7-29-2022

Salpingectomy for Sterilization in Patients with a Documented Ovarian Cancer Family History

Shera Shevin
Yale Physician Associate Program, shera.shevin@yale.edu

SALPINGECTOMY FOR STERILIZATION IN PATIENTS WITH A DOCUMENTED OVARIAN CANCER FAMILY HISTORY

A Thesis presented to
The Faculty of the School of Medicine
Yale University

In Candidacy for the Degree of
Master of Medical Science

July 2022

Shera Shevin, PA-SII
Class of 2022
Yale Physician Associate Program

Elena Ratner, MD
Professor
Obstetrics, Gynecology, and
Reproductive Sciences

Table of Contents

ACKNOWLEDGEMENTS

The authors would like to acknowledge and thank Johanna D'Addario, MHS, PA-C, for her mentorship and other contributions related to this Thesis.

LIST OF ABBREVIATIONS

ACOG: American College of Obstetricians and Gynecologists
ACS: American Cancer Society
AMH: Anti-Müllerian Hormone
BS: Bilateral Salpingectomy
BSDO: Bilateral Salpingectomy with Delayed Oophorectomy
BSO: Bilateral Salpingo-Oophorectomy
CD: Cesarean Delivery
CI: Confidence Interval
CPT: Current Procedural Terminology
EBL: Estimated Blood Loss
EOC: Epithelial Ovarian Cancer
FDR: First Degree Relative
GP: General Practitioner
HGSOC: High Grade Serous Ovarian Cancer
HIPAA: Health Insurance Portability and Accountability Act
HR: Hazard Ratio
HRT: Hormone Replacement Therapy
ICER: Incremental Cost-Effectiveness Ratio
IRB: Institutional Review Board
LGSOC: Low Grade Serous Ovarian Cancer
NIS: National Inpatient Sample
NP: Nurse Practitioner
OCP: Oral Contraceptive Pill
OR: Odds Ratio
OS: Opportunistic Salpingectomy
PA: Physician Assistant
PACU: Post Anesthesia Care Unit
PI: Principal Investigator
PID: Pelvic Inflammatory Disease
QALYs: Quality Adjusted Life Years
RCT: Randomized Controlled Trial
RR: Relative Risk
RRBSO: Risk Reducing Bilateral Salpingo-Oophorectomy
SEER: Surveillance, Epidemiology, and End Result
SGO: Society of Gynecologic Oncology
SQRGC: Swedish Quality Register for Gynecological Cancer
STIC: Serous Tubal Intraepithelial Carcinoma

LIST OF TABLES AND FIGURES

ABSTRACT

Ovarian cancer is the most lethal gynecologic cancer. The leading risk factor for ovarian cancer is a family history of breast and/or ovarian cancer, but known genetic mutations contribute only a small percentage of heritable risk. Due to flawed early detection methods, risk management relies on prevention. Because some ovarian cancers originate in the fallopian tubes, researchers are exploring bilateral salpingectomy for risk reduction. However, utilization of the procedure has not been measured in patients with a documented ovarian cancer family history but no known genetic mutation. **We aim to determine if a greater proportion of patients with an ovarian cancer family history will utilize bilateral salpingectomy for sterilization compared to those without a family history.** Specifically, we will retrospectively review insurance claims data to examine the association between family history documentation and bilateral salpingectomy. The findings will help establish guidelines for risk reduction in families with ovarian cancer.

CHAPTER 1 – INTRODUCTION

1.1 BACKGROUND

Epidemiology

Ovarian cancer is the fifth leading cause of cancer-related death in women and the most lethal gynecologic cancer with an estimated 21,410 new cases diagnosed in the United States in 2021[1]. This corresponds to a lifetime risk ranging from one in 50 to one in 75 or a 1.3-2% risk of developing ovarian cancer[2-8]. Epithelial ovarian cancer (EOC) accounts for approximately 90% of all ovarian cancer cases[9] and high grade serous ovarian cancer (HGSOC) comprises about 70-80% of these EOC cases[3,4]. The disease is highly deadly and HGSOC accounts for the most deaths[10] because a vast majority of HGSOC are diagnosed at a late stage, when the disease has already progressed[3,4,11,12]. Five-year overall survival for ovarian cancer is about 40%[2], however, median progression-free survival for patients with late-stage ovarian cancer is about 18 months[4].

Risk Factors and the Genetic Landscape

EOC risk is divided into high-, intermediate-, and low-risk categories ($\geq$10%, 5-9%, and $\leq$4% lifetime risk, respectively). Estimates of cumulative lifetime risk for various known epidemiologic or genetic risk factors have been calculated from population-based retrospective cohort and case control studies. Some authors have developed risk models by combining such population-based studies[13,14]. However, according to our literature review, there currently is not a single agreed upon risk model for EOC at this time.

There are many known risk factors for the development of EOC. Ovulation contributes to ovarian neoplasia and factors that increase the number of ovulatory cycles

are associated with increased EOC risk. Such factors include early age of menarche, late age of menopause, and nulliparity. Inversely, factors that reduce the number of ovulatory cycles—pregnancy, breastfeeding, and use of oral contraceptive pills (OCPs)—are associated with a protective effect[4,9].

The leading risk factor for EOC is a family history of breast and/or ovarian cancer[4,15]. In fact, compared to other solid tumors, EOC has one of the highest proportions of cases that are attributed to an inherited risk[16]. The cumulative lifetime risk associated with various genetic mutations and clinical categories is demonstrated in Table 1. Approximately 10-20% of ovarian cancer cases occur in patients with an underlying genetic mutation and a majority of these are due to *BRCA1/BRCA2* mutations[5,17,18]. *BRCA1* mutation carriers have a 13-60% lifetime risk for ovarian cancer and *BRCA2* mutation carriers have a 10-30% lifetime risk[4,6]. Thus, patients with a *BRCA1/2* mutation are considered to be at a "high risk" for ovarian cancer.

While *BRCA1/2* are some of the most well-known, and more common, mutations associated with ovarian cancer, additional gene mutations have been identified in recent years. Lynch Syndrome is an autosomal dominant syndrome associated with mutations in mismatch repair genes (*MSH2, MLH1, PMS2,* and *MSH6*) that increases risk for colorectal, endometrial, and ovarian cancer. Among the genes impacted by Lynch Syndrome, mutations in *MSH2* and *MLH1* are most associated with ovarian cancer and they confer a 6-24% risk for the development of ovarian cancer[4,19,20]. Additionally, mutations in *RAD51C, RAD51D* and *BRIP1* are associated with a 5-11.2%, 10-12%, and 5.8% risk of ovarian cancer, respectively[4,21,22].

Table 1: Current landscape of ovarian cancer risk. RR = relative risk; FDR = first degree relative

Clinical Category		Lifetime Risk (%)
	General Population	1.3-2[2-8]
Genetic Mutations	*BRCA1*	40-60[4,6]
	BRCA2	10-30[4,6]
	RAD51C	5-11.2[22]
	RAD51D	10-12[21]
	BRIP1	5.8[4,6]
	MSH2 (Lynch Syndrome)	6-24[4,19,20]
	MLH1 (Lynch Syndrome)	6-20[4,19,20]
Unknown *BRCA* Status	1 FDR diagnosed <50 years	~6-9.4 (4.72 RR)[15]
	1 FDR diagnosed >50 years	~3.3-5 (2.53 RR)[15]
***BRCA* Negative**	1 FDR diagnosed <50 years	~4.3-7.7 (3.83 RR)[15]
	1 FDR diagnosed >50 years	~2.4-3.8 (1.88 RR)[15]

1.2 STATEMENT OF THE PROBLEM

The Problem with Genetics

While approximately 10-20% of ovarian cancer cases occur in *BRCA1/2* carriers with their high-risk designation, *BRCA1/2* mutations are only part of the story and about 60% of excess familial risk remains unexplained[23]. Thus, there is substantial disease burden among patients without a *BRCA1/2* mutation and possibly still in patients with a significant family history. In fact, Manchanda et al.[6] estimated that only 25% of the familial relative risk for ovarian cancer is due to a *BRCA1/2* mutation. Furthermore, according to the National Health Interview Survey, only about 10.5% of patients with ovarian cancer in the US have undergone genetic testing[24] and black women with a history of cancer are less likely to undergo genetic testing or counseling[25]. Consequently, there is a significant proportion of patients that are unaware of their genetic susceptibility for ovarian cancer.

It is estimated that first-degree relatives (FDRs) of EOC patients have a three-fold increased risk for EOC compared to the general population[15]. However, Jervis et al.[15] demonstrated that this risk is further complicated by the age of diagnosis of the patient.

As demonstrated by Table 1, the FDR's EOC risk increases if their family member was diagnosed before the age of 50. Furthermore, FDRs whose family member has an unknown genetic status have an increased relative risk (RR) for EOC compared to those that are confirmed to be *BRCA1/2* negative (4.72 RR and 3.83 RR, respectively, if diagnosed <50 years; 2.53 RR and 1.88 RR, respectively, if diagnosed >50 years)[15]. In all cases, HGSOC confers a higher risk for FDRs than other histologies[4,6,15]. Therefore, the risk to FDRs varies greatly depending on these factors. For example, the FDR of a patient diagnosed with serous EOC before 50 years of age and with an unknown genetic status could have up to an 11% risk of developing EOC, putting them into the high-risk category[15].

It is estimated that 63% of ovarian cancer cases occur in patients with >4% lifetime risk and 53% in patients with $\geq$5% lifetime risk[6]. Many FDRs fall into this intermediate-risk category and thus might represent a sizeable portion of EOC burden. Additionally, with the decreased utilization of genetic testing, some FDRs might even have an unknown high-risk genetic status. Therefore, it is imperative to optimize identification of FDRs by taking a detailed ovarian cancer family history. According to Andrews et al.[26], hereditary cancer risk assessment must include assessment of risk, education, and counseling; all of which can be conducted by a physician, genetic counselor, or other provider with expertise in cancer genetics. Nurses, medical assistants, advanced practice providers (APPs), including physician assistants (PAs) and nurse practitioners (NPs), and other medical providers that participate in patient care should all be trained to take an oncologic family history. This would optimize our ability to identify FDRs, assess risk, and provide education about risk reducing options.

The Problem with Early Detection

Early detection for many diseases relies on symptom awareness and screening, both of which are limited in the case of EOC, contributing to the significant proportion of late stage diagnoses. EOC has been referred to as the "Silent Killer"[27]. Although symptoms do exist, they are vague, easily overlooked, and frequently attributed to aging, weight gain, or several other benign conditions including menopause[28].

Bankhead et al.[27] examined the presenting symptoms of a group of patients with EOC in the UK. All patients experienced symptoms prior to diagnosis and the most common were early satiety or appetite loss, abdominal distension or bloating, urinary changes, and pelvic or abdominal pain[27]. In 2007, the American Cancer Society (ACS), Gynecologic Cancer Foundation, and Society of Gynecologic Oncology (SGO) released a consensus statement on symptoms of EOC[29]. The symptoms discovered by Bankhead et al.[27] confirm all that were agreed upon in the consensus statement. However, both patients and general practitioners (GPs) falsely attributed symptoms to other causes, which deterred patients from pursuing medical care and GPs from referring to gynecologic oncologists. This delayed diagnoses for a median of 12 months after symptom onset[27]. Although EOC is not truly a silent killer, symptom awareness is still flawed as a method for risk reduction.

Methods for screening and surveillance include serum CA-125 and transvaginal ultrasounds, but their use has not been found to have any mortality benefit[6,18,30-32]. Additionally, serum CA-125 has a high false positive rate and less than a 3% predictive value[30]. This has the risk of causing both unnecessary anxiety and surgery. Therefore, preventative interventions are considered most effective because screening and early

detection efforts have been unsuccessful[16,32,33]. Once patients at an elevated risk for EOC are identified, providers must be able to effectively manage their risk and recommend the most effective risk reducing intervention.

Current Recommendations for Risk Reduction

Given the limitations of early detection and the underuse of genetic testing, risk reduction is the cornerstone of preventing EOC diagnoses and deaths. Beyond the reduced risk associated with pregnancy and breastfeeding, chemoprevention and surgical prophylaxis are the key methods for EOC risk reduction. Chemoprevention with OCPs has a significant benefit for EOC risk: for every five years of OCP use, the risk of EOC decreases by 20% for the first 15 years of use[34]. However, the use of OCPs for primary EOC risk reduction is actually not recommended in the general population[23]. OCPs are associated with an increased risk for thromboembolic events and other adverse events. That risk likely negates the EOC risk reducing potential for average risk patients[35]. Thus, EOC risk reduction is a secondary benefit for those that take OCPs for contraception or other medical purposes. Therefore, surgical options for primary prevention are more compelling[32].

Current clinical practice recommends premenopausal surgical prophylaxis with risk reducing bilateral salpingo-oophorectomy (RRBSO) for high-risk patients[6]. This includes patients with Lynch Syndrome and mutations in *BRCA1/2, RAD51C, RAD51D,* and *BRIP1*[26]. *BRCA1/2* carriers are recommended to undergo premenopausal RRBSO for an optimal risk reduction[30] of 79-96%[12,36]. Although it is highly effective for EOC prevention, the most significant problem with premenopausal RRBSO is that it causes surgical menopause[37].

Surgical menopause causes an abrupt drop in estrogen, progesterone, and testosterone production[38]. It is associated with negative effects on cardiovascular health, bone health, sexual function, and cognitive function and an increased risk for depression, anxiety, metabolic syndrome, and parkinsonism[6,12,30,36-38]. Additionally, if surgical menopause occurs before the age of 45, there is an increased risk for menopausal symptoms and patients have a decreased life expectancy[18,39]. Hormone replacement therapy (HRT) has been shown to improve some of the consequences of early menopause including sexual dysfunction, cardiovascular disease, vasomotor symptoms, and bone health in both the general population and those with surgical menopause[30,36,37]. However, despite the advantages of HRT, the side effects of RRBSO have discouraged *BRCA1/2* carriers from undergoing RRBSO and only an estimated 57-70% of *BRCA1/2* carriers undergo RRBSO[5,40,41].

Recommendations for FDRs

According to current guidelines, surgical prophylaxis with RRBSO is only recommended for high-risk patients with $\geq$10% EOC risk. Furthermore, according to current literature, there are no guidelines that specifically address options for surgical risk reduction for patients in the intermediate-risk category, although they represent a significant portion of EOC diagnoses. By default, screening and chemoprevention are the current standard of care for FDRs as they likely fall within this intermediate-risk category[23]. The risk stratification options for FDRs are inherently limited and, therefore, we must explore other options.

Manchanda et al.[6,42,43] have argued for changing the threshold for EOC surgical prophylaxis from its current level at $\geq$10% risk to include FDRs and other intermediate-

risk patients. Postmenopausal RRBSO in patients with ≥5% EOC risk has been found to be cost-effective and saves both life-years and quality adjusted life years (QALYs)[43]. The same is true for premenopausal patients with ≥4% EOC risk[42]. Thus, prophylactic surgical options can and should be considered for FDRs. However, RRBSO still is not an ideal option given the initiation of surgical menopause.

The Future of Risk Reduction and the Tubal Origin Theory

Surgical menopause has spurred conversation about alternative options for surgical prophylaxis. In the 1990s, the *BRCA1/2* gene mutations were discovered and the affected patients began undergoing RRBSO. Their pathology specimens revealed precursor malignant lesions in the distal one-third of the fallopian tube, coupled with benign ovaries[3,28,44]. Crum et al.[45] described this process of carcinogenesis as serous tubal intraepithelial carcinoma (STIC). STIC lesions were found in about 80% of RRBSO specimens in which early malignancies were found[3] and they share a similar histology and genetic signature with HGSOC[2]. Thus, it was hypothesized that the distal fallopian tube, including the fimbriated end, is the origin of HGSOC rather than the ovarian surface epithelium[2,45,46].

