estrogen, that the persistent pain a patient is having is less likely to be hormonally driven, and therefore less likely to be responsive to surgery. When a patient has had hysterectomy with conservation of one or both ovaries and presents to their physician/surgeon with persistent pelvic pain, oophorectomy may be performed "empirically" with the hopes of improving pelvic pain, as endometriosis is an estrogen driven disease. However, reoperation (by way of oophorectomy, adhesiolysis or other) is not a guarantee that a patient's pain improves.

Future studies focusing on patient reported outcomes following reoperation should examine patient pain experiences more closely.

There are a number of potential clinical implications of these research findings, particularly for patients with endometriosis who are considering hysterectomy. Patients can be counselled that re-operation rates are quite low regardless of oophorectomy status, and though re-operation is lowest with bilateral oophorectomy, other pain-related health utilization outcomes, including the need to visit a physician for the indication of pelvic pain or endometriosis, or the usage of opioid medications within the first five years after surgery, are in fact quite similar. This is reassuring especially for younger patients who would want to preserve at least one ovary and avoid surgical menopause.

To this point there has not been good data to be able to counsel patients undergoing hysterectomy for endometriosis on the chance of requiring ovarian hormonal suppression postoperatively, which may contribute to the patient and practitioner's decision to move forward with BSO for the most "definitive" method of estrogen suppression. Our study shows that the rates of OCP and other hormonal medication use in women who had hysterectomy with ovarian conservation is very low (<3% filling a single prescription for OCP and <6% filling a single prescription for another hormonally suppressive medication and ongoing days of use very low). This is encouraging to empower patients with the knowledge that the chance of requiring hormonal medications after surgery is low even with ovarian conservation. This observation is important, because residual ovaries after hysterectomy are thought to be a possible cause of persistent or recurrent pain, by providing systemic estrogen that could theoretically stimulate any residual endometriosis or by pain related to ovulation. Our data, which shows a low rate of

hormonally suppressive medications after hysterectomy with ovarian conservation, suggests that these scenarios may be quite rare. Therefore, patients and clinicians may not need to proceed with BSO solely to avoid the use of hormones for ovarian suppression after hysterectomy for endometriosis.

We found suboptimal rates of HRT usage in patient undergoing hysterectomy with BSO/BO, even when they were considerably below the average age of natural menopause. Given the known risks associated with premenopausal surgical menopause without sufficient HRT addback, this carries significant health implications for women undergoing hysterectomy BSO for endometriosis. This again should be considered when counselling patients about hysterectomy for endometriosis, with or without ovarian conservation, and the morbidity and mortality of BSO should be discussed with the patient, as well as counseling provided regarding HRT.

Another potential implication of our findings is that that persistent or recurrent pelvic pain after hysterectomy for endometriosis may not be hormonally-related in many cases, given only small differences based on the hysterectomy alone group and the hysterectomy with BSO/BO group. Non-hormonal etiologies of persistent or recurrent pain post-hysterectomy might include the bladder, bowel, and musculoskeletal and nervous system, or involve central nervous system sensitization. Recognition of non-hormonal etiologies is important, as their treatment is non-surgical. A proper history, physical exam and treatment plan is imperative to identify and address these causes of pain ideally prior to undergoing hysterectomy. These sources of pain may also contribute to persistent pelvic pain after hysterectomy which may lead

to reoperation (particularly oophorectomy for those who have ovaries to remove) and pain may persist even after reoperation if these issues are not properly diagnosed and addressed. Thus, identification of non-hormonal causes of persistent or recurrent pain could avoid unnecessary re-operations.

