THE EFFECT OF UTERINE SEPTUM RESECTION ON FERTILITY AND LIVE BIRTH RATES

by © Karen Splinter (Thesis) submitted to the School of Graduate Studies in partial fulfillment of the requirements for the degree of

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Abstract

Objectives: To determine if patients who undergo a hysteroscopic uterine septum resection have higher live birth rates than patients with a normal hysteroscopy and unexplained infertility.

Study Methods: Using surgical billing records from Newfoundland and Labrador Fertility Services, a cohort of patients undergoing hysteroscopic uterine septum resection from October 2003 to June 2011 were identified. The study patients were matched with the next four patients from Newfoundland and Labrador Fertility Services undergoing a diagnostic hysteroscopy who had otherwise unexplained infertility. The patients were followed from surgery for at least one year to determine if they had a pregnancy and the outcome of that pregnancy. Both groups included patients with primary infertility, secondary infertility, and recurrent pregnancy loss. The primary outcome was live birth rate, with a p value <0.05 defining statistical significance. Secondary outcomes included pregnancy rate, preterm birth rate, and markers of obstetric and neonatal morbidity; with p value <0.01 defining statistical significance.

Results: A total of 50 eligible patients underwent hysteroscopic uterine septum resection (SR) during the specified timeline and were matched with 189 patients who had a diagnostic hysteroscopy (DH) for unexplained infertility. The groups were similar in age, BMI, years trying to conceive and surgeon. Univariate analysis demonstrated a significant difference in live birth rates between the groups (52.0% (SR) compared with 33.3% (DH), RR 1.56 [1.12-2.18], p=0.015). Subgroup analysis demonstrated a significant different in live birth rates between the secondary infertility group (66.7% (SR) compared with 32.4% (DH), RR 2.06 [1.22-3.47], p=0.023). Logistic regression analysis also found a higher live birth rate in the SR group (OR 2.35 [1.17-4.74], p=0.016). Postoperative pregnancy rates were higher in the SR group (72.0% compared with 41.2%, RR 1.74 (1.38-2.21), p<0.001), and this finding was confirmed by logistic regression (OR 3.78 [1.80-7.93], p<0.001). The SR group had a higher proportion of patients with risk factors for preterm delivery (29.6% compared with 10.8%, p=0.035) and composite neonatal morbidity (11.5% compared with 6.5%, p=0.029); but these differences did not meet statistical significance for secondary outcomes. Of live births, there was no significant difference in rate of preterm birth between the two groups (10.8% compared with 6.1%, p=0.37) or gestational age at delivery (268 days compared with 274 days, p=0.10).

Conclusions: Hysteroscopic uterine septum resection may result in higher pregnancy rates and live births in patients with infertility, compared to patients undergoing a diagnostic hysteroscopy for unexplained infertility.

Keywords

Metroplasty, Uterine Septum, Hysteroscopic Uterine Septum Resection, Infertility, Preterm Birth, Pregnancy, Live Birth

General Summary

The purpose of this research was to determine if patients with a uterine septum experience better pregnancy outcomes after surgical treatment, compared to other patients who had a normal uterus but were experiencing infertility with no obvious cause identified (unexplained infertility). Patients with surgical correction of a uterine septum were more likely to become pregnant postoperatively (72.0 % vs 41.2%) and have a live birth (52.0% vs. 33.3%).

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No funding was directly received to support this research project. The majority of the project was completed concurrently during my residency program at Memorial University of Newfoundland. However, the Department of Obstetrics and Gynecology financially supported my travel to present the preliminary results at various conferences and resident research days.

The design of this research project does not consider publications from the last decade. This research project was started in July 2007 as I began my Obstetrics &

Gynecology residency training at Memorial University of Newfoundland. Data collection finished before I graduated from the program and preliminary results were presented at a national conference in June 2012. I naively hoped to complete the final data analysis and chapters of my thesis before beginning my clinical practice in northern Ontario. Unfortunately, setting up a new practice stole my attention, and the project was unfinished in 2012. I then experienced multiple health concerns and maternity leave, but gradually the final draft, with the exhaustive help and support of my supervisors, was completed in 2022. Although the literature review was updated in 2021, some of the clinical decisions presented in the study design and the standard of care for fertility patients at our center from 2007-2012 may now seem out of date from current practices. Wherever possible, I have tried to comment on relevant changed to best practices.