Studies have shown that fallopian tube carcinogenesis is also common in other forms of EOC[47]. Some EOC are believed to develop from benign precursor lesions in the endometrium that migrate to the ovaries and peritoneum through the fallopian tubes. This is the proposed method by which endometriosis increases EOC risk[48]. Additionally, the endosalpinx and the ovary are exposed to inflammation resulting from an ovulating follicle and from viral/bacterial infections as in pelvic inflammatory disease (PID)[49]. Tubal ligation can and has been found to reduce risk for some histologies, like clear cell

and endometrioid ovarian cancers, by blocking the flow of cells from the lower reproductive tract[44,49,50]. However, STIC lesions occur in the distal fallopian tube, including the fimbriae, and these sections are not removed in a tubal ligation so its impact for HGSOC is less clear. Thus, in order to have optimal risk reduction, the theory is that the entire fallopian tube must be removed[3,49,51].

In 2011, Greene et al.[51] proposed a two-step surgical option for bilateral salpingectomy with delayed oophorectomy (BSDO) for *BRCA1/2* carriers. Salpingectomy would theoretically reduce risk for EOC—including HGSOC—, and ovarian preservation would delay the onset of surgical menopause and reduce its associated negative health impacts. There are a few multicenter prospective clinical trials underway that assess BSDO in high-risk patients (Table 2). However, the timing of the two surgeries has not been agreed upon as there are not any prospective data about the efficacy of BSDO for HGSOC prophylaxis yet. Current theories recommend salpingectomy occurring after the completion of childbearing and oophorectomy likely occurring either closer to the time of natural menopause or postmenopausal[37,52].

Opportunistic salpingectomy (OS) is another option for EOC risk reduction. This refers to the complete removal of bilateral fallopian tubes for the primary prevention of EOC in a patient undergoing pelvic surgery for a benign indication[33,53,54]. Additionally, it includes bilateral salpingectomy (BS) as an alternative to bilateral tubal ligation (BTL) for sterilization[41]. BS can reduce the risk of EOC by 42-78% compared to 13-41% for BTL alone[55]. Tubal sterilization is both safe and highly effective and it is the most common method of contraception used worldwide[56]. It can be performed as postpartum sterilization or interval sterilization. Postpartum sterilization is performed during cesarean

delivery (CD) or by mini-laparotomy after a vaginal delivery[50,56] while interval sterilization is performed more than 6 weeks postpartum or in a patient that is nulliparous[3,50,54,56].

Since the development of the tubal origin theory for HGSOC, the American College of Obstetricians and Gynecologists (ACOG) and the Society of Gynecologic Oncology (SGO) released statements in 2015 and 2013, respectively, recommending that providers consider BS at the time of benign hysterectomy or sterilization in the general population[12,46,57]. However, again, there are no specific guidelines recommending these procedures for FDRs.

Table 2: Clinical trials investigating risk reducing salpingectomy in patients at increased risk for ovarian cancer; adapted from Gaba et al.[52]. BSDO = bilateral salpingectomy with delayed oophorectomy; RRBSO = risk reducing bilateral salpingo-oophorectomy; BS = bilateral salpingectomy.

Study	Country	Study Arms	Primary Outcome
PROTECTOR (ISRCTN25173360)	UK	BSDO, RRBSO, Controls (no surgery)	Sexual function
TUBA (NCT02321228)	Netherlands	BSDO, RRBSO	Menopause quality of life
Radical fimbriectomy for young *BRCA1/2* mutation carriers (NCT01608074)	France	Radical fimbriectomy	Number of ovarian or primary peritoneal cancers occurring between fimbriectomy and menopause
Prophylactic salpingectomy with delayed oophorectomy (NCT01907789)	US	BSDO, RRBSO, ovarian cancer screening	Proportion of participants undergoing oophorectomy after salpingectomy
WISP (NCT02760849)	US	BSDO, RRBSO	Sexual function
SOROCk (NCT0425105)	US	BS, RRBSO	Ovarian or primary peritoneal cancer diagnoses

1.3 GOALS AND OBJECTIVES

Given the current state of the literature, it is clear that FDRs have been excluded from the conversation about surgical prevention of ovarian cancer. With the release of practice guidelines from the SGO and ACOG, more patients are undergoing BS rather

than BTL for sterilization[46,58-61]. Karia et al.[60] discovered greater uptake of BS for sterilization among patients with a family history of breast and/or ovarian cancer and among patients with a genetic mutation for breast and/or ovarian cancer compared to the general population. However, we wonder if the same is true for a population without a known predisposing genetic mutation and only an ovarian cancer family history.

Thus, the purpose of this study is to determine if a greater proportion of patients with a documented ovarian cancer family history, but no known genetic marker for ovarian cancer, utilize BS for sterilization compared to patients without a documented family history. Indirectly, we aim to determine if providers make an effort to educate patients in this population to consider surgical contraception with BS after the completion of childbearing rather than utilizing other contraceptive options such as BTL or long-acting reversible contraception (LARC). Providers could improve FDRs' access to a potential method for EOC risk reduction through education about the benefits of BS compared to BTL.

1.4 HYPOTHESIS

It is hypothesized that a greater proportion of patients with a documented ovarian cancer family history, but no known genetic susceptibility for ovarian cancer, utilize BS for sterilization compared to patients without a documented family history.

REFERENCES

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer Statistics, 2021. *CA: A Cancer Journal for Clinicians.* 2021;71(1):7-33.
2. Catanzarite T, Eskander RN. Opportunistic Salpingectomy at the Time of Urogynecologic Surgery: Why, in Whom, and How? *Female Pelvic Medicine & Reconstructive Surgery.* 2020;26(6):401-406.
3. Castellano T, Zerden M, Marsh L, Boggess K. Risks and Benefits of Salpingectomy at the Time of Sterilization. *Obstetrical & Gynecological Survey.* 2017;72(11):663-668.
4. Flaum N, Crosbie EJ, Edmondson RJ, Smith MJ, Evans DG. Epithelial ovarian cancer risk: A review of the current genetic landscape. *Clin Genet.* 2020;97(1):54-63.
5. Holman LL, Friedman S, Daniels MS, Sun CC, Lu KH. Acceptability of prophylactic salpingectomy with delayed oophorectomy as risk-reducing surgery among BRCA mutation carriers. *Gynecologic Oncology.* 2014;133(2):283-286.
6. Manchanda R, Menon U. Setting the Threshold for Surgical Prevention in Women at Increased Risk of Ovarian Cancer. *International Journal of Gynecological Cancer.* 2018;28(1):34-42.
7. Arts-de Jong M, Harmsen MG, Hoogerbrugge N, Massuger LF, Hermens RP, de Hullu JA. Risk-reducing salpingectomy with delayed oophorectomy in BRCA1/2 mutation carriers: Patients' and professionals' perspectives. *Gynecologic Oncology.* 2015;136(2):305-310.
8. Nebgen DR, Hurteau J, Holman LL, et al. Bilateral salpingectomy with delayed oophorectomy for ovarian cancer risk reduction: a pilot study in women with BRCA1/2 mutations. *Gynecologic oncology.* 2018.
9. La Vecchia C. Ovarian cancer: epidemiology and risk factors. *Eur J Cancer Prev.* 2017;26(1):55-62.
10. Reade CJ, Finlayson S, McAlpine J, Tone AA, Fung-Kee-Fung M, Ferguson SE. Risk-reducing salpingectomy in Canada: a survey of obstetrician-gynaecologists. *J Obstet Gynaecol Can.* 2013;35(7):627-634.
11. Boerner T, Long Roche K. Salpingectomy for the Risk Reduction of Ovarian Cancer: Is It Time for a Salpingectomy-alone Approach? *Journal of Minimally Invasive Gynecology.* 2021;28(3):403-408.
12. Long Roche KC, Abu-Rustum NR, Nourmoussavi M, Zivanovic O. Risk-reducing salpingectomy: Let us be opportunistic. *Cancer.* 2017;123(10):1714-1720.
13. Jervis S, Song H, Lee A, et al. A risk prediction algorithm for ovarian cancer incorporating BRCA1, BRCA2, common alleles and other familial effects. *J Med Genet.* 2015;52(7):465-475.
14. Pearce CL, Stram DO, Ness RB, et al. Population distribution of lifetime risk of ovarian cancer in the United States. *Cancer Epidemiol Biomarkers Prev.* 2015;24(4):671-676.
15. Jervis S, Song H, Lee A, et al. Ovarian cancer familial relative risks by tumour subtypes and by known ovarian cancer genetic susceptibility variants. *J Med Genet.* 2014;51(2):108-113.

16. Norquist BM. Challenges in the identification of inherited risk of ovarian cancer: where should we go from here? *Gynecol Oncol.* 2019;152(1):3-6.
17. Gaba F, Blyuss O, Chandrasekaran D, et al. Attitudes towards risk-reducing early salpingectomy with delayed oophorectomy for ovarian cancer prevention: a cohort study. *BJOG Int J Obstet Gynaecol.* 2021;128(4):714-726.
18. Swanson CL, Bakkum-Gamez JN. Options in Prophylactic Surgery to Prevent Ovarian Cancer in High-Risk Women: How New Hypotheses of Fallopian Tube Origin Influence Recommendations. *Curr Treat Options Oncol.* 2016;17(5):20.
19. Barrow E, Hill J, Evans DG. Cancer risk in Lynch Syndrome. *Fam Cancer.* 2013;12(2):229-240.
20. Bonadona V, Bonaïti B, Olschwang S, et al. Cancer risks associated with germline mutations in MLH1, MSH2, and MSH6 genes in Lynch syndrome. *Jama.* 2011;305(22):2304-2310.
21. Loveday C, Turnbull C, Ramsay E, et al. Germline mutations in RAD51D confer susceptibility to ovarian cancer. *Nat Genet.* 2011;43(9):879-882.
22. Loveday C, Turnbull C, Ruark E, et al. Germline RAD51C mutations confer susceptibility to ovarian cancer. *Nat Genet.* 2012;44(5):475-476; author reply 476.
23. Menon U, Karpinskyj C, Gentry-Maharaj A. Ovarian Cancer Prevention and Screening. *Obstetrics & Gynecology.* 2018;131(5):909-927.
24. Childers CP, Childers KK, Maggard-Gibbons M, Macinko J. National Estimates of Genetic Testing in Women With a History of Breast or Ovarian Cancer. *J Clin Oncol.* 2017;35(34):3800-3806.
25. Halbert CH, Kessler L, Stopfer JE, Domchek S, Wileyto EP. Low rates of acceptance of BRCA1 and BRCA2 test results among African American women at increased risk for hereditary breast-ovarian cancer. *Genet Med.* 2006;8(9):576-582.
26. Andrews L, Mutch DG. Hereditary Ovarian Cancer and Risk Reduction. *Best Pract Res Clin Obstet Gynaecol.* 2017;41:31-48.
27. Bankhead CR, Collins C, Stokes-Lampard H, et al. Identifying symptoms of ovarian cancer: a qualitative and quantitative study. *Bjog.* 2008;115(8):1008-1014.
28. Falconer H, Yin L, Grönberg H, Altman D. Ovarian cancer risk after salpingectomy: A nationwide population-based study. *Journal of the National Cancer Institute.* 2015;107(2).
29. Tanne JH. US cancer groups highlight symptoms of early ovarian cancer. *BMJ.* 2007;334(7607):1290-1291.
30. Alexandre M, Black J, Whicker M, Minkin MJ, Ratner E. The management of sexuality, intimacy, and menopause symptoms (SIMS) after prophylactic bilateral salpingo-oophorectomy: How to maintain sexual health in "previvors". *Maturitas.* 2017;105:46-51.
31. Balsarkar G. Opportunistic Salpingectomy as an Ovarian Cancer Primary Prevention Strategy. *Journal of Obstetrics & Gynaecology of India.* 2017;67(4):243-246.
32. Gelderblom ME, IntHout J, Hermens RPMG, et al. STop OVarian CAncer (STOPOVCA) young: Protocol for a multicenter follow-up study to determine the

long-term effects of opportunistic salpingectomy on age at menopause. *Maturitas.* 2022;159:62-68.
33. Dilley SE, Havrilesky LJ, Bakkum-Gamez J, et al. Cost-effectiveness of opportunistic salpingectomy for ovarian cancer prevention. *Gynecologic Oncology.* 2017;146(2):373-379.
34. Tschernichovsky R, Goodman A. Risk-Reducing Strategies for Ovarian Cancer in BRCA Mutation Carriers: A Balancing Act. *Oncologist.* 2017;22(4):450-459.
35. Kwon JS, McAlpine JN, Hanley GE, et al. Costs and benefits of opportunistic salpingectomy as an ovarian cancer prevention strategy. *Obstetrics & Gynecology.* 2015;125(2):338-345.
36. Swanson CL, Bakkum-Gamez JN. Preventing Ovarian Cancer in High-risk Women: One Surgery at a Time. *Clin Obstet Gynecol.* 2020;63(1):64-73.
37. Harmsen MG, IntHout J, Arts-de Jong M, et al. Salpingectomy With Delayed Oophorectomy in BRCA1/2 Mutation Carriers: Estimating Ovarian Cancer Risk. *Obstetrics & Gynecology.* 2016;127(6):1054-1063.
38. Anderson CK, Wallace S, Guiahi M, Sheeder J, Behbakht K, Spillman MA. Risk-reducing salpingectomy as preventative strategy for pelvic serous cancer. *Int J Gynecol Cancer.* 2013;23(3):417-421.
39. Chandrasekaran D, Menon U, Evans G, et al. Risk reducing salpingectomy and delayed oophorectomy in high risk women: views of cancer geneticists, genetic counsellors and gynaecological oncologists in the UK. *Fam Cancer.* 2015;14(4):521-530.
40. Kwon JS, Tinker A, Pansegrau G, et al. Prophylactic salpingectomy and delayed oophorectomy as an alternative for BRCA mutation carriers. *Obstet Gynecol.* 2013;121(1):14-24.
41. Kwon JS. Cost-effectiveness of Ovarian Cancer Prevention Strategies. *Clin Obstet Gynecol.* 2017;60(4):780-788.
42. Manchanda R, Legood R, Antoniou AC, Gordeev VS, Menon U. Specifying the ovarian cancer risk threshold of 'premenopausal risk-reducing salpingo-oophorectomy' for ovarian cancer prevention: a cost-effectiveness analysis. *J Med Genet.* 2016;53(9):591-599.
43. Manchanda R, Legood R, Pearce L, Menon U. Defining the risk threshold for risk reducing salpingo-oophorectomy for ovarian cancer prevention in low risk postmenopausal women. *Gynecol Oncol.* 2015;139(3):487-494.
44. Ely LK, Truong M. The Role of Opportunistic Bilateral Salpingectomy vs Tubal Occlusion or Ligation for Ovarian Cancer Prophylaxis. *Journal of Minimally Invasive Gynecology.* 2017;24(3):371-378.
45. Crum CP, Drapkin R, Miron A, et al. The distal fallopian tube: a new model for pelvic serous carcinogenesis. *Curr Opin Obstet Gynecol.* 2007;19(1):3-9.
46. Baltus T, Brown J, Kapurubandara S. A retrospective cohort study of tubal occlusion or salpingectomy for permanent contraception in Australia. *Australian and New Zealand Journal of Obstetrics and Gynaecology.* 2021.
47. Danis RB, Della Badia CR, Richard SD. Postpartum Permanent Sterilization: Could Bilateral Salpingectomy Replace Bilateral Tubal Ligation? *Journal of Minimally Invasive Gynecology.* 2016;23(6):928-932.