In summary, conservation of one or both ovaries should be strongly considered at the of hysterectomy for endometriosis. There still remains case-by-case exceptions where BSO may be considered. This may include cases of severe stage IV endometriosis that are at higher risk of recurrent pain secondary to residual endometriosis lesions under the influence of estrogen. BSO may also be indicated with severe bilateral adnexal disease where the ovaries are not salvageable. There are likely also specific cases that are very sensitive to ovarian estrogen production and/or ovulation pain, who cannot tolerate hormonal suppression, in whom BSO may need to be performed. If BSO is performed in younger patients, our data indicate that long-term follow-up is essential to ensure long-term HRT is being used and to prevent the metabolic consequences of premature hypoestrogenism. Nevertheless, while there may be these exceptions, in general it appears that hysterectomy with or without ovarian conservation may yield similar long-term outcomes.

3.3 Strengths and limitations

This study was strengthened by its population-based nature, representing real-world practice, as well as its large scale (4489 patients) and long period of follow-up (median 10.0 years). There was also comprehensiveness of the outcomes studied, including not only rates of reoperation, but actual surgical procedures performed, and diagnoses associated with reoperations. We also included non-surgical pain-related health services use, such as physician

visits for endometriosis and pelvic pain and the use of hormonal medications used to suppress endometriosis, as surrogate markers for persistence of pelvic pain after hysterectomy for endometriosis. Another strength was a sensitivity analysis based on oophorectomy as a reoperation.

An additional strength of our study was that reoperations did not require an associated diagnosis of endometriosis. As we saw in the diagnostic codes associated with reoperation, endometriosis was only recorded approximately 30% of the time, which is consistent with clinical experience in that at the time of reoperation endometriosis is not always seen. Our results differ from Bougie et al [68], although there were similarities in methodology (both retrospective cohort studies using clinical databases using ICD coding of diagnoses and surgical procedures). Bougie et al found a rate of repeat surgery of 1.9% for women with hysterectomy without BSO and 0.4% for women with hysterectomy and BSO over the total follow up period (median 10 years). They stratified by types of reoperations divided into "none", "laparoscopy", "major" and "minor", with oophorectomy falling under "major" surgery and lysis of adhesions falling under "minor" surgery, and they required the diagnosis of endometriosis to be present for all reoperations. Additionally, in their study the women undergoing hysterectomy were on average slightly older (41.8 years for hysterectomy with ovarian conservation and 44.5 for hysterectomy with BSO) so that after a median of 10 years of post operative follow up, more women would be post-menopausal and therefore less likely to undergo reoperation. In contrast, we saw a higher rate of reoperation when using procedure codes as the main identifier of reoperation in endometriosis patients (13.0% for hysterectomy alone, 12.2% for hysterectomy with USO/UO and 5.3% for hysterectomy with BSO). Our study also examined three groups (hysterectomy alone, hysterectomy and USO, hysterectomy and BSO), and our cohort was younger on average

(39.5 for hysterectomy alone, 40.3 for hysterectomy with USO/UO and 42.2 for hysterectomy with BSO/BO). Thus, we found a higher rate of reoperation among our cohorts.

Limitations of our study include those inherent to database research, such as errors in coding and difficulty with the precision of diagnostic and procedure codes. For example, fourteen patients with BSO at the time of index surgery were reported to undergo oophorectomy as a reoperation, which may represent subsequent surgery for an ovarian remnant or may reflect incorrect coding either at the time of index surgery or at the reoperation. It likely reflects a combination of both. Additionally, although we are interested in the differences in persistent pelvic pain between the groups, we must rely on surrogate outcomes to infer the existence of persistent pelvic pain (such as rates of reoperation, usage of opioid medications and physician visits). Although validated pain and quality of life questionnaires exist[134], these are not items that exist in retrospective database research. Future research would benefit from patient reported outcomes.

We are also limited by only capturing prescriptions filled without having data on the diagnosis associated with the patient prescription. In the PharmaNet dataset, analgesia and opioid prescriptions are not captured with a diagnosis, so there is no guarantee that these medications were prescribed or taken for endometriosis or chronic pelvic pain specifically. It is possible that these medications were used for non-endometriosis related pain conditions. However, given the large sample size of all three cohorts, the number of patients taking analgesia for endometriosis-related pain versus other conditions would be assumed to be approximately evenly distributed between groups and it is most important to examine the differences between groups rather than the absolute rate of use; thus this is unlikely to have biased our results.