Finally, I must express my very profound gratitude to my family for providing me with unfailing support and continuous encouragement throughout my years of study and through the process of researching and writing this thesis. This accomplishment would not have been possible without them.

Thank you.

Karen Splinter

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List of Abbreviations

ART	assisted reproductive technologies
BMI	body mass index
DH	diagnostic hysteroscopy (control group)
hCG	human chorionic gonadotropin
HSG	hysterosalpingogram
IUGR	intrauterine growth restriction
IUI	intrauterine insemination
IVF	in vitro fertilization
MeSH	medical subject headings
MRI	magnetic resonance imaging
NICU	neonatal intensive care unit
OBGYN	obstetrician and gynecologist
PPROM	preterm premature rupture of membranes
REI	reproductive endocrinology and infertility
SIS	saline sonohysterogram
SR	septum resection (study group)
TPTL	threatened preterm labour
TVUS	transvaginal ultrasonography

Chapter 1: Introduction

1.1 The Problem

1.1.1. Infertility

Infertility is defined as the failure to become pregnant after 12 months of regular, unprotected intercourse and affects 10-15% of couples [1]. The term "subfertility" can be used to describe couples with decreased fecundability but who do not fulfill the definition of infertility [1].

The prevalence of infertility is increasing. The 2009-2010 Canadian Community Health Survey estimated the prevalence of infertility among Canadian couples (female partner age 18 to 44) to be between 11.5-15.7% [2]. This is a dramatic increase from previous estimates of 5.4% reported in the Canadian Fertility Survey in 1984 [3] and 8.5% reported in the Royal Commission on New Reproductive Technologies in 1993 [4]. This rise is likely multifactorial and can be attributed to environmental factors, lifestyle changes and overall health, but the primary reason is likely advancing maternal age at time of attempting first pregnancy. The proportion of first-born children to patients with "advanced maternal age" (greater than or equal to 35 years old) increased from 3% in

1985 to 11% in 2008 [5]. As more persons attend postsecondary education and work full-time there is a trend towards later childbearing.

The definition of infertility after 1 year of unprotected intercourse relates to fecundability. The likelihood of conceiving a pregnancy each cycle (fecundability) is 20-25% across all age groups [1]. Historical data has shown that 50% of couples will achieve pregnancy in 3 months, 75% in 6 months and 85% or more within 1 year [6]. This data, however, relates to young, healthy couples. Guttmacher reviewed epidemiological data from Hutterite communities in 1940-1950s [6]. These traditional, religious communities were prosperous farmers with no need to limit birth rates or family size for fear of malnutrition or starvation. The subjects married on average at age 22 and often had completed their first pregnancy by age 23 [6]. Social factors and lifestyle impediments were also uncommon, as their diet was plentiful and nutritious, obesity was rare and sexually transmitted infections (STI) relatively non-existent in the devout, monogamous community. Infertility in this population was only 3.4% [6]. Although this population no longer represents the average modern couple, the fecundability calculated from this Hutterite community remains the benchmark for fertility counselling.

The fecundability and fecundity of a couple will naturally decrease with advancing age. This is caused by many factors, including decreased quantity and quality of oocytes and increased risk of spontaneous abortion and ectopic pregnancy [1]. The likelihood of tubal damage will increase with age due to a cumulative lifelong risk of exposure to sexually transmitted infections. The incidence of co-morbidities such as diabetes, obesity and hypertension, as well as the additive exposure of environmental factors including smoking, alcohol, marijuana and other household and personal chemicals may further contribute to the age-related fertility decline [1]. Education on the effects of ageing, and healthy lifestyle on reproduction, is an important adjunct to address the declining fertility in our society.

Infertility can have a significant impact on the physical, emotional and financial well-being of patients. Infertility can have psychological effects similar to a diagnosis of cancer or heart disease [7]. Infertility also has a societal impact. It has been linked to depression, marital discord, reduced job performance and social isolation. The cost of diagnosing and treating infertility in the USA exceeds $5 billion USD per year [8].