48. Darelius A, Kristjansdottir B, Dahm-Kahler P, Strandell A. Risk of epithelial ovarian cancer Type I and II after hysterectomy, salpingectomy and tubal ligation-A nationwide case-control study. *International Journal of Cancer.* 2021;149(8):1544-1552.
49. Callahan RL, Kopf GS, Strauss JF, 3rd, Tworoger SS. Tubal contraception and ovarian cancer risk: a global view. *Contraception.* 2017;95(3):223-226.
50. Creinin MD, Zite N. Female tubal sterilization: the time has come to routinely consider removal. *Obstetrics & Gynecology.* 2014;124(3):596-599.
51. Greene MH, Mai PL, Schwartz PE. Does bilateral salpingectomy with ovarian retention warrant consideration as a temporary bridge to risk-reducing bilateral oophorectomy in BRCA1/2 mutation carriers? *Am J Obstet Gynecol.* 2011;204(1):19.e11-16.
52. Gaba F, Piek J, Menon U, Manchanda R. Risk-reducing early salpingectomy and delayed oophorectomy as a two-staged alternative for primary prevention of ovarian cancer in women at increased risk: a commentary. *Bjog.* 2019;126(7):831-839.
53. Anonymous. ACOG Committee Opinion No. 774: Opportunistic Salpingectomy as a Strategy for Epithelial Ovarian Cancer Prevention. *Obstetrics & Gynecology.* 2019;133(4):e279-e284.
54. Jones NL, Schulkin J, Urban RR, et al. Physicians' Perspectives and Practice Patterns Toward Opportunistic Salpingectomy in High- and Low-Risk Women. *Cancer Invest.* 2017;35(1):51-61.
55. Gockley AA, Elias KM. Fallopian tube tumorigenesis and clinical implications for ovarian cancer risk-reduction. *Cancer Treat Rev.* 2018;69:66-71.
56. Clark NV, Endicott SP, Jorgensen EM, et al. Review of Sterilization Techniques and Clinical Updates. *Journal of Minimally Invasive Gynecology.* 2018;25(7):1157-1164.
57. Subramaniam A, Einerson BD, Blanchard CT, et al. The cost-effectiveness of opportunistic salpingectomy versus standard tubal ligation at the time of cesarean delivery for ovarian cancer risk reduction. *Gynecol Oncol.* 2019;152(1):127-132.
58. Powell CB, Alabaster A, Simmons S, et al. Salpingectomy for Sterilization: Change in Practice in a Large Integrated Health Care System, 2011-2016. *Obstet Gynecol.* 2017;130(5):961-967.
59. McAlpine JN, Hanley GE, Woo MMM, et al. Opportunistic salpingectomy: Uptake, risks, and complications of a regional initiative for ovarian cancer prevention. *American Journal of Obstetrics and Gynecology.* 2014;210(5):471.e471-471.e411.
60. Karia PS, Joshu CE, Visvanathan K. Uptake and Predictors of Opportunistic Salpingectomy for Ovarian Cancer Risk Reduction in the United States. *Cancer Prevention Research.* 2021;14(12):1101-1110.
61. Kim AJ, Barberio A, Berens P, et al. The Trend, Feasibility, and Safety of Salpingectomy as a form of Permanent Sterilization. *Journal of Minimally Invasive Gynecology.* 2019;26(7):1363-1368.

CHAPTER 2 – REVIEW OF THE LITERATURE

2.1 INTRODUCTION

We conducted a thorough review of the literature for studies that were published between 2011 and July 2022 using Ovid Medline and PubMed. Searches for the primary articles were conducted using a combination of the following search terms: "salpingectomy", "tubectomy", "interval salpingectomy", "opportunistic salpingectomy", "tubal contraception", "tubal excision", "tubal ligation", "tubal occlusion", "ovarian cancer", "ovarian neoplasm", "ovarian cancer prevention", and "prophylactic surgical procedures". Articles were included if they were published in English. We evaluated each article to determine its relevancy to our proposed research topic. We included cohort studies, case control studies, randomized controlled trials (RCT), case studies, meta-analyses, and systematic reviews that examined the empirical relationship between BS and BTL. Furthermore, we assessed reference lists of the primary articles and included additional articles if relevant.

2.2 OVARIAN CANCER RISK REDUCTION

As previously noted in Table 2, long-term prospective studies examining the effects of BS for EOC risk reduction are ongoing. Therefore, our literature review did not reveal any prospective data in this area. However, it did reveal three retrospective studies[1-3] demonstrating not only the efficacy of BS, but its superior efficacy compared to BTL.

Madsen et al.[1] carried out a retrospective nationwide register-based case-control study in Denmark during 1982-2011. Their objective was to compare BS and BTL with respect to EOC risk reduction as stratified by histologic subtype. They utilized several

nationwide registries for sampling and data collection including the Civil Registration System, Danish Cancer Registry, Pathology Data Bank, National Patient Register, Danish Prescription Registry, and Danish Fertility Database. The Danish Cancer Registry utilizes the International Classification of Diseases (ICD), version 10 and the ICD for Oncology to track cancer diagnoses. Cases included all patients in Denmark that were diagnosed with primary EOC between the ages of 30-84 years, during the study period. Fifteen age-matched female population controls were selected for each case. Controls were excluded if they had a history of bilateral salpingo-oophorectomy (BSO) or bilateral oophorectomy.

The impact of the exposures (BTL and BS) on EOC risk was estimated by conditional logistic regression. During the study period, 428 total participants underwent BS and 6,546 patients underwent BTL. The age-adjusted odds ratio (OR) of developing EOC after BS was 0.61 (95% confidence interval [CI] 0.37-0.99) and 0.81 after BTL (95% CI 0.72-0.90)[1]. The authors conducted further subgroup analyses regarding histological subtypes within the BTL group but were not able to do the same in the BS group due to its small sample size. The reason for the small BS sample size might be due to the fact that data collection ceased around the time that national organizations released guidelines encouraging OS. Additionally, the results were not adjusted to control for parity, use of OCPs, family history of ovarian cancer, gynecologic comorbidities, or other well-known covariates. This limits confirmation that the results were in fact caused by the relationship being studied and not impacted by external variables.

In 2015, Falconer et al.[2] conducted a retrospective population-based cohort study in Sweden to examine the association between benign gynecologic surgery and ovarian

and tubal cancer risk. Similar to the methods of Madsen et al.[1], the authors utilized a nationwide population-based register to identify the cohort. The unexposed population included all women in the Swedish Inpatient Register above the age of 18 years between 1973 and 2009. Patients were excluded if they had a history of gynecologic surgery or a diagnosis of primary ovarian or tubal cancer prior to entering the cohort. Patients were considered exposed if they underwent hysterectomy, hysterectomy with BSO, salpingectomy, or BTL during the study period as determined by the Swedish Classification of Operations and Major Procedures. Hysterectomies with BS constituted only a small proportion of patients and were excluded. The primary outcome was a diagnosis of ovarian and/or tubal cancer during the study period as defined by discharge ICD codes from the Swedish Inpatient Register.

The cohort included 5,449,119 patients and of these, 251,465 were exposed (39% hysterectomy, 14.9% hysterectomy with BSO, 13.7% salpingectomy, and 32.5% BTL). Cox proportional hazard models were used to estimate hazard ratios (HR) for the primary outcome among the exposed compared to the unexposed. All exposures were associated with a statistically significant reduction in ovarian and/or tubal cancer risk when HR were adjusted for age, calendar time, parity, and education status. Hysterectomy with BSO was associated with the greatest effect (HR 0.06; 95% CI 0.03-0.12), followed by salpingectomy (HR 0.65; 95% CI 0.52-0.81), BTL (HR 0.72; 95% CI 0.64-0.81), and hysterectomy alone (HR 0.79; 95% CI 0.70-0.88)[2].

In subgroup analysis, there were 3,051 BS procedures and 19,552 unilateral salpingectomy procedures performed. It is important to note that the Swedish Classification of Operations and Major Procedures coding system changed in 1997 and

reporting of salpingectomy laterality declined after the change. Therefore, the salpingectomies that occurred after 1997 were not included in the laterality subgroup analysis. Despite this, BS was associated with an additional 50% decrease in ovarian cancer risk compared to unilateral salpingectomy (HR 0.35; 95% CI 0.17-0.73 vs HR 0.71; 95% CI 0.56-0.91, respectively). The results support the known risk reducing benefits of hysterectomy with BSO, but also demonstrate the superior risk reducing potential of BS compared to BTL.

Darelius et al.[3] compared the effects of benign BS and BTL for EOC risk reduction in another Swedish study. Specifically, they conducted a retrospective case-control study to examine their efficacy in reducing risk of different histologic subtypes of EOC. Cases were classified into Type I and Type II EOC based on their histological subtype. Type I EOC include mucinous, low-grade endometrioid, clear cell, and seromucinous cancers, as well as low-grade serous ovarian cancer (LGSOC). On the other hand, Type II EOC include HGSOC, high-grade endometrioid carcinoma, undifferentiated carcinoma, and malignant mixed mesodermal tumors.

Darelius et al.[3] utilized the nationwide Swedish Quality Register for Gynecological Cancer (SQRGC) to identify cases. The SQRGC includes information about patient and tumor characteristics, surgical and oncologic interventions, outcomes, and five years of follow-up information after diagnosis. Cases included patients diagnosed with EOC between 2008-2014 as defined by ICD codes. Patients were excluded if they had been diagnosed with EOC before 2008 or had ever undergone bilateral oophorectomy. The exposures of BS and BTL were determined using the Swedish Classification of Operations and Major Procedures.

A total of 4,040 cases were included. Of these, 25.6% were Type I EOC and 74.4% were Type II EOC. The vast majority of Type II cases (92.8%) were HGSOC, while Type I cases were more evenly distributed. Ten controls were randomly assigned to each case and were matched based on age, parity, and level of education. The authors found that endometriosis and history of PID were more common among cases than controls but only endometriosis reached significance.

Darelius et al.[3] found that BTL was associated with reduced Type I EOC risk, however, the results were not significant (OR 0.66; 95% CI 0.36-1.20). BS was not associated with an effect on Type I EOC risk (OR 1.00; 95% CI 0.28-3.61). On the other hand, there was a significant reduction in Type II EOC risk after BS (OR 0.10; 95% CI 0.01-0.71) but not after BTL (OR 0.80; 95% CI 0.57-1.11). OR were adjusted for endometriosis and PID.

This retrospective case control study by Darelius et al.[3] is one of the first to examine EOC risk, stratified by histology, following BS. However, by dividing these subtypes into Type I and Type II, the authors were unable to examine each subtype individually. Almost 92% of the Type II EOC in this sample were HGSOC, which reduces generalizability of the results to other Type II EOC.

A notable strength of all three retrospective studies is in their sampling methods. By utilizing data from high-quality population-based registries, all authors were able to eliminate the risk of recall bias and reduce selection bias. Additionally, the databases included a depth of patient information allowing Falconer et al.[2] and Darelius et al.[3] to control for some notable confounding variables. However, they were unable to control for

vital confounders such as family history of ovarian/breast cancer, breastfeeding, and OCP use, among others, as this information was not included in the registries.

Additionally, the registries did not include information about the surgical indications for BS. As a proxy for surgical indication, Madsen et al.[1] reviewed the primary hospital diagnoses associated with the admission when salpingectomy was performed. Ectopic pregnancy vastly outweighed the other indications for salpingectomy[1]. In the end, the salpingectomies in the three studies cannot necessarily be called "opportunistic" as the indications are unknown. Therefore, the specific benefit of OS, as it is defined—salpingectomy at the time of benign hysterectomy or for sterilization for the purpose of EOC risk reduction—cannot be determined from the results. Despite this, the results are promising and all demonstrate that BS is a potentially effective risk reducing option for EOC, and is potentially superior to BTL.

2.3 OPERATIVE SAFETY AND FEASIBILITY

Many studies have addressed operative feasibility and safety of BS and BTL. Authors have examined various major and minor surgical complications as a measure of safety. As a proxy for surgical feasibility, authors have explored operative time (OT) and the required number of laparoscopic ports, as appropriate. Studies have compared BS and BTL at each possible sterilization opportunity: after vaginal delivery, at the time of CD, and interval via laparoscopy. Their findings will be discussed here.

Sterilization After Vaginal Delivery

Danis et al.[4] conducted a retrospective case series at a university hospital in Philadelphia, PA. The primary objective was to compare OT and postoperative complications between BTL and BS that were performed within 24 hours of vaginal

delivery. OT was calculated by comparing incision start time and time out of the operating room. Postoperative complications were included if they occurred within 30 days postoperatively. Eighty patients were included in the analysis. Sixty-four (80%) patients underwent BTL while 16 (20%) underwent BS. They found that BS cases were slightly longer than BTL cases (71.44 ± 5.81 minutes vs 59.13 ± 16 minutes, respectively; $p = 0.003$). Differences in estimated blood loss (EBL) ($p > 0.05$) and other surgical complications between the two groups were not statistically significant ($p = 0.71$). Among the patients in the BTL group, two experienced postoperative ileus, one experienced excessive bleeding at the mesosalpinx, and one had an incision site hematoma. There were no complications reported in the BS cohort.

Danis et al.[4] demonstrated that there is no difference in surgical complications or EBL between postpartum laparoscopic BTL and BS after vaginal delivery. However, the authors showed that BS cases were about 12 minutes longer than BTL cases. Ultimately, the authors are some of the first to study this unique population and present such reassuring results. Future studies will need to include a larger sample size in order to improve generalizability.

Sterilization During Cesarean Delivery

Subramaniam et al.[5] carried out an RCT during which patients were randomized to undergo either BS or BTL during elective CD at $\geq$ 35 weeks gestation. Patients were excluded if they were a known *BRCA1/2* mutation carrier, had undergone prior tubal surgery, or had urgent/emergent CD during the study period. A total of 65 patients were randomized: 27 underwent BS while 38 underwent BTL. Surgeries with concomitant BS were longer by an average of 15 minutes compares to those with BTL (75.4 ± 29.1 vs

60.0 ± 23.3 minutes, respectively; p = 0.04)[5]. The authors did not find a statistically significant difference in intra- or postoperative complications between groups including EBL, readmission, reoperation, pain score, hematocrit change, blood transfusion, and intensive care unit admission.

Ganer Herman et al.[6] conducted a very similar RCT at a different institution. They included 34 patients that were randomized to undergo BS or BTL (16 and 18 patients, respectively) at the time of elective CD. Exclusion criteria included prior tubal surgery, personal history of breast cancer, family history of ovarian cancer, known *BRCA1/2* mutation carrier state, and emergent CD. BS surgeries were an average of 13 minutes longer than BTL (66.0 ± 20.5 vs 52.3 ± 15.8 minutes, respectively; p = 0.01). Change in postoperative hemoglobin was similar between groups (p = 0.39). There were no incidences of excessive bleeding requiring intraoperative blood transfusion, injury to adjacent organs, blood transfusion due to symptomatic anemia, or fever $\geq$ 38 ºC in either group during the study period.

In the final RCT of this section, Garcia et al.[7] continued to demonstrate the safety of BS for sterilization during scheduled CD. Patients were excluded if they had a known congenitally or surgically absent fallopian tube, a known hereditary cancer syndrome, or if they required CD after a trial of labor. The cohort included 37 patients undergoing CD: 19 patients were randomized to the BS group and 18 to the BTL group. In comparison to the results of Subramaniam et al.[5] and Ganer Herman et al.[6], the authors did not find a statistically significant difference in average OT between the two groups. Surgeries with concomitant BS were an average of 8 minutes longer than BTL (p = 0.34)[7]. However, the authors again found no difference in surgical complications between groups. There was

no difference in EBL, change in hematocrit, length of stay, transfusion requirements, reoperation, or wound infection; as well as incidences of readmission, emergency department visits, or clinic visits within seven days of discharge.