In our cohort, more than 50% of all patients underwent surgery using open/abdominal approach, which may be reflective of a lower technicity index of surgeries performed early in the study period. This may not be representative of today's surgical practices, as the technicity index of hysterectomies in Canada has been increasing significantly over the last decade[135], although some surgeons may favour an open/abdominal approach for more surgically complex cases, such as with advanced stage endometriosis. Accordingly, we were also limited by the lack of data on the stage of endometriosis at index surgery, as the surgical management is different for Stage I endometriosis as compared to Stage IV endometriosis (Stage IV being more challenging to complete a full excision of endometriosis and requiring more advanced surgical skills)[85,136].

3.4 Recommendations for future research

At this point, it would not be considered ethical to conduct a randomized controlled trial of patients randomized to hysterectomy with ovarian conservation versus BSO (without addback HRT) given the known risks of BSO without addback HRT. It would, however, be useful to conduct a prospective study on patients who have hysterectomy for endometriosis with or without ovarian conservation and track actual pain related outcomes, as well as other measures of quality of life, through the use of validated questionnaires and compare outcomes of those with ovarian conservation versus those who have BSO and are adherent to HRT versus those who have BSO and are not adherent to HRT by using prescription records. It would be unlikely, however, to be able to follow a large cohort of patients in this manner without a pooled multi-centre trial.

Research should prioritize examining pain related outcomes in patients who have hysterectomy for endometriosis and then have subsequent oophorectomy, to determine if their

pain *after* oophorectomy is different before and after oophorectomy, and whether their outcomes are similar or dissimilar to those who underwent hysterectomy with BSO at index surgery, who are unable to undergo oophorectomy as a reoperation.

Additional research is needed to further understand what is currently driving some patients and clinicians to consider BSO at the time of hysterectomy. A mixed-methods approach would be useful to characterize some of these driving factors. For example, the traditional conception of hysterectomy/BSO as "definitive" surgical treatment for endometriosis may be a factor, although our results indicate that hysterectomy alone may be itself "definitive" in most cases, regardless of oophorectomy status. There may also be lack of understanding of the multifactorial nature of pain persistence or recurrence after hysterectomy, and that non-hormonal factors need to be considered and treated without necessarily resorting to re-operation.

Similar approaches should also be used to investigate the reasons for low rates of HRT uptake and continuation when clinically indicated in patients with endometriosis. It is likely there is misunderstanding about the benefits/risks of HRT in the context of endometriosis, early surgical menopause, versus spontaneous menopause at an older age. There may also be social and financial factors at play that affect patients' ability to access HRT for many years. As well, health care providers may not be clearly counselling patients that HRT should be continued until the average of menopause (age 51). Gynecologic surgeons also may not be following these patients beyond the immediate post-operative period, and so it is important to have a multidisciplinary approach, and educate family physicians about the importance of using HRT in patients with premenopausal surgical menopause.

Finally, knowledge translation (KT) is necessary to disseminate this new information to both clinicians and patients. Creative KT solutions will be needed, as we attempt to address the

"myth" of hysterectomy/BSO as generally being considered the "definitive" treatment of endometriosis and to address the low rates of HRT use when long-term therapy is beneficial. Engagement with endometriosis patient partners and patient advocacy groups, as well as clinician stakeholders, will be important to ensure the success of KT.

3.5 Conclusion

Our data suggests that BSO at the time of hysterectomy for endometriosis does not lead to significant and clinically meaningful differences in reoperation or in use of pain related health services, including physician visits and opioid use. Patients who have hysterectomy for endometriosis with ovarian conservation have low usage rates of OCP and other hormonal suppression medications for endometriosis. For those who undergo premenopausal BSO, adherence to HRT regimens is suboptimal. Given the known increased morbidity and mortality associated with premenopausal BSO, we suggest strong consideration of ovarian conservation at the time of hysterectomy for endometriosis.

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