The etiology of infertility can be diverse but is often thought of in four broad categories [1]. The cause can be related to the female partner, male partner, a combination of both partners or is unexplained. Infertility can also be further categorized into primary infertility (never been pregnant) and secondary infertility (previously achieved a pregnancy, including miscarriages). The etiology of infertility can be different in couples who have primary infertility, those who have had a successful term delivery and those with frequent miscarriages (recurrent pregnancy loss) [1]. Traditionally this categorization has helped guide investigations into causes of infertility. Diagnoses for many couples overlap, so many centers employ a standardized approach for infertility investigations for all couples, regardless of the reproductive history. This approach would include assessment for ovulation, ovarian reserve (egg quality and quantity), semen analysis (assessment of sperm quality and quantity) and documentation fallopian tubal patency.

The traditional (or most common at the time of the study) test for tubal patency is the hysterosalpingogram (HSG) [1]. HSG can also suggest internal defects of the uterine cavity, such as a uterine septum, other Mullerian anomalies, large submucosal fibroids or polyps. It is a relatively inexpensive test and does not require sedation or operating room time. However, in the event tubal blockage or a uterine filling defect is diagnosed, patients will need to proceed with further investigations. These can include imaging studies such as a 3D trans-vaginal ultrasound, a saline sonohysterogram (SIS) or magnetic resonance imaging (MRI) or laparoscopy/hysteroscopy.

Direct visualization of the uterine cavity with hysteroscopy is not a first line investigation [1]. A uterine septum might be viewed or suspected during testing for fallopian tubal patency but could easily be undiagnosed. Access to MRI is limited and costly. In 2007, 3D ultrasound was not available at our center. Patients with a uterine septum would most characteristically present with recurrent pregnancy loss, but these patients can also present with primary infertility or secondary infertility after a healthy term pregnancy. For this reason, at the time of study design, our center offered diagnostic hysteroscopy to many patients with unexplained primary and secondary infertility after initial routine investigations, not just those with a high likelihood of a uterine defect. Only those patients with otherwise unexplained infertility (i.e. all other investigations were within normal limits) were included in the study.

During the study period, patients with evidence of a uterine septum on imaging were offered surgical management as the standard of care. This surgical procedure could concurrently confirm the diagnosis of a uterine septum and treat the problem by removing the septum during the operation. From 2003 to 2012 if a patient at our centre had evidence of a uterine septum on imaging, she was counselled on the pregnancy implications and recommended to have treatment. Typically, an MRI was performed to distinguish a bicornuate uterus from a septate uterus before hysteroscopic septum resection was offered. The majority of patients proceeded with a hysteroscopic uterine septum resection with or without a laparoscopic assessment for other causes of subfertility.

Patients with unexplained infertility who have evidence of ovulation, appropriate semen analysis and tubal patency but are still unable to conceive with superovulation and intrauterine insemination (IUI) treatment may undergo an operative assessment of the uterine cavity with a diagnostic hysteroscopy. An HSG is only 46-53% sensitive and 87-95% specific for diagnosing tubal pathology [9]. Surgical assessment can be done as outpatient procedure with a hysteroscopy and/or laparoscopy to investigate any other pathology that might be contributing to their infertility, such as adhesions or endometriosis. None of the standard baseline investigations for fertility will rule out endometriosis, a cause attributed to 25% to 50% of infertile patients [10,11]. Operative assessment was more frequent in our centre since Newfoundland and Labrador did not offer in vitro fertilization (IVF) in the province. Before couples embark on the expense and time commitment to travel out of province for IVF, every effort is made to maximize their potential for success.

1.1.2. Müllerian Anomalies

Müllerian defects arise from errors in embryogenesis, due to improper development of the para-mesonephric ducts [1, 12].. They have a variety of effects on fertility and obstetrical performance and are classified by the American Society of Reproductive Medicine [12].

The overall prevalence of Mullerian defects is rare, affecting about 5.5% of all patients [1, 13]. However, the incidence is higher in infertile patients (8.0%), in those with a previous pregnancy loss (13.3%) and highest in those with a history of a pregnancy loss and infertility (24.5%) [13]. Although some forms of Müllerian defects are associated with minimal obstetrical risk, others are linked to significant morbidity, including first and second trimester losses, intrauterine growth restriction (IUGR), fetal malpresentation, and preterm birth [14–20]. Fertile persons with a uterine malformation experience a greater than five-fold increase in late first-trimester and second-trimester pregnancy losses and a significantly lower live birth rate [17].