On the other hand, in a retrospective cohort study by Ida et al.[8], the authors compared BS and BTL at the time of CD. They included patients with singleton pregnancies and excluded patients that underwent any procedure other than CD or sterilization. BTL was performed in 45 patients and BS was performed in 22 patients between 2013 and 2015. The authors found that BS procedures were 3.5 minutes longer than BTL but the results were not statistically significant ($p = 0.053$). Additionally, patients that underwent BS had 69 mL more blood loss (including amniotic fluid) than those that underwent BTL (916 mL vs 847 mL) but again the results were not significant ($p = 0.475$). The RCTs in this section all excluded emergent, urgent, or unplanned CDs, but Ida et al.[8] did not address this aspect in their inclusion criteria. However, it has been found that there is no difference in surgical safety if sterilization occurs during either elective or unscheduled CD[9].

All four studies were limited by their very small sample sizes, but the data that have been presented in this section show that BS for sterilization at the time of CD is safe in terms of surgical complications. However, another retrospective study found that patients with three or more prior CD were at an increased risk for pelvic adhesions that made total salpingectomy at the time of CD difficult to complete successfully[10]. This phenomenon was not addressed in the studies included in this section. Moreover, it would need to be further explored in a dedicated study to better understand and quantify any associated risk.

Sterilization at Any Time

Hanley et al.[11] conducted a retrospective cohort study in British Columbia, Canada to further examine postoperative safety of BTL compared to BS. The authors identified all patients who underwent interval and postpartum tubal sterilization between 2008-2014 using the Discharge Abstract Database, which contains information about all hospital stays and surgeries in British Columbia. They specifically identified patients that had undergone BS by including patients with ICD-10 code Z30.2 for an "encounter for sterilization"[11].

The authors analyzed physician visits within 2 weeks postoperatively to examine incidences of surgical infections and complications, orders for laboratory tests and imaging, and whether one cohort was more likely to fill prescriptions for antibiotics or analgesics compared to the other. Prescription information was abstracted from BC PharmaNet, which is a database of all outpatient prescription drugs. The study cohort included 19,424 patients who underwent BTL and 5,839 who underwent BS.

After adjusting for age, gynecologic diagnoses, and surgical approach, patients in the BS group were more likely to fill a prescription for an analgesic within 2 weeks postoperatively, even after controlling for patients that used prescription analgesics preoperatively (OR 1.21; 95% CI 1.14-1.29). However, these results do not demonstrate likelihood of actually taking prescription analgesics. Some patients may have filled the prescriptions "just in case" and might not have actually needed or taken them for pain management. There were no statistically significant differences in any of the other variables between the two groups. Thus, the results add to data supporting the safety of

BS for sterilization. Additionally, the results of the current study have the added benefit of its much larger sample size.

Two other retrospective studies[12,13] also demonstrated no statistically significant differences in intraoperative or postoperative complications between patients who underwent interval laparoscopic BS or BTL. This is true even as BS uptake increased following the release of ACOG and SGO practice guidelines (*see Chapter 2.6*). However, it has been found that BS cases are more likely to require three or more surgical ports compared with two ports in BTL cases ($p < 0.001$)[12,13]. Additionally, BS procedures were an average of 11[13] and 23[12] minutes longer than BTL ($p \leq 0.01$).

Conclusion

All of the studies presented in this section demonstrate the operative safety of BS for sterilization. In terms of safety, authors have examined surgical infections, major and minor complications, postoperative bleeding, postoperative pain, injury to adjacent organs, postoperative anemia requiring blood transfusions, intensive care unit admissions, EBL, and length of hospital stay. Differences in safety measures were not statistically significant between BS and BTL cohorts.

Assessment of operative feasibility via OT is slightly more complicated. At the time of CD, OT difference was found to range from 3.5 to 15 minutes[5-8] in favor of longer BS procedures, but only two studies demonstrated significance[5,6]. If performed within 24 hours of vaginal delivery, BS cases are about 12 minutes longer than BTL[4] and between 12-23 minutes longer if performed as laparoscopic interval sterilization[12,13]. Some studies specifically outlined the Parkland or Modified Pomeroy techniques as those used for the BTL cases that were included[4-7]. On the other hand, some authors did not

define their BTL technique[11-13] and all authors included various levels of detail regarding BS surgical methods. If surgical methods differed between studies, it would be difficult to compare OT across studies.

Additionally, all studies except those of Ida et al.[8] and Danis et al.[4] calculated OT from skin incision to skin closure. Danis et al.[4] used the time out of the operating room as a surrogate for procedure end rather than using the time of incision closure. There are many possible confounding variables that lengthen the time between incision closure and exiting the operating room—for example, time to extubation, wound care, and bed availability in the post anesthesia care unit (PACU)—all of which are independent of actual procedure length, feasibility, or safety. Furthermore, Ida et al.[8] did not even describe their methods for calculating OT. Thus, the results of both studies cannot be reliably compared to other results presented in this section.

Lastly, some studies mentioned that residents of various levels of experience assisted the attending physician with the CD[5], BTL[4,6], or BS[4]. If a trainee was participating in any part of the operation, it is possible that this would contribute to a longer OT due to their inexperience and time taken for teaching. Again, this could affect our ability to compare results both within and across studies. Ultimately, research that controls for these confounders is needed in order to fully assess operative feasibility as defined by OT. Despite these limitations and the slightly increased procedure time, BS appears to be feasible for postpartum and interval sterilization.

2.4 POSTOPERATIVE OVARIAN FUNCTION

One of the chief theoretical benefits of BS is EOC risk reduction while preserving ovarian function and preventing surgical menopause. However, some scientists expressed

concern that complete removal of the fallopian tubes might disrupt ovarian perfusion, negatively impact ovarian function, and ultimately elicit menopausal symptoms. Moreover, there is concern that even more risk to ovarian function exists if BS is performed at the time of CD. It is hypothesized that the procedure is more challenging due to engorged pelvic vessels and anatomical changes that are associated with a gravid abdomen[6]. In this section, we will present data regarding ovarian function following BS and BTL.

Ganer Herman et al.[6] conducted an RCT to compare ovarian reserve after BTL and BS for sterilization at the time of CD (*see Chapter 2.3 for a description of methodology*). The authors used anti-müllerian hormone (AMH) as a validated marker for ovarian reserve[6] and measured it preoperatively and again six to eight weeks postoperatively. Thirty-four patients were enrolled and randomized to BS (n = 16) and BTL (n = 18). There were no differences in preoperative and postoperative AMH between groups (preoperative $p = 0.21$; postoperative $p = 0.78$).

Although the study has a small sample size and brief follow-up period, it benefits from its randomized design. Additionally, this pilot trial presents some of the first prospective results that support BS as a safe procedure for ovarian function. Moreover, the results show that ovarian function is preserved after sterilization at the time of CD despite the concern for increased surgical complexity.

In a retrospective cohort study in Canada, Hanley et al.[14] examined indicators of menopause as a proxy for ovarian function. The authors used the methods of another study conducted in British Columbia[11] to identify patients ≤ 50 years old who underwent tubal sterilization between 2008-2014. They included 18,621 patients who underwent

BTL and 4,952 who underwent BS. After adjusting for year of surgery, age, gynecologic comorbidities, and surgical approach, hazard ratios were calculated for the variables of interest. Results revealed no difference in risk for a physician visit for menopausal diagnoses or symptoms (adjusted HR 0.92; 95% CI 0.77-1.10) as well as risk for filling an HRT prescription (adjusted HR 1.00; 95% CI 0.89-1.12) between groups.

This study benefits from its large sample size and population-based sampling method. However, there is a significant risk of self-reporting bias as patients were required to seek medical care for menopausal symptoms in order to be captured as a positive outcome. Additionally, the authors used menopausal symptoms as a surrogate for ovarian function although some patients can experience "menopausal symptoms" years before actual the cessation of menses[15]. Lastly, some patients are apprehensive about HRT use despite experiencing symptoms so its use does not accurately reflect the menopausal transition[15,16].

Although the body of literature comparing BS and BTL in terms of ovarian function is small, the results are reassuring. Studies have shown no difference in AMH, menopausal symptoms, or HRT use between patients that undergo either procedure. More studies are needed to fully ascertain the relationship between salpingectomy and ovarian function. Additionally, it would be even more beneficial if these studies use direct indicators of ovarian perfusion and function rather than surrogate variables.

2.5 COST EFFECTIVENESS

Research regarding BS safety, feasibility, and risk reducing potential is still in relatively early stages and few prospective data have been published. Thus, various

authors are striving to evaluate the cost effectiveness of BS given the current state of the literature.

Kwon et al.[17] published the first cost-effectiveness study in 2015. They conducted a Markov Monte Carlo simulation model to estimate the average lifetime costs and benefits of BS in a large hypothetical cohort of premenopausal patients undergoing sterilization at 35 years of age. The authors utilized data from Canadian healthcare databases to estimate costs and probabilities. They found that BS was slightly more costly ($9,720 ± $3.74 vs $9,339 ± $26.74) but more effective (22.45 ± 0.02 vs 22.43 ± 0.02 years of life expectancy gained) compared to BTL. An incremental cost-effectiveness ratio (ICER) is defined as the cost per one additional QALY gained and a lower ICER indicates a more cost-effective strategy. Kwon et al.[17] calculated an ICER of $27,278 per QALY for BS compared to BTL. In a cohort of 25,000 patients, their model predicted that BS would result in 68 fewer ovarian cancer diagnoses compared to BTL. Their results were stable when the simulation was applied to the US with associated costs and probabilities. Of note, the authors did not include the increased risk for ectopic pregnancy after BTL in their model, and this would have likely contributed to even greater cost effectiveness of BS.

Overall, the results of Kwon et al.[17] indicate a number needed to treat of 366 (95% CI 338-379) with BS to prevent one case of ovarian cancer compared with BTL. This is comparable to the number needed to vaccinate against human papillomavirus of 324 to prevent one case of cervical cancer. The authors' results translate to about one week of life expectancy gained for BS compared to BTL, while it has been shown that the life expectancy gained from triennial Papanicolaou testing starting at age 30 years is

an average of just under two days. However, in contrast to cervical cancer, there is no screening test for ovarian cancer so BS is the most cost-effective and safe option for risk reduction.

Dilley et al.[18] conducted another cost effectiveness study focused on data from the United States. The authors included a theoretical cohort of 300,000 patients who underwent laparoscopic sterilization at 35 years of age. Again, authors estimated that BS is slightly more costly than BTL ($6,395 vs $5,926) but still found that BS is more cost effective. They calculated an ICER for BS of $31,432 per QALY. In comparison to BTL, BS for laparoscopic sterilization was found to result in 690 fewer ovarian cancer diagnoses, 260 fewer ovarian cancer deaths, 210 fewer unintended pregnancies, and 3,000 additional QALYs in this large cohort. Thus, not only does laparoscopic BS prevent ovarian cancer diagnoses and deaths, it is a cost-effective method per QALY gained.

Moreover, Naumann et al.[19] explored cost effectiveness, as well as the impact of BS on ovarian cancer mortality, among patients between the ages of 20-85 years. They utilized the Surveillance, Epidemiology, and End Result (SEER) database and ACS data for estimates of survival and mortality rates. Additionally, they utilized the Nordic tumor registry to estimate the risk reducing potential of BS. Compared to other studies, the authors estimated cost effectiveness from the point of view of overall healthcare costs rather than societal expenditures. Their model predicted that BS will reduce ovarian cancer mortality by 8.13%. If the excess cost of BS was estimated to be $433.91 compared to BTL, the model found an ICER of $5,469 per QALY gained accounting only for the excess cost of the salpingectomy alone.

Naumann et al.[19] estimated that BS may save $445 million annually in healthcare costs when considering the impact of ovarian cancer prevention with respect to the cost of ovarian cancer treatment. Furthermore, cost savings would only improve as newer, and more expensive, targeted treatment modalities are employed. Of note, their model is unique in that it is adjusted to account for age at the time of surgery whereas previous models have examined cost effectiveness assuming BS occurs only at 35 years of age.

Subramaniam et al.[20] narrowed their scope to specifically evaluate cost effectiveness of sterilization at the time of CD from a societal perspective. The authors conducted a systematic literature search using PubMed to determine estimates of probabilities, utilities, and cost for their model. They estimated that BS is slightly more costly than BTL ($2,376.88 vs $1,904.92) but found that BS was more cost effective with an ICER of $26,616 per QALY. Additionally, their model revealed that BS would result in 17 fewer ovarian cancer diagnoses, 13 fewer ovarian cancer deaths, and 25 fewer unintended pregnancies compared to BTL in a theoretical cohort of 10,000 patients.

Venkatesh et al.[21] also examined societal cost effectiveness among a theoretical cohort of patients undergoing sterilization at the time of CD. They included 110,000 patients in their cohort, with the assumption that all were 35 years of age. Similar to Subramaniam et al.[20], the authors also conducted a literature search using PubMed in order to estimate the various rates and costs for their model. They estimated procedural costs for BS and BTL and found that BS is slightly more expensive ($9,348 vs $8,629). Despite its increased cost, BS was found to be more cost effective than BTL with an ICER of about $23,189 per QALY. Compared to BTL, BS would result in 422 fewer ovarian cancer diagnoses, 252 fewer ovarian cancer deaths, 20 fewer unintended

intrauterine pregnancies, and 57 fewer ectopic pregnancies in their very large cohort. Venkatesh et al.[21] also conducted a separate high-risk analysis with BRCA1/2 carriers and those with Lynch syndrome. They found that BS was both less expensive and more effective than BTL for this group.

All five studies presented in this section demonstrate that BS is a cost-effective strategy for ovarian cancer prevention at the time of either postpartum or interval sterilization. All ICERs were less than about $32,000 which falls far below the assumed Willingness to Pay threshold of $100,000—the assumption that most Americans are willing to spend $100,000 per QALY gained. However, it is difficult to compare ICERs between studies. Each study used different data sources and estimates for the probabilities, utilities, and costs utilized in their models, and adjusted for different covariates in their analyses. Moreover, with limited prospective data about ovarian cancer risk reduction and morbidity associated with BS, all authors relied on assumptions from retrospective studies that have their own limitations. Of note, only one study examined cost effectiveness through the lens of ovarian cancer family history. It would be interesting to examine cost effectiveness specifically in an intermediate risk cohort, including FDRs.

2.6 OPPORTUNISTIC SALPINGECTOMY UPTAKE AND THE EFFECT OF FAMILY HISTORY

We have established that in comparison to BTL, BS is safe, feasible, cost effective, and an effective risk reducing option. Now, we will explore the uptake of BS as different countries and regions release practice guidelines encouraging OS. In the United States, the SGO and ACOG released their practice guidelines in 2013 and 2015,

respectively[12,20,22]. The same will be addressed for other countries and regions as necessary moving forward. The following studies examine the change in uptake of BS for sterilization and the factors that contribute to this change.

In September 2010, a Canadian gynecologic tumor group started an initiative for ovarian cancer prevention in response to some of the early information released regarding the Tubal Origin Theory[23]. Their initiative was one of the first of its kind. It was directed to all obstetrician gynecologists in British Columbia and involved education regarding the Tubal Origin Theory and recommendations to utilize BS for sterilization. McAlpine et al.[23] then conducted a retrospective cohort study to examine the effects of the educational initiative. They gathered data about all BS procedures that were conducted in British Columbia for sterilization between 2008-2011 using the methods of Hanley et al.[11] (*see Chapter 2.3*). It is important to note that the authors included sterilizations that were performed at hospitals and at day (ambulatory) surgery centers.

The authors included 1,569 patients that underwent BS and 13,317 patients that underwent BTL. The proportion of BS increased from 0.5% in 2008 to 33.3% in 2011 ($p < 0.001$). It is important to note that 98.1% of the salpingectomies that occurred in 2010 occurred after the initiative was released in September. Moreover, the authors found that the number of surgeries with an associated ICD-10 code of "risk reducing/prophylactic surgery" increased across the study period from 1 in 2008 to 97 in 2011 ($p < 0.001$). This demonstrates providers' knowledge of its risk reducing potential and increased uptake of OS for sterilization. Unfortunately, the authors did not share results stratified by surgical setting (inpatient vs outpatient).

The Royal Australian and New Zealand College of Obstetricians and Gynecologists released their own OS guidelines in 2014. Baltus et al.[12] examined the uptake, feasibility, and perioperative outcomes (*see Chapter 2.3*) of laparoscopic BS as an alternative to BTL in Australia between 2014-2020. The authors conducted a retrospective cohort study of all tubal sterilization procedures conducted at two Australian hospitals. Surgical data were derived from the hospitals' surgical registries, which included surgical codes as well as free text titles. Salpingectomy procedures were excluded if they occurred at the time of CD or hysterectomy, and if they were associated with diagnosis codes for ectopic pregnancy, hydrosalpinx, and tubo-ovarian abscess.

A total of 414 patients were included. During the study period, 92 patients underwent BS and 322 underwent BTL for interval sterilization. Uptake of BS increased throughout the study period from 0% to 72% by 2020 ($p < 0.05$). The overall number of laparoscopic sterilization procedures that occurred in 2020 decreased dramatically from 49 in 2019 to 18 in 2020. This is likely due to the Covid-19 pandemic and its associated restrictions on elective procedures. This possibly led to an overrepresentation of the uptake of BS in 2020 as the proportion of BS procedures increased from 31% to 46% to 47% to 72% in 2017, 2018, 2019, and 2020, respectively.

Kim et al.[13] conducted a similar retrospective cohort study at four university-affiliated hospitals in Houston, TX, and New York, NY. The authors included all patients 21 years or older who underwent interval sterilization via laparoscopy between April 2013 and September 2016. Exclusion criteria included postpartum sterilizations, ectopic pregnancies, sterilizations at the time of other surgical procedures, *BRCA1/2* mutation carriers, and patients with a diagnosis of breast, uterine, or ovarian cancer. Each

hospital's surgical database was used to identify procedures by searching Current Procedural Terminology (CPT) codes for sterilization, tubal occlusion, ligation, fulguration, and salpingectomy. There were 454 total patients in the cohort and across the study period, 40% of patients underwent BS while 60% underwent BTL. The total sample size was similar to that of Baltus et al.[12], but there was a greater total proportion of BS procedures performed in this cohort. The rate of BS increased from 5.8% in 2013 to 77.5% by 2016 ($p < 0.0001$).

Despite their promising results, Baltus et al.[12] and Kim et al.[13] only included a few hospitals with fairly small sample sizes. Thus, their generalizability is limited[12,13]. Additionally, neither study identified any patient or provider demographic factors that had a statistically significant effect on BS uptake. In both studies, groups were similar based on age, BMI, parity, and history of abdominal surgery. Kim et al.[13] also included race, medical comorbidities, and family history of breast or ovarian cancer as demographic variables, but none of which were different between groups.

The Kaiser Permanente Health System in Northern California published their own policy statement in May 2013 just before ACOG and SGO released their guidelines. Powell et al.[24] examined the change in BS uptake from June 1, 2011, to May 31, 2016 within the Health System. They retrospectively reviewed the medical record and included all patients who underwent surgical sterilization during the study period. Patients were excluded if they underwent simultaneous hysterectomy or oophorectomy, had a diagnosis of ectopic pregnancy, had a personal history of ovarian cancer, or were a *BRCA1/2* or Lynch Syndrome mutation carrier.

The study cohort included 10,741 patients of which 9,007 underwent BTL and 1,734 underwent BS. The authors also stratified the cohort by sterilization opportunity: at the time of CD, postpartum (within 3 days of vaginal delivery), and interval. Utilization of BS increased significantly during the study period both overall (0.4% to 35.5%; $p < 0.001$) and for each sterilization opportunity: during CD (0.1% to 9.2%; $p < 0.001$), postpartum (0% to 4.5%; $p = 0.003$), and interval (1% to 78.1%; $p < 0.001$). There is a hospital policy within the Health System that prohibits postpartum sterilizations, but the authors did not provide any further details about this policy so these results should be examined with caution. Additionally, the authors found that rates of salpingectomy increased significantly in response to the Health System's policy guideline compared to before it was released ($p < 0.001$). Otherwise, patient characteristics—age, parity, race, BMI, and socioeconomic status—were similar between BS and BTL cohorts.

Mandelbaum et al.[25] significantly improved on the sample size limitations of Baltus et al.[12] and Kim et al.[13]. They utilized the National Inpatient Sample (NIS) to identify all patients in the US that underwent sterilization at the time of CD between October 2015 and December 2018. The ICD-10 Procedure Coding System was used to identify the procedures of interest. They included 397,260 patients who underwent BS and 203,400 patients who underwent BTL during the study period. From 2015-2018, the proportion of CDs that included BS increased from 28.7% to 84.4% ($p <0.001$). Patients were more likely to undergo BS at a large, urban, teaching hospital in the Midwest or West regions (all $p < 0.001$). It is important to note that a proportion of sterilization procedures may have also included hysterectomy or oophorectomy, but the authors did

not report the exact numbers of such procedures. Therefore, this inhibits the extent to which their results can be interpreted.

Karia et al.[26] included 322,295 patients between the ages of 18 and 50 that had undergone BS (13,462 patients) or BTL (308,833) for sterilization between 2010 and 2017 in their retrospective cohort study. In order to identify their population, the authors analyzed deidentified data from the Truven Health Analytics MarketScan Commercial Claims and Encounters Database, which includes a large sample of Americans with commercial, employer-sponsored health insurance. The database includes inpatient and outpatient encounters at hospitals and ambulatory surgical centers. The authors excluded patients with ectopic pregnancy, PID, and pelvic infections.

The authors found that the proportion of BS procedures increased from 1% in 2010 to 32% in 2017 and patients were more likely to undergo BS between 2014-2017 compared to 2010-2013 (RR 10.68; 95% CI 10.19-11.18). Karia et al.[26] explored predictors of BS uptake within the cohort. They found that patients living in rural areas were less likely to undergo BS than patients living in urban areas (RR 0.87; 95% CI 0.83-0.91); and that patients were more likely to undergo BS in outpatient surgical centers compared to inpatient settings (RR 3.42; 95% CI 3.28-3.56). This is an important finding as most other authors limited their cohorts to patients that underwent inpatient sterilizations. Additionally, although they included outpatient sterilizations in their sample, McAlpine et al.[23] did not present any results stratified by this variable. In this regard, the results of Karia et al.[26] provide a more complete view of BS uptake.

Most notably, Karia et al.[26] examined if a family history of or genetic mutation for breast or ovarian cancer was a predictor of BS uptake. They found that patients were

more likely to undergo BS if they had a family history of breast or ovarian cancer (RR 1.38; 95% CI 1.31-1.46) or if they had a genetic mutation for breast or ovarian cancer (RR 2.84; 95% CI 2.31-3.49) compared to those without a family history or a predisposing genetic mutation. This likely demonstrates that providers are knowledgeable about the Tubal Origin Theory and consider a patient's ovarian cancer risk when counseling them about the benefits of long-term contraception options.

In conclusion, all data presented in this section show that uptake of BS for sterilization has increased significantly in response to the release of various practice guidelines recommending OS. This demonstrates that providers are likely performing BS for the purposes of sterilization and EOC risk reduction, making them truly opportunistic procedures. We must compare studies with caution as some authors focus on different regions of the US and both Karia et al.[26] and Mandelbaum et al.[25] demonstrated that OS uptake varies across the US. The differences based on region and urban vs rural environments might further indicate an effect of socioeconomic status on healthcare uptake. Moreover, we must further examine effects of Medicaid and private insurance plans on OS uptake.

2.8 REVIEW OF RELEVANT METHODOLOGY

Now that we have reviewed the current state of the literature, we will summarize and compare the relevant methodology used to study various aspects of sterilization techniques.

Study Design

Three studies in this chapter utilized a randomized controlled design, all of which examined operative feasibility and safety of sterilizations at the time of CD[5-7]. RCTs are

considered to be the gold standard as they reduce selection bias and limit the effect of confounders. However, since trials are highly controlled, they might not always represent real life situations. For example, all three RCTs excluded sterilizations performed at the time of emergent, urgent, or unscheduled CD. While it may be less ethical to randomize patients into intervention groups in an emergency situation, patients do undergo sterilizations in these situations. Therefore, the results cannot be generalized to these populations. Moreover, RCTs can be logistically difficult to carryout. Studies must be conducted at multiple sites in order for the results to be valid and generalizable, which is highly demanding for researchers.

A vast majority of the studies presented in this chapter utilized a retrospective design[1-4,8,11-14,23-26]. This is likely due to the reasonably recent transition to the recommendation and performance of OS. There has not been a sufficient amount of time since the adoption of OS for sterilization to conduct and publish long-term prospective data on the topic. However, since retrospective studies are dependent on previously collected data, it is possible that all relevant factors and confounders may not have been identified or recorded. For example, all three studies that examined ovarian cancer risk reduction were not able to control for OCP use in their results because it was not included in their data source, although it is a well-known confounding variable[1-3].

Despite its disadvantages, a retrospective design is the most effective method for examining uptake of BS for sterilization. The design eliminates risk for recall bias and reduces selection bias. Additionally, it is more efficient than prospective studies as data collection simply requires accessing a data source. This way, we can include a larger volume of data without significantly altering the time needed for data collection.

Sampling Techniques and Sample Sizes

The retrospective studies in this chapter utilized a variety of sampling techniques, but many authors shared one aspect of their design: they utilized ICD diagnosis and CPT procedure codes to identify patients and procedures of interest. Unfortunately, the coding system is prone to human error and inaccuracy. Furthermore, every aspect of healthcare does not have a diagnosis or procedure code so it is impossible to include all relevant variables. However, the codes are consistent across large health systems and even internationally.

Sample size varied considerably across studies. The smallest studies included a few hospitals or a single health system for their sample[4,8,12,13,24]. The source for their diagnosis and procedure codes was either the hospital's medical record or operative database. However, by defining their sample in terms of a few hospitals or a single health system, they sacrificed their sample size. Small sample sizes lead to difficulty critically analyzing the differences between groups for infrequent outcomes and generalizing results to larger populations. Other authors utilized British Columbia population databases to include all exposed patients in the province, which increased sample sizes[11,14,23]. However, the sampling techniques of all of these smaller studies limits their populations to certain regions or cities, which limits generalizability to other areas.

The rest of the authors utilized national, population-based databases for sampling, which afforded them very large sample sizes. The most notable and relevant examples are the studies by Mandelbaum et al.[25] and Karia et al.[26] that examined BS uptake in the US. Mandelbaum et al.[25] utilized the National Inpatient Sample, which is publicly available, deidentified, and includes patient demographics, resource use, and hospital information

for more than 90% of the US population including patients with all kinds of insurance. However, it is restricted to inpatient data by definition.

On the other hand, Karia et al.[26] analyzed deidentified data from the Truven Health Analytics MarketScan Commercial Claims and Encounters Database, which includes a large sample of Americans with commercial, employer-sponsored health insurance. The database includes inpatient and outpatient encounters at hospitals and ambulatory surgical centers, demographic characteristics, admitting and discharge ICD-9 and ICD-10 codes, and CPT codes. The greatest benefit of this method is the inclusion of ambulatory surgical encounters as the authors found that a majority of sterilizations are performed outpatient. The most notable disadvantage of their sampling method is that it is limited to patients with employer-sponsored health insurance.

However, a brief PubMed search revealed a remedy for this sampling limitation. Truven Health Analytics MarketScan also has a Medicaid-based database. A number of studies have utilized this Multi-State Medicaid Database and have even used the two databases together[27-30]. The Medicaid database includes patients from less than half of American states but the data structure and variables are similar between the two databases allowing them to be used together. Additionally, by utilizing the Medicaid database, we would improve on the insurance limitations of Karia et al.[26] while including the outpatient data that Mandelbaum et al.[25] excluded.

Selection Criteria and Potential Confounders

Selection criteria varied across studies in our literature review. The studies in Chapter 2.7 will be presented here due to their relevancy to our proposed methods. All studies included bilateral sterilization procedures conducted during a given time frame. It

is beneficial to include some time before the release of the SGO guideline and more substantial amount of time after its release. In order to include a large sample but also avoid the effects of Covid-19 on surgical uptake, our proposed study will take place between 2011-2019. Moreover, we will include patients between the ages of 18[24,26] and 50 years of age. Karia et al.[26] excluded patients above the age of 50 years as sterilization procedures are rare in this age group.

Authors also excluded patients with known gynecologic or breast cancers[13,24-26], PID[26], hydrosalpinx, tubo-ovarian abscess[12], ectopic pregnancy[12,13,24,26], and patients undergoing concurrent procedures at the time of sterilization[12,13] except CD[23,24,26]. Karia et al. are the only authors that stratified BS uptake by family history and genetic mutations. Family history of and genetic mutations for breast and or ovarian cancer were determined based on ICD-9 and ICD-10 codes. Since there is no diagnosis code to express ovarian cancer FDRs, the diagnosis code for family history of ovarian cancer will be the best surrogate for our study.

Throughout our literature review, we have identified numerous possible confounders that will need to be considered in our proposed protocol. It has been found that patients who underwent BS were slightly older, less likely to have delivered a baby in the same hospital stay (i.e. more likely to undergo interval sterilization), less likely to have hydrosalpinx, and of higher income compared to patients who underwent BTL (all $p < 0.001$). Furthermore, they were more likely to have a diagnosis code for endometriosis, a benign uterine or ovarian neoplasm, abnormal bleeding, and PID (all $p < 0.001$)[3,11,23]. Uptake of BS and BTL also differed based on region[25,26], race, insurance payer, and hospital size[25].

2.9 CONCLUSION

After examining the current state of the literature regarding BS and BTL, it is clear that more comprehensive research is needed. Prospective studies are needed to fully understand the implications of transitioning to increased BS uptake. However, the available literature shows that BS is likely effective for EOC risk reduction, as well as being a safe and feasible surgical procedure despite its longer OT when performed at the time of CD, postpartum, or for interval sterilization. When these results were compiled, cost-effectiveness models showed that BS might be slightly more expensive but is ultimately more cost-effective than BTL. Lastly, uptake of OS has increased significantly in various regions and countries in the last 10 years and some results even show that providers are considering a patient's EOC risk at the time of preoperative counseling for sterilization.