Of all Mullerian anomalies, the septate uterus is associated with the poorest reproductive outcome, with fetal survival rates of 6-28% and spontaneous abortion rates exceeding 60% [21–24]. A septate uterus results from the failure of resorption of the medial segment of the Müllerian ducts. It is the most common recognized congenital anomaly of the female reproductive tract, accounting for 80-90% of all major malformations in patients with recurrent pregnancy loss [25–27]. Diagnosis of a uterine septum is more common in the infertile population [17,25,28,29]. However, a 2016 review by the American Society for Reproductive Medicine (ASRM) determined there was insufficient evidence to conclude a uterine septum is associated with primary infertility [30].

Uterine septa are also associated with secondary infertility [31]. Approximately 15 to 25% of spontaneous abortions are thought to be caused by Müllerian fusion defects; almost all of these are associated with uterine septa [31]. Patients with recurrent pregnancy losses (multiple spontaneous abortions) have a higher incidence of uterine septa [31]. A large study of 689 patients undergoing investigations for infertility found a significant difference in prior obstetrical outcomes when compared to the general population [32]. Compared to the general population, the patients diagnosed with a uterine septum were more likely to have a history of first trimester loss (41.1% vs 12.1%) and second trimester loss (12.6% vs 6.9%) [32]. The 2016 ASRM review concluded there was fair evidence that a uterine septum contributes to miscarriage and preterm birth [30].

Surgical treatments directed at the underlying disorder can reduce obstetrical risks for specific malformations [33]. The gold standard for treatment of a uterine septum is hysteroscopic uterine septum resection or metroplasty (Figure 1) [12,30,34,35]. The hysteroscopic approach replaced the transabdominal approach near the end of the 20th century [34,36]. Hysteroscopic uterine septum resection achieves comparable efficacy to the abdominal approach, with reduced morbidity and shorter interval to conception. It also eliminates sequelae of laparotomy (specifically pelvic adhesions and transfundal uterine scar to compromise the safety of vaginal delivery) and does not reduce the volume of the uterine cavity [12,34,35].

A 2014 editorial review by Paradisi *et al.* spoke favourably on hysteroscopic resection.

> *"The aim of metroplasty is to restore a normal anatomy of the uterine cavity as a prerequisite for a positive implantation and subsequent good obstetrical outcomes. This treatment clearly demonstrates its effectiveness both in recurrent abortion and in primary unexplained infertility."* [37]
>
> *"The hysteroscopic metroplasty with its simplicity, safety, and improved reproductive outcomes has liberalized the approach to treatment. Today, hysteroscopic metroplasty is a common practice to treat septate uterus with salutary effects both in infertile patients and in patients with recurrent pregnancy loss or premature labor, especially if in-vitro fertilization is being contemplated."* [37]

However, the authors duly noted some hesitation amongst experts in the field existed due to the lack of prospective randomized controlled trials to evaluate this surgical treatment [37].