REFERENCES

1. Madsen C, Baandrup L, Dehlendorff C, Kjær SK. Tubal ligation and salpingectomy and the risk of epithelial ovarian cancer and borderline ovarian tumors: A nationwide case-control study. *Acta Obstetricia et Gynecologica Scandinavica.* 2015;94(1):86-94.
2. Falconer H, Yin L, Grönberg H, Altman D. Ovarian cancer risk after salpingectomy: A nationwide population-based study. *Journal of the National Cancer Institute.* 2015;107(2).
3. Darelius A, Kristjansdottir B, Dahm-Kahler P, Strandell A. Risk of epithelial ovarian cancer Type I and II after hysterectomy, salpingectomy and tubal ligation-A nationwide case-control study. *International Journal of Cancer.* 2021;149(8):1544-1552.
4. Danis RB, Della Badia CR, Richard SD. Postpartum Permanent Sterilization: Could Bilateral Salpingectomy Replace Bilateral Tubal Ligation? *Journal of Minimally Invasive Gynecology.* 2016;23(6):928-932.
5. Subramaniam A, Blanchard CT, Erickson BK, et al. Feasibility of Complete Salpingectomy Compared With Standard Postpartum Tubal Ligation at Cesarean Delivery: A Randomized Controlled Trial. *Obstet Gynecol.* 2018;132(1):20-27.
6. Ganer Herman H, Gluck O, Keidar R, et al. Ovarian reserve following cesarean section with salpingectomy vs tubal ligation: a randomized trial. *American Journal of Obstetrics & Gynecology.* 2017;217(4):472.e471-472.e476.
7. Garcia C, Moskowitz OM, Chisholm CA, et al. Salpingectomy Compared With Tubal Ligation at Cesarean Delivery: A Randomized Controlled Trial. *Obstet Gynecol.* 2018;132(1):29-34.
8. Ida T, Fujiwara H, Matsubara S, Taniguchi Y, Kohyama A. Salpingectomy for tubal sterilization at cesarean section: No extra time and no extra bleeding compared with tubal ligation. *Clinical and Experimental Obstetrics and Gynecology.* 2017;44:879-881.
9. Ferrari F, Forte S, Prefumo F, Sartori E, Odicino F. Opportunistic salpingectomy during postpartum contraception procedures at elective and unscheduled cesarean delivery. *Contraception.* 2019;99(6):373-376.
10. Lehn K, Gu L, Creinin MD, Chen MJ. Successful completion of total and partial salpingectomy at the time of cesarean delivery. *Contraception.* 2018;98(3):232-236.
11. Hanley GE, Kwon JS, Finlayson SJ, Huntsman DG, Miller D, McAlpine JN. Extending the safety evidence for opportunistic salpingectomy in prevention of ovarian cancer: a cohort study from British Columbia, Canada. *American Journal of Obstetrics & Gynecology.* 2018;219(2):172.e171-172.e178.
12. Baltus T, Brown J, Kapurubandara S. A retrospective cohort study of tubal occlusion or salpingectomy for permanent contraception in Australia. *Australian and New Zealand Journal of Obstetrics and Gynaecology.* 2021.
13. Kim AJ, Barberio A, Berens P, et al. The Trend, Feasibility, and Safety of Salpingectomy as a form of Permanent Sterilization. *Journal of Minimally Invasive Gynecology.* 2019;26(7):1363-1368.

14. Hanley GE, Kwon JS, McAlpine JN, Huntsman DG, Finlayson SJ, Miller D. Examining indicators of early menopause following opportunistic salpingectomy: a cohort study from British Columbia, Canada. *American Journal of Obstetrics & Gynecology.* 2020;223(2):221.e221-221.e211.
15. Minkin MJ. Menopause: Hormones, Lifestyle, and Optimizing Aging. *Obstet Gynecol Clin North Am.* 2019;46(3):501-514.
16. Alexandre M, Black J, Whicker M, Minkin MJ, Ratner E. The management of sexuality, intimacy, and menopause symptoms (SIMS) after prophylactic bilateral salpingo-oophorectomy: How to maintain sexual health in "previvors". *Maturitas.* 2017;105:46-51.
17. Kwon JS, McAlpine JN, Hanley GE, et al. Costs and benefits of opportunistic salpingectomy as an ovarian cancer prevention strategy. *Obstetrics & Gynecology.* 2015;125(2):338-345.
18. Dilley SE, Havrilesky LJ, Bakkum-Gamez J, et al. Cost-effectiveness of opportunistic salpingectomy for ovarian cancer prevention. *Gynecologic Oncology.* 2017;146(2):373-379.
19. Naumann RW, Hughes BN, Brown J, Drury LK, Herzog TJ. The impact of opportunistic salpingectomy on ovarian cancer mortality and healthcare costs: a call for universal insurance coverage. *Am J Obstet Gynecol.* 2021;225(4):397.e391-397.e396.
20. Subramaniam A, Einerson BD, Blanchard CT, et al. The cost-effectiveness of opportunistic salpingectomy versus standard tubal ligation at the time of cesarean delivery for ovarian cancer risk reduction. *Gynecol Oncol.* 2019;152(1):127-132.
21. Venkatesh KK, Clark LH, Stamilio DM. Cost-effectiveness of opportunistic salpingectomy vs tubal ligation at the time of cesarean delivery. *Am J Obstet Gynecol.* 2019;220(1):106.e101-106.e110.
22. Long Roche KC, Abu-Rustum NR, Nourmoussavi M, Zivanovic O. Risk-reducing salpingectomy: Let us be opportunistic. *Cancer.* 2017;123(10):1714-1720.
23. McAlpine JN, Hanley GE, Woo MMM, et al. Opportunistic salpingectomy: Uptake, risks, and complications of a regional initiative for ovarian cancer prevention. *American Journal of Obstetrics and Gynecology.* 2014;210(5):471.e471-471.e411.
24. Powell CB, Alabaster A, Simmons S, et al. Salpingectomy for Sterilization: Change in Practice in a Large Integrated Health Care System, 2011-2016. *Obstet Gynecol.* 2017;130(5):961-967.
25. Mandelbaum RS, Matsuzaki S, Sangara RN, et al. Paradigm shift from tubal ligation to opportunistic salpingectomy at cesarean delivery in the United States. *American Journal of Obstetrics and Gynecology.* 2021;225(4):399.e391-399.e332.
26. Karia PS, Joshu CE, Visvanathan K. Uptake and Predictors of Opportunistic Salpingectomy for Ovarian Cancer Risk Reduction in the United States. *Cancer Prevention Research.* 2021;14(12):1101-1110.
27. Chen J, Cox S, Kuklina EV, Ferre C, Barfield W, Li R. Assessment of Incidence and Factors Associated With Severe Maternal Morbidity After Delivery Discharge Among Women in the US. *JAMA Netw Open.* 2021;4(2):e2036148.

28. Payne AB, Adamski A, Abe K, et al. Epidemiology of cerebral venous sinus thrombosis and cerebral venous sinus thrombosis with thrombocytopenia in the United States, 2018 and 2019. *Res Pract Thromb Haemost.* 2022;6(2):e12682.
29. Soliman AM, Surrey ES, Bonafede M, Nelson JK, Vora JB, Agarwal SK. Health Care Utilization and Costs Associated with Endometriosis Among Women with Medicaid Insurance. *J Manag Care Spec Pharm.* 2019;25(5):566-572.
30. Yang X, Desai K, Agrawal N, et al. Characteristics, treatment patterns, healthcare resource use, and costs among pediatric patients diagnosed with neurofibromatosis type 1 and plexiform neurofibromas: a retrospective database analysis of a medicaid population. *Curr Med Res Opin.* 2021;37(9):1555-1561.

CHAPTER 3 – STUDY METHODS

3.1 STUDY DESIGN

We are proposing a retrospective cohort study to examine the uptake of BS for sterilization among patients with a family history of ovarian cancer, but no known genetic mutation for ovarian cancer, compared to the general population. We will compare the proportion of sterilizations that were carried out by either BS or BTL between 2011 and 2019 in this unique population.

3.2 POPULATION, SAMPLING, AND RECRUITMENT

The study population will include all patients between the ages of 18 and 50 years who underwent BS or BTL for sterilization in the US during the study period. Patients will be recruited using deidentified data from the Truven Health Analytics MarketScan Commercial Claims and Encounters Database, as well as the Multi-State Medicaid Database. The databases contain claims for all encounters at hospitals and ambulatory surgical centers, which include CPT codes, demographic characteristics, and admitting and discharge ICD-9 and ICD-10 codes. Procedures of interest will be identified using CPT, ICD-9, and ICD-10 codes and surgical indication will be deduced based on the diagnosis code that is associated with the surgical claim. Patient data including age, year of surgery, insurance type (public vs private), surgical setting (inpatient vs outpatient), gynecologic diagnoses, family history of ovarian cancer, genetic mutation for ovarian cancer, region of residence, and location of residence will also be collected.

Inclusion and Exclusion Criteria

Appendices A and B provide diagnosis and procedure codes for inclusion and exclusion criteria, respectively, and Appendix C provides other notable codes. Patients

will be included if they have an insurance claim for sterilization, bilateral tubal ligation, bilateral salpingectomy, or prophylactic removal of fallopian tubes. Patients will be excluded if they have claims for hysterectomy, oophorectomy, salpingo-oophrectomy, partial salpingectomy or tubal ligation, unilateral salpingectomy or tubal ligation, prophylactic removal of ovaries, or any procedure related to an ectopic pregnancy. Moreover, patients will be excluded if their sterilization surgery was performed at the same time as any other procedure, except CD. Lastly, patients will be excluded if they have diagnosis codes for a gynecologic malignancy, breast malignancy, ectopic pregnancy, pelvic infection, or PID.

Family history of and genetic mutation for ovarian/breast cancers will be assessed based on ICD-9/ICD-10 codes. Patients will be classified as having a documented family history if they have a diagnosis code for family history of ovarian/breast cancer but do not have a diagnosis code for genetic susceptibility for ovarian/breast cancer or family history of carrier of genetic disease. The opposite will be true for patients with a genetic mutation for ovarian/breast cancer. Therefore, patients will be excluded if they have a diagnosis code for “family history of breast cancer”, “genetic susceptibility for ovarian cancer”, “genetic susceptibility for breast cancer”, or “family history of carrier of genetic disease”. Patients with a documented ovarian cancer family history will be included in our exposed population and patients that do not have any of the above diagnosis codes will serve as our unexposed population.

3.3 SUBJECT PROTECTION AND CONFIDENTIALITY

We will submit our study protocol to the Yale University Institutional Review Board (IRB) prior to study initiation. We will submit a request for exemption

determination as outlined by Yale University's IRB Policy 100.4: Exemption from IRB Approval Criteria. According to 45 CFR 46.101(b)(4), research can be considered for exemption if it utilizes existing data that is recorded in a way that participants cannot be identified. Our study falls into this category as all data from Truven Health Analytics MarketScan is deidentified.

Moreover, we will apply for a Waiver of Informed Consent and Waiver of Documentation of Informed Consent based on the criteria stated in Yale University's IRB Policy 200.3 and 200.4. According to 45 CFR 46.116(d) and 45 CFR 46.117(c), research can be considered for a Waiver of Informed Consent and Waiver of Documentation of Informed Consent if it involves no more than minimal risk to the participants and if the consent form would be the only record linking the participant with the research. We will be retrospectively analyzing medical and surgical information, will have no interaction with the participants, and will not be prescribing any treatments or interventions so there will be no risk to the participants. Additionally, since we will be using deidentified data, the consent form would be the only link to patients within our study.

Although our data will be deidentified, our study will be performed in accordance with the policies and procedures of the Health Insurance Portability and Accountability Act (HIPAA) in order to ensure confidentiality. All researchers involved in this study will undergo HIPAA training prior to study onset. Moreover, all data will be stored on password-protected, encrypted servers that comply with HIPAA standards.

3.4 VARIABLES AND CONFOUNDERS

Our main exposure is a documented family history of ovarian cancer without a known genetic mutation for ovarian cancer, while patients without a family history of or

genetic mutation for ovarian cancer will serve as our unexposed population. The primary outcome will be the proportion of patients of each group that underwent BS for sterilization compared to BTL, which is operationalized as a dichotomous variable. We will also identify potential confounding variables as outlined in Chapter 2.8. Dichotomous confounding variables include insurance type (public vs private), surgical setting (inpatient vs outpatient), and location of residence (urban vs rural). Nominal confounding variables include sterilization opportunity (at the time of CD, postpartum, or interval), gynecologic diagnoses, and region of residence. Lastly, age, a continuous variable, and year of surgery, an ordinal variable, are also potential confounders.

3.5 DATA COLLECTION

As described in Section 3.2, data collection will consist of a review of an insurance claims database using ICD-10, ICD-9, and CPT codes. First, bilateral sterilization procedures that occurred between 2011 and 2019 will be identified. Procedures will be excluded if the patient was younger than 18 years of age or older than 50 years of age. Partial or unilateral sterilizations will be excluded. Additionally, sterilizations will be excluded if they were performed at the same time as any procedure except CD. Once all appropriate sterilizations are identified, we will assess family history status. Sterilizations will then be distributed into groups based on the patient's family history status (with or without ovarian cancer family history).

3.6 SAMPLE SIZE CALCULATION

We utilized *Power and Precision* Version 4.0 (BioStat Inc.) to calculate the sample size that is required for our results to be appropriately powered and reach statistical significance (Appendix D). The results of Karia et al.[1] were used to estimate

our expected effect size. The authors examined if a family history of breast and/or ovarian cancer was a predictor of BS uptake. They found that the proportion of patients with a family history of breast and/or ovarian cancer that underwent BS for sterilization was 0.07. On the other hand, the proportion of patients without a family history or genetic mutation for breast and/or ovarian cancer that underwent BS for sterilization was 0.04. The methods of Karia et al.[1] are similar to ours although we will be excluding patients with a family history of breast cancer. Thus, given the assumed effect size of 0.03 and an alpha of 0.05 (95% CI), we will need a total of 1428 patients in order to yield a statistical power of 0.8. Thus, we will need to include 714 patients with a family history of ovarian cancer and 714 patients without a family history that underwent sterilization during the study period.

3.7 ANALYSIS

Demographics and other variables that describe the study sample will be analyzed with a Student t-test for continuous variables, Wilcoxon rank sum test for ordinal variables, and Chi squared test for categorical variables. The primary outcome will be analyzed with a Chi squared test. The proportion of BS for sterilization will be calculated for each year during the study period and compared using a Chi squared test. Data will be further stratified by sterilization opportunity and compared similarly. We will evaluate change in uptake of salpingectomy prior to the release of the SGO practice guideline in 2013 and after guideline release by calculating the collective proportion of BS between 2011-2013 and between 2014-2019 then comparing the two results using a Chi squared test. Outcomes will be adjusted for age, insurance type, surgical setting, timing of surgery, gynecologic diagnoses, region of residence, and location of residence using

multiple logistic regression. A multiple logistic regression model will also be utilized to determine if any potential confounder that we have identified is a predictor of BS use in our population. Statistical significance will be defined by $p < 0.05$.

3.8 TIMELINE AND RESOURCES

We anticipate that the proposed study will be performed over 10 to 12 months. The initial phase of the study, which includes IRB submission and data collection, will take about six months. We anticipate that the process of data collection will take a moderate amount of time due to the nature of using a large national database. Data analysis will be carried out in about two to three months. Lastly, we will prepare and edit the final manuscript during a two- to three-month period.

The principal investigator (PI) will be Elena Ratner, MD, and the co-PI will be Shera Shevin, PA-SII. The PI will be responsible for project oversight and manuscript editing. Co-PI Shevin will be responsible for data collection, data analysis, manuscript preparation, and manuscript editing. In addition, we anticipate requiring the help of two research assistants during the data collection phase of the study and one statistician during the data analysis phase.

REFERENCES

1. Karia PS, Joshu CE, Visvanathan K. Uptake and Predictors of Opportunistic Salpingectomy for Ovarian Cancer Risk Reduction in the United States. *Cancer Prevention Research.* 2021;14(12):1101-1110.

CHAPTER 4 – CONCLUSION

4.1 ADVANTAGES AND DISADVANTAGES

It is our understanding that this will be the first study of its kind to examine uptake of BS among patients with a documented ovarian cancer family history but without a known genetic mutation for ovarian cancer. Additionally, our study has the notable advantage of addressing BS in both inpatient and outpatient settings, and among patients with Medicaid and private, employer-based health insurances.

McAlpine et al.[1] and Karia et al.[2] were the only authors described in Chapter 2.7 that included both inpatient and outpatient surgical data in their samples. However, McAlpine et al.[1] did not present results stratified by surgical setting or by insurance type. Karia et al.[2] found that a majority of sterilizations occur in outpatient settings; however, their results were limited to patients with commercial, employer-based health insurance. Mandelbaum et al.[3] included patients with all kinds of insurance but restricted their sample to inpatient procedures. Therefore, our results can be generalized to a unique and wider population than other current literature. Moreover, many studies that have been published thus far, do not present data after 2016. Therefore, our study will have the benefit of presenting more recent data as knowledge of the Tubal Origin Theory has spread.

There are some limitations to our study design. First, as is true with other retrospective studies, we are limited by the data that is presented in the Truven Health Analytics MarketScan Commercial Claims and Encounters Database and Medicaid Multi-State Database. The Databases lack information regarding parity, BMI, race, income, socioeconomic status, or hospital size. However, insurance type (i.e. Medicaid or

employer-based) can be used as a proxy for income and socioeconomic status. Moreover, there is a possibility that some codes may be inaccurately reported and without a medical record to cross reference, we cannot verify the accuracy of our data.

Another limitation lies in the identification of FDRs, or for our purposes, patients with an ovarian cancer family history. In a UK study of a cohort of ovarian cancer patients, it was found that a majority of them had an incomplete or insufficient family history taken by their GP prior to their diagnosis[4]. By using retrospective, deidentified data, we are unable to verify family history data within our cohort; therefore, we will use the *documentation* of family history as our exposure. If clinicians do take a family history but do not document and code it, they are likely to forget the information by the next encounter with the patient. Thus, we can assume that they will not consider this patient's family history during preoperative counseling and the patient is effectively unexposed. On the other hand, we make the assumption that all clinicians in our sample conduct a detailed chart review for every patient, and consider their disease risk factors during patient encounters, which is likely not the case in practice. Furthermore, we assume that all providers include a diagnosis code for family history of ovarian cancer and link that code to sterilization procedures, as appropriate.

Lastly, it is important to note that patients with Medicaid are disproportionately impacted by sterilization nonfulfillment compared to patients with private insurance. This is due, in part, to a policy regarding sterilization that is unique to Medicaid. In response to a eugenics movement in the 1970s, a federal policy arose that mandates a specific Title XIX consent form must be signed preoperatively. The problem lies in that the policy also requires a waiting period between the signing of the consent form and the performance of

sterilization[5]. Our study cannot examine sterilization fulfillment because it will not measure intent or desire for sterilization. Therefore, we will need to examine our results regarding patients with Medicaid with caution.

4.2 CLINICAL AND PUBLIC HEALTH SIGNIFICANCE

By examining our unique population, we can make inferences about clinicians' preoperative counseling for patients desiring sterilization. If there is greater uptake of BS among patients in our exposed group compared to the unexposed group, we could deduce that clinicians are likely considering a patient's EOC risk status during preoperative counseling and educating them about the risk reducing potential of BS. Therefore, patients with an intermediate EOC risk would have access to a potential method for surgical risk reduction that they did not have prior to 2013.

However, even if our results do not confirm our hypothesis, they will still have a beneficial effect on clinical practice. If we find that there is no difference in the uptake of BS between patients with a documented family history of ovarian cancer and those without, this will alert clinicians to a necessary change in clinical practice. In fact, it would confirm the need for dedicated risk reducing strategies and guidelines for FDRs, and indicate the need for increased patient and provider education.

REFERENCES

1. McAlpine JN, Hanley GE, Woo MMM, et al. Opportunistic salpingectomy: Uptake, risks, and complications of a regional initiative for ovarian cancer prevention. *American Journal of Obstetrics and Gynecology*. 2014;210(5):471.e471-471.e411.
2. Karia PS, Joshu CE, Visvanathan K. Uptake and Predictors of Opportunistic Salpingectomy for Ovarian Cancer Risk Reduction in the United States. *Cancer Prevention Research.* 2021;14(12):1101-1110.
3. Mandelbaum RS, Matsuzaki S, Sangara RN, et al. Paradigm shift from tubal ligation to opportunistic salpingectomy at cesarean delivery in the United States. *American Journal of Obstetrics and Gynecology.* 2021;225(4):399.e391-399.e332.
4. Lanceley A, Eagle Z, Ogden G, et al. Family history and women with ovarian cancer: is it asked and does it matter?: An observational study. *Int J Gynecol Cancer.* 2012;22(2):254-259.
5. Arora KS, Wilkinson B, Verbus E, et al. Medicaid and fulfillment of desired postpartum sterilization. *Contraception.* 2018;97(6):559-564.

APPENDICES

APPENDIX A

Inclusion Criteria. Adapted from Karia et al.[1], and Levy et al.[2]. ICD = International Classification of Diseases; CPT = Current Procedural Terminology.

Description	ICD-10 Code	ICD-9 Code	CPT Code
Family history of malignant neoplasm of ovary	Z80.41	V16.41	--
Encounter for prophylactic removal of fallopian tube(s)	Z40.03	V50.49	--
Encounter for sterilization	Z30.2	V25.2	--
Bilateral tubal ligation (includes postpartum after vaginal delivery and at the time of cesarean delivery)	Z98.51, 0UL7*, 0U57*, 0UB7*	V26.51, 66.2x, 66.3x	58565, 58600, 58605, 58611, 58615, 58670, 58671
Bilateral salpingectomy	0UT7*	66.51	58700, 58661 (with Z30.2)
Cesarean delivery	O82, 10D00Z0, 10D00Z1, 10D0072	74.0, 74.1, 74.2	59510, 59514, 59515, 59618, 59620, 59622
Vaginal delivery with or without instrumentation	O80, 10D07Z3, 10D07Z4, 10D07Z5, 10D07Z6, 10D07Z8	650, 72.0, 72.2x, 72.3x, 72.5x, 72.7x, 72.8, 72.9	59400, 59409, 59410, 59610, 59612, 59614

APPENDIX B

Exclusion criteria. Adapted from Karia et al.[1], and Levy et al.[2]. ICD = International Classification of Diseases; CPT = Current Procedural Terminology.

Description	ICD-10 Code	ICD-9 Code	CPT Code
Genetic susceptibility to malignant neoplasm of ovary	Z15.02	V84.02	--
Genetic susceptibility to malignant neoplasm of breast	Z15.01	V84.01	--
Family history of breast cancer	Z80.3	V16.3	--
Family history of carrier of genetic disease	Z84.81	V18.9	--
Personal history of ovarian cancer	Z85.43	V10.43	--
Personal history of malignant neoplasm of genital organs	Z85.40, Z85.41, Z85.42, Z85.44	V10.40, V10.41, V10.42, V10.44	--
Personal history of malignant neoplasm of breast	Z85.3	V10.3	--
Neoplasm of uncertain/unspecified behavior of female GU system (including ovary)	D39.1x, D39.8, D49.59	236.0, 236.1, 236.2, 236.3	--
Malignant neoplasm of fallopian tubes, surrounding	C57.x, C79.82	184.x	--

ligaments, adnexa, and other female genital organs			
Malignant neoplasm of vulva	C51.x, N90.1	184.4	--
Malignant neoplasm of vagina	C52, N89.1	184.0	--
Malignant neoplasm of cervix uteri	C53.x	180.x	--
Malignant neoplasm of corpus uteri	C54.x, C55	179.x, 182.x	--
Malignant neoplasm of ovary	C56.x, C79.6x	183.x	--
Malignant neoplasm of breast	C50.x, C79.81	174.x	--
Encounter for prophylactic removal of ovary(s)	Z40.02	V50.42	--
Salpingitis and hydrosalpinx	N70.x, N71.x, N72.x,	614.x	--
Pelvic inflammatory disease	N73.x, N74.x	614.9, 615.x, 616.0, 616.9,	
Ectopic pregnancy	O08.x, O00.x	633.x, 639.x	--
Hysterectomy (subtotal, total, or radical via abdominal, vaginal, or laparoscopic routes)	0UT9*	68.3x, 68.4x, 68.5x, 68.6x, 68.7x, 68.9	58541, 58543, 58550, 58553, 58570, 58572, 58260, 58267, 58270, 58275, 58280, 58290, 58294, 58285, 58150, 58180, 58152, 58200, 58210, 58953, 58954, 58957, 58958, 59525, 58240
Bilateral or unilateral oophorectomy; bilateral or unilateral salpingo-oophorectomy	0UT0*, 0UT1*, 0UT2*	65.3x, 65.4x, 65.5x, 65.6x	58720, 58940, 58943, 58950, 58951, 58592, 58956, 58571, 58552, 58573, 58262, 58263, 58542, 58554, 58544, 58291, 58292, 58548, 58661, 58575, 58952
Unilateral salpingectomy	0UT5*, 0UT6*	66.4, 66.52	--
Unilateral tubal ligation	0U55*, 0U56*, 0UL5*, 0UL6*	66.92	--
Bilateral or unilateral partial salpingectomy	0UB50ZZ, 0UB53ZZ, 0UB54ZZ, 0UB57ZZ, 0UB58ZZ, 0UB60ZZ, 0UB63ZZ, 0UB64ZZ, 0UB67ZZ, 0UB68ZZ, 0UB70ZZ, 0UB73ZZ, 0UB74ZZ, 0UB77ZZ, 0UB78ZZ	66.63, 66.69	--
Salpingectomy with or without removal of ectopic pregnancy	10T2* with 0UB5*, 10T2* with 0UB6*	66.62, 74.3	59120, 59121, 59130, 59136,

			59140, 59150, 59151

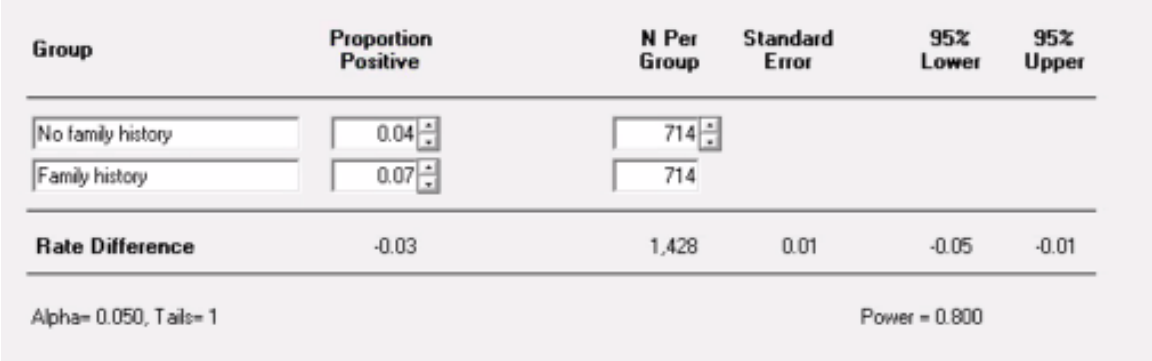
APPENDIX C

Notable Identifiers. Adapted from Karia et al.[1] ICD = International Classification of Diseases; CPT = Current Procedural Terminology.

Description	ICD-10 Code	ICD-9 Code	CPT Code
Cesarean delivery	O82, 10D00Z0, 10D00Z1, 10D0072	74.0, 74.1, 74.2	59510, 59514, 59515, 59618, 59620, 59622
Vaginal delivery with or without instrumentation	O80, 10D07Z3, 10D07Z4, 10D07Z5, 10D07Z6, 10D07Z8	650, 72.0, 72.2x, 72.3x, 72.5x, 72.7x, 72.8, 72.9	59400, 59409, 59410, 59610, 59612, 59614
Dysmenorrhea	N94.4, N94.5, N94.6	625.3	--
Endometriosis	N80.x	617.x	--
Abnormal menstruation/bleeding	N91.0, N91.1, N91.2, N91.5, N92.x, N93.0, N93.8, N93.9, N95.x	626.x, 627.x	--
Uterine fibroids	D25.x	218.x	--
Benign neoplasms and cysts	D21.5, D26.x, D27.x, D28.x, Q50.4, Q50.5, N83.0x, N83.1x N83.2x, N84.0, N84.9	215.6, 219.x, 220, 221.x, 620.0, 620.1x, 620.2x, 621.0, 752.11	--
Pelvic organ prolapse	N81.x	618.x	--
Hydrosalpinx	N70.91	614.1	--
Tubo-ovarian abscess	N70.93	614.2	--

APPENDIX D

Sample size calculation using *Power and Precision* Version 4.0 (BioStat Inc.).



REFERENCES

1. Karia PS, Joshu CE, Visvanathan K. Uptake and Predictors of Opportunistic Salpingectomy for Ovarian Cancer Risk Reduction in the United States. *Cancer Prevention Research.* 2021;14(12):1101-1110.
2. Levy D, Casey S, Zemtsov G, Whiteside JL. Salpingectomy versus Tubal Occlusion for Permanent Contraception during Cesarean Delivery: Outcomes and Physician Attitudes. *J Minim Invasive Gynecol.* 2021;28(4):860-864.

BIBLIOGRAPHY

1. Alexandre M, Black J, Whicker M, Minkin MJ, Ratner E. The management of sexuality, intimacy, and menopause symptoms (SIMS) after prophylactic bilateral salpingo-oophorectomy: How to maintain sexual health in "previvors". *Maturitas.* 2017;105:46-51.
2. Anderson CK, Wallace S, Guiahi M, Sheeder J, Behbakht K, Spillman MA. Risk-reducing salpingectomy as preventative strategy for pelvic serous cancer. *Int J Gynecol Cancer.* 2013;23(3):417-421.
3. Andrews L, Mutch DG. Hereditary Ovarian Cancer and Risk Reduction. *Best Pract Res Clin Obstet Gynaecol.* 2017;41:31-48.
4. Anonymous. ACOG Committee Opinion No. 774: Opportunistic Salpingectomy as a Strategy for Epithelial Ovarian Cancer Prevention. *Obstetrics & Gynecology.* 2019;133(4):e279-e284.
5. Arora KS, Wilkinson B, Verbus E, et al. Medicaid and fulfillment of desired postpartum sterilization. *Contraception.* 2018;97(6):559-564.
6. Arts-de Jong M, Harmsen MG, Hoogerbrugge N, Massuger LF, Hermens RP, de Hullu JA. Risk-reducing salpingectomy with delayed oophorectomy in BRCA1/2 mutation carriers: Patients' and professionals' perspectives. *Gynecologic Oncology.* 2015;136(2):305-310.
7. Balsarkar G. Opportunistic Salpingectomy as an Ovarian Cancer Primary Prevention Strategy. *Journal of Obstetrics & Gynaecology of India.* 2017;67(4):243-246.
8. Baltus T, Brown J, Kapurubandara S. A retrospective cohort study of tubal occlusion or salpingectomy for permanent contraception in Australia. *Australian and New Zealand Journal of Obstetrics and Gynaecology.* 2021.
9. Bankhead CR, Collins C, Stokes-Lampard H, et al. Identifying symptoms of ovarian cancer: a qualitative and quantitative study. *Bjog.* 2008;115(8):1008-1014.
10. Barrow E, Hill J, Evans DG. Cancer risk in Lynch Syndrome. *Fam Cancer.* 2013;12(2):229-240.
11. Boerner T, Long Roche K. Salpingectomy for the Risk Reduction of Ovarian Cancer: Is It Time for a Salpingectomy-alone Approach? *Journal of Minimally Invasive Gynecology.* 2021;28(3):403-408.
12. Bonadona V, Bonaïti B, Olschwang S, et al. Cancer risks associated with germline mutations in MLH1, MSH2, and MSH6 genes in Lynch syndrome. *Jama.* 2011;305(22):2304-2310.
13. Callahan RL, Kopf GS, Strauss JF, 3rd, Tworoger SS. Tubal contraception and ovarian cancer risk: a global view. *Contraception.* 2017;95(3):223-226.
14. Castellano T, Zerden M, Marsh L, Boggess K. Risks and Benefits of Salpingectomy at the Time of Sterilization. *Obstetrical & Gynecological Survey.* 2017;72(11):663-668.
15. Catanzarite T, Eskander RN. Opportunistic Salpingectomy at the Time of Urogynecologic Surgery: Why, in Whom, and How? *Female Pelvic Medicine & Reconstructive Surgery.* 2020;26(6):401-406.