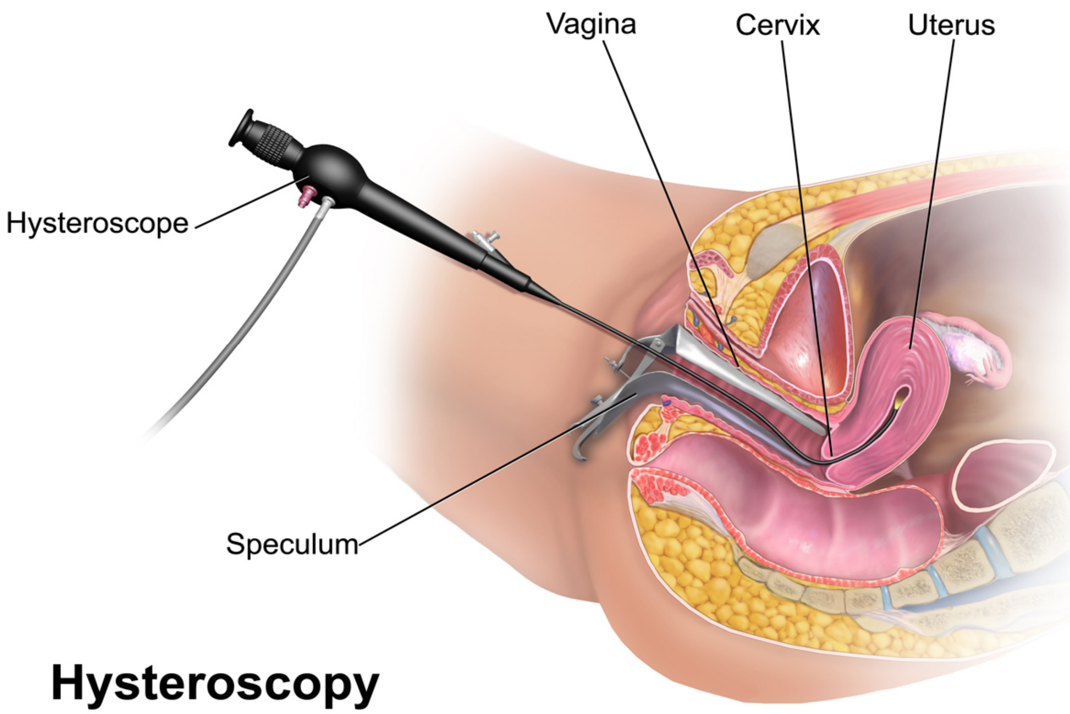

Figure 1: Hysteroscopy © Bruce Blaus / CC-BY-SA-4.0

Patients who have undergone uterine septum resection still have increased pregnancy complications, as show in previous studies. Ayhan, Yücel, Tuncer and Kisnisci published a cohort of 49 patients, resulting in 40 pregnancies [38]. A total of 22 (55%) were preterm [38]. In the study by Colacurci *et al.* involving a cohort of 69 uterine septum resection patients, 5 of 46 pregnancies (10.9%) were preterm [39]. Pabuçcu and Gomel followed 61 patients who subsequently had 25 pregnancies [40]. These resulted in 18 live births (27.8% preterm) and 7 spontaneous abortions [40]. Mollo *et al.* compared 44 patients with unexplained infertility and a uterine septum to 132 controls with unexplained infertility and normal anatomy [41]. Postoperatively, 38.6% of patients became pregnant after septum resection compared to 20.4% in the control group [41]. However, 17.6% of pregnancies were preterm in the postoperative group compared to only 3.7% in the infertility group who had no uterine surgery [41]. This difference suggests that although septum resection increases likelihood of successful pregnancy, it includes a higher risk of preterm delivery. The pathophysiology of preterm labour in postoperative hysteroscopic uterine septum resection patients remain unclear.

1.1.3. Preterm Birth

Any birth before 37 weeks 0 days gestational age is considered preterm [42]. The incidence of preterm birth in Canada has increased from 6.3% in 1983 to 7.8% in 2012 [43–46]. This rise is multifactorial, but has largely been impacted by an increase in multiple gestations (via assisted reproductive technologies (ART)), increasing comorbidities in mothers requiring indicated preterm birth (e.g. diabetes, obesity, advanced maternal age, hypertension) as well as overall improved survival and functioning of preterm infants making it a more acceptable choice to intervene and deliver preterm than several decades ago [42].

Preterm birth may be due preterm premature rupture of membranes (PPROM) (20-30%), idiopathic preterm labour (40-50%) and indicated deliveries for maternal or fetal health (20-30%) [47]. Patients with uterine anomalies (including septa) are at higher risk for preterm birth [37-40]. Patients with a history cervical instrumentation and excisional procedures are also at higher risk [48–54]. Ironically it is possible that cervical dilation with hysteroscopic resection of a uterine septum may improve the pregnancy outcome in one regard but hamper it in another.

The sequelae of preterm birth can be many [47]. Preterm infants are at risk of short-term and long-term consequences. Examples of short-term risks include death, sepsis, prolonged neonatal intensive care unit (NICU) admissions, respiratory distress syndrome, necrotizing enterocolitis, and intraventricular hemorrhage [55]. Examples of long-term risks include bronchopulmonary dysplasia, feeding difficulties, blindness, deafness, cerebral palsy and lower IQ [55]. Mortality decreases dramatically as gestational age increases [56]. The goal of preterm birth prevention involves increased survival but also decreased morbidity. The majority of significant morbidity and mortality occurs with infants born before 28 weeks' gestation [55]. Infants born in a tertiary care center after 34 weeks' gestation have survival rates of 99% [57]. Therefore, interventions to improve pregnancy outcomes should achieve a live birth, but also a healthy infant. This is most likely to occur at gestational ages above 34 weeks.