16. Chandrasekaran D, Menon U, Evans G, et al. Risk reducing salpingectomy and delayed oophorectomy in high risk women: views of cancer geneticists, genetic counsellors and gynaecological oncologists in the UK. *Fam Cancer.* 2015;14(4):521-530.
17. Chen J, Cox S, Kuklina EV, Ferre C, Barfield W, Li R. Assessment of Incidence and Factors Associated With Severe Maternal Morbidity After Delivery Discharge Among Women in the US. *JAMA Netw Open.* 2021;4(2):e2036148.
18. Childers CP, Childers KK, Maggard-Gibbons M, Macinko J. National Estimates of Genetic Testing in Women With a History of Breast or Ovarian Cancer. *J Clin Oncol.* 2017;35(34):3800-3806.
19. Clark NV, Endicott SP, Jorgensen EM, et al. Review of Sterilization Techniques and Clinical Updates. *Journal of Minimally Invasive Gynecology.* 2018;25(7):1157-1164.
20. Creinin MD, Zite N. Female tubal sterilization: the time has come to routinely consider removal. *Obstetrics & Gynecology.* 2014;124(3):596-599.
21. Crum CP, Drapkin R, Miron A, et al. The distal fallopian tube: a new model for pelvic serous carcinogenesis. *Curr Opin Obstet Gynecol.* 2007;19(1):3-9.
22. Danis RB, Della Badia CR, Richard SD. Postpartum Permanent Sterilization: Could Bilateral Salpingectomy Replace Bilateral Tubal Ligation? *Journal of Minimally Invasive Gynecology.* 2016;23(6):928-932.
23. Darelius A, Kristjansdottir B, Dahm-Kahler P, Strandell A. Risk of epithelial ovarian cancer Type I and II after hysterectomy, salpingectomy and tubal ligation-A nationwide case-control study. *International Journal of Cancer.* 2021;149(8):1544-1552.
24. Dilley SE, Havrilesky LJ, Bakkum-Gamez J, et al. Cost-effectiveness of opportunistic salpingectomy for ovarian cancer prevention. *Gynecologic Oncology.* 2017;146(2):373-379.
25. Ely LK, Truong M. The Role of Opportunistic Bilateral Salpingectomy vs Tubal Occlusion or Ligation for Ovarian Cancer Prophylaxis. *Journal of Minimally Invasive Gynecology.* 2017;24(3):371-378.
26. Falconer H, Yin L, Grönberg H, Altman D. Ovarian cancer risk after salpingectomy: A nationwide population-based study. *Journal of the National Cancer Institute.* 2015;107(2).
27. Ferrari F, Forte S, Prefumo F, Sartori E, Odicino F. Opportunistic salpingectomy during postpartum contraception procedures at elective and unscheduled cesarean delivery. *Contraception.* 2019;99(6):373-376.
28. Flaum N, Crosbie EJ, Edmondson RJ, Smith MJ, Evans DG. Epithelial ovarian cancer risk: A review of the current genetic landscape. *Clin Genet.* 2020;97(1):54-63.
29. Gaba F, Blyuss O, Chandrasekaran D, et al. Attitudes towards risk-reducing early salpingectomy with delayed oophorectomy for ovarian cancer prevention: a cohort study. *BJOG Int J Obstet Gynaecol.* 2021;128(4):714-726.
30. Gaba F, Piek J, Menon U, Manchanda R. Risk-reducing early salpingectomy and delayed oophorectomy as a two-staged alternative for primary prevention of ovarian cancer in women at increased risk: a commentary. *Bjog.* 2019;126(7):831-839.

31. Ganer Herman H, Gluck O, Keidar R, et al. Ovarian reserve following cesarean section with salpingectomy vs tubal ligation: a randomized trial. *American Journal of Obstetrics & Gynecology.* 2017;217(4):472.e471-472.e476.
32. Garcia C, Moskowitz OM, Chisholm CA, et al. Salpingectomy Compared With Tubal Ligation at Cesarean Delivery: A Randomized Controlled Trial. *Obstet Gynecol.* 2018;132(1):29-34.
33. Gelderblom ME, IntHout J, Hermens RPMG, et al. STop OVarian CAncer (STOPOVCA) young: Protocol for a multicenter follow-up study to determine the long-term effects of opportunistic salpingectomy on age at menopause. *Maturitas.* 2022;159:62-68.
34. Gockley AA, Elias KM. Fallopian tube tumorigenesis and clinical implications for ovarian cancer risk-reduction. *Cancer Treat Rev.* 2018;69:66-71.
35. Greene MH, Mai PL, Schwartz PE. Does bilateral salpingectomy with ovarian retention warrant consideration as a temporary bridge to risk-reducing bilateral oophorectomy in BRCA1/2 mutation carriers? *Am J Obstet Gynecol.* 2011;204(1):19.e11-16.
36. Halbert CH, Kessler L, Stopfer JE, Domchek S, Wileyto EP. Low rates of acceptance of BRCA1 and BRCA2 test results among African American women at increased risk for hereditary breast-ovarian cancer. *Genet Med.* 2006;8(9):576-582.
37. Hanley GE, Kwon JS, Finlayson SJ, Huntsman DG, Miller D, McAlpine JN. Extending the safety evidence for opportunistic salpingectomy in prevention of ovarian cancer: a cohort study from British Columbia, Canada. *American Journal of Obstetrics & Gynecology.* 2018;219(2):172.e171-172.e178.
38. Hanley GE, Kwon JS, McAlpine JN, Huntsman DG, Finlayson SJ, Miller D. Examining indicators of early menopause following opportunistic salpingectomy: a cohort study from British Columbia, Canada. *American Journal of Obstetrics & Gynecology.* 2020;223(2):221.e221-221.e211.
39. Harmsen MG, IntHout J, Arts-de Jong M, et al. Salpingectomy With Delayed Oophorectomy in BRCA1/2 Mutation Carriers: Estimating Ovarian Cancer Risk. *Obstetrics & Gynecology.* 2016;127(6):1054-1063.
40. Holman LL, Friedman S, Daniels MS, Sun CC, Lu KH. Acceptability of prophylactic salpingectomy with delayed oophorectomy as risk-reducing surgery among BRCA mutation carriers. *Gynecologic Oncology.* 2014;133(2):283-286.
41. Ida T, Fujiwara H, Matsubara S, Taniguchi Y, Kohyama A. Salpingectomy for tubal sterilization at cesarean section: No extra time and no extra bleeding compared with tubal ligation. *Clinical and Experimental Obstetrics and Gynecology.* 2017;44:879-881.
42. Jervis S, Song H, Lee A, et al. A risk prediction algorithm for ovarian cancer incorporating BRCA1, BRCA2, common alleles and other familial effects. *J Med Genet.* 2015;52(7):465-475.
43. Jervis S, Song H, Lee A, et al. Ovarian cancer familial relative risks by tumour subtypes and by known ovarian cancer genetic susceptibility variants. *J Med Genet.* 2014;51(2):108-113.

44. Jones NL, Schulkin J, Urban RR, et al. Physicians' Perspectives and Practice Patterns Toward Opportunistic Salpingectomy in High- and Low-Risk Women. *Cancer Invest.* 2017;35(1):51-61.
45. Karia PS, Joshu CE, Visvanathan K. Uptake and Predictors of Opportunistic Salpingectomy for Ovarian Cancer Risk Reduction in the United States. *Cancer Prevention Research.* 2021;14(12):1101-1110.
46. Kim AJ, Barberio A, Berens P, et al. The Trend, Feasibility, and Safety of Salpingectomy as a form of Permanent Sterilization. *Journal of Minimally Invasive Gynecology.* 2019;26(7):1363-1368.
47. Kwon JS, McAlpine JN, Hanley GE, et al. Costs and benefits of opportunistic salpingectomy as an ovarian cancer prevention strategy. *Obstetrics & Gynecology.* 2015;125(2):338-345.
48. Kwon JS, Tinker A, Pansegrau G, et al. Prophylactic salpingectomy and delayed oophorectomy as an alternative for BRCA mutation carriers. *Obstet Gynecol.* 2013;121(1):14-24.
49. Kwon JS. Cost-effectiveness of Ovarian Cancer Prevention Strategies. *Clin Obstet Gynecol.* 2017;60(4):780-788.
50. La Vecchia C. Ovarian cancer: epidemiology and risk factors. *Eur J Cancer Prev.* 2017;26(1):55-62.
51. Lanceley A, Eagle Z, Ogden G, et al. Family history and women with ovarian cancer: is it asked and does it matter?: An observational study. *Int J Gynecol Cancer.* 2012;22(2):254-259.
52. Lehn K, Gu L, Creinin MD, Chen MJ. Successful completion of total and partial salpingectomy at the time of cesarean delivery. *Contraception.* 2018;98(3):232-236.
53. Levy D, Casey S, Zemtsov G, Whiteside JL. Salpingectomy versus Tubal Occlusion for Permanent Contraception during Cesarean Delivery: Outcomes and Physician Attitudes. *J Minim Invasive Gynecol.* 2021;28(4):860-864.
54. Long Roche KC, Abu-Rustum NR, Nourmoussavi M, Zivanovic O. Risk-reducing salpingectomy: Let us be opportunistic. *Cancer.* 2017;123(10):1714-1720.
55. Loveday C, Turnbull C, Ramsay E, et al. Germline mutations in RAD51D confer susceptibility to ovarian cancer. *Nat Genet.* 2011;43(9):879-882.
56. Loveday C, Turnbull C, Ruark E, et al. Germline RAD51C mutations confer susceptibility to ovarian cancer. *Nat Genet.* 2012;44(5):475-476; author reply 476.
57. Madsen C, Baandrup L, Dehlendorff C, Kjær SK. Tubal ligation and salpingectomy and the risk of epithelial ovarian cancer and borderline ovarian tumors: A nationwide case-control study. *Acta Obstetricia et Gynecologica Scandinavica.* 2015;94(1):86-94.
58. Manchanda R, Legood R, Antoniou AC, Gordeev VS, Menon U. Specifying the ovarian cancer risk threshold of 'premenopausal risk-reducing salpingo-oophorectomy' for ovarian cancer prevention: a cost-effectiveness analysis. *J Med Genet.* 2016;53(9):591-599.
59. Manchanda R, Legood R, Pearce L, Menon U. Defining the risk threshold for risk reducing salpingo-oophorectomy for ovarian cancer prevention in low risk postmenopausal women. *Gynecol Oncol.* 2015;139(3):487-494.

60. Manchanda R, Menon U. Setting the Threshold for Surgical Prevention in Women at Increased Risk of Ovarian Cancer. *International Journal of Gynecological Cancer.* 2018;28(1):34-42.
61. Mandelbaum RS, Matsuzaki S, Sangara RN, et al. Paradigm shift from tubal ligation to opportunistic salpingectomy at cesarean delivery in the United States. *American Journal of Obstetrics and Gynecology.* 2021;225(4):399.e391-399.e332.
62. McAlpine JN, Hanley GE, Woo MMM, et al. Opportunistic salpingectomy: Uptake, risks, and complications of a regional initiative for ovarian cancer prevention. *American Journal of Obstetrics and Gynecology.* 2014;210(5):471.e471-471.e411.
63. Menon U, Karpinskyj C, Gentry-Maharaj A. Ovarian Cancer Prevention and Screening. *Obstetrics & Gynecology.* 2018;131(5):909-927.
64. Minkin MJ. Menopause: Hormones, Lifestyle, and Optimizing Aging. *Obstet Gynecol Clin North Am.* 2019;46(3):501-514.
65. Naumann RW, Hughes BN, Brown J, Drury LK, Herzog TJ. The impact of opportunistic salpingectomy on ovarian cancer mortality and healthcare costs: a call for universal insurance coverage. *Am J Obstet Gynecol.* 2021;225(4):397.e391-397.e396.
66. Nebgen DR, Hurteau J, Holman LL, et al. Bilateral salpingectomy with delayed oophorectomy for ovarian cancer risk reduction: a pilot study in women with BRCA1/2 mutations. *Gynecologic oncology.* 2018.
67. Norquist BM. Challenges in the identification of inherited risk of ovarian cancer: where should we go from here? *Gynecol Oncol.* 2019;152(1):3-6.
68. Payne AB, Adamski A, Abe K, et al. Epidemiology of cerebral venous sinus thrombosis and cerebral venous sinus thrombosis with thrombocytopenia in the United States, 2018 and 2019. *Res Pract Thromb Haemost.* 2022;6(2):e12682.
69. Pearce CL, Stram DO, Ness RB, et al. Population distribution of lifetime risk of ovarian cancer in the United States. *Cancer Epidemiol Biomarkers Prev.* 2015;24(4):671-676.
70. Powell CB, Alabaster A, Simmons S, et al. Salpingectomy for Sterilization: Change in Practice in a Large Integrated Health Care System, 2011-2016. *Obstet Gynecol.* 2017;130(5):961-967.
71. Reade CJ, Finlayson S, McAlpine J, Tone AA, Fung-Kee-Fung M, Ferguson SE. Risk-reducing salpingectomy in Canada: a survey of obstetrician-gynaecologists. *J Obstet Gynaecol Can.* 2013;35(7):627-634.
72. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer Statistics, 2021. *CA: A Cancer Journal for Clinicians.* 2021;71(1):7-33.
73. Soliman AM, Surrey ES, Bonafede M, Nelson JK, Vora JB, Agarwal SK. Health Care Utilization and Costs Associated with Endometriosis Among Women with Medicaid Insurance. *J Manag Care Spec Pharm.* 2019;25(5):566-572.
74. Subramaniam A, Blanchard CT, Erickson BK, et al. Feasibility of Complete Salpingectomy Compared With Standard Postpartum Tubal Ligation at Cesarean Delivery: A Randomized Controlled Trial. *Obstet Gynecol.* 2018;132(1):20-27.

75. Subramaniam A, Einerson BD, Blanchard CT, et al. The cost-effectiveness of opportunistic salpingectomy versus standard tubal ligation at the time of cesarean delivery for ovarian cancer risk reduction. *Gynecol Oncol.* 2019;152(1):127-132.
76. Swanson CL, Bakkum-Gamez JN. Options in Prophylactic Surgery to Prevent Ovarian Cancer in High-Risk Women: How New Hypotheses of Fallopian Tube Origin Influence Recommendations. *Curr Treat Options Oncol.* 2016;17(5):20.
77. Swanson CL, Bakkum-Gamez JN. Preventing Ovarian Cancer in High-risk Women: One Surgery at a Time. *Clin Obstet Gynecol.* 2020;63(1):64-73.
78. Tanne JH. US cancer groups highlight symptoms of early ovarian cancer. *BMJ.* 2007;334(7607):1290-1291.
79. Tschernichovsky R, Goodman A. Risk-Reducing Strategies for Ovarian Cancer in BRCA Mutation Carriers: A Balancing Act. *Oncologist.* 2017;22(4):450-459.
80. Venkatesh KK, Clark LH, Stamilio DM. Cost-effectiveness of opportunistic salpingectomy vs tubal ligation at the time of cesarean delivery. *Am J Obstet Gynecol.* 2019;220(1):106.e101-106.e110.
81. Yang X, Desai K, Agrawal N, et al. Characteristics, treatment patterns, healthcare resource use, and costs among pediatric patients diagnosed with neurofibromatosis type 1 and plexiform neurofibromas: a retrospective database analysis of a medicaid population. *Curr Med Res Opin.* 2021;37(9):1555-1561.