Preterm delivery also affects the parents, both in emotional stress and financial stress from lost employment hours and prolonged hospital stays [58]. The cost to the health care system is also significant, with yearly costs in Canada estimated to be up to $117,000 for a baby born weighing less than 750 grams [58].

Using the Canadian Institute for Health Information Discharge Abstract Database and Management Information Systems for 2005-2006, Lim et al. noted the average hospital cost for singleton newborns was approximately nine times higher for preterm newborns than for those born full-term [58]. Singleton newborns born at extremely preterm gestational ages (<28 weeks) had the highest average cost ($84,235 CAD) and stayed in the hospital an average of 40 times longer than singletons born at full-term [58].

Many attempts have been made over the years to develop screening tests and interventions to reduce the incidence of preterm birth. These include medications, surgical procedures and lifestyle changes [46-53]. In this study, many patients were followed in pregnancy with serial transvaginal ultrasonographic (TVUS) assessment of cervical length. A few patients received a cervical cerclage. Other commonly used methods employed to prevent preterm birth include progesterone therapy (intramuscular or intravaginal), bed rest, screening and treatment of bacterial vaginosis and interpregnancy surgeries to remove uterine pathology such as a uterine septum or fibroid [46].

1.1.3.1. Transvaginal Ultrasonographic Assessment of Cervical Length

Cervical length in pregnancy remains relatively stable from 10 to 24 weeks' gestation and then gradually decreases for most patients as pregnancy progresses, with a more rapid shortening from 33 to 38 weeks [59]. The routine measurement of all patients' cervical lengths in pregnancy was not recommended at the time of this study, but in patients with identified risk factors TVUS cervical length assessment may be useful. The average cervical length at 24 weeks' gestation is 34-35 mm [60–62]. If cervical length is greater than 25 mm after 24 weeks', preterm birth is less likely [63]. There is no consensus on the frequency and duration of TVUS cervical length assessment. Some centers will begin as early as 16 weeks' gestational age, some will do it at the routine anatomy scan (18-20 weeks) and some as the fetus approaches viability (24 weeks) [47-53]. Some patients can undergo a rapid change in cervical length and some patients will present with a shortened cervical length but remain stable until labour begins weeks or months later [49, 51]. The goal of TVUS assessment of cervical length is to identify patients at increased risk and offer a therapy to reduce their risk [46-53]. Therapies offered include progesterone and cerclage [64]. If recognized early enough, identifying patients at a significant increased risk for preterm birth within the next week will allow for administration of antenatal steroids, to improve fetal lung maturity and reduce other neonatal morbidities [65].

1.1.3.2. Cerclage

A cervical cerclage refers to a surgical procedure to mechanically reinforce the cervix, using sutures or synthetic tape [66]. This is most often done with a transvaginal approach at the end of the first trimester or beginning of the second , but can also be done transabdominally or laparoscopically outside of pregnancy [66]. Some patients will also have TVUS cervical length assessment and have a transvaginal cerclage placed if cervical shortening is documented [53, 65]. A “rescue” cerclage can also be placed if a patient presents urgently with cervical incompetence (painless premature cervical dilation) discovered on examination [53, 65]. Placement of cerclage can be associated with risks including failed procedure, infection, bleeding, premature rupture of membranes, cerclage displacement, and preterm labour leading to miscarriage and preterm birth [67–69].

1.1.3.3. Progesterone

Progesterone is thought to aid in preventing preterm birth via an anti-inflammatory effect and increasing progesterone in gestational tissues, thereby counteracting the physiologic decrease in progesterone that leads to preterm birth [70–78]. During most years of this cohort study (2003 to 2011), routine use of progesterone to reduce preterm birth was not yet adopted. However, it is now routinely recommended in several clinical scenarios [79–81]. Romero et all in 2012 reported a meta-analysis of patients with a short cervix that showed that vaginal progesterone reduced the risk of preterm birth before 33 weeks (relative risk [RR] 0·58, 95% CI 0·42–0·80) and reduced a composite of neonatal mortality and morbidity (RR 0·57, 0·40–0·81) [82].

National and international societies have published guidelines on the use of progesterone for prevention of preterm birth [83–86]. The Society for Maternal-Fetal Medicine (SMFM) published a review in 2013 that “sought to provide evidence-based guidelines for using progestogens for the prevention of preterm birth.’ [79]. In Canada, the SOGC published updated guidelines in 2020 [86]. The SMFM review examined the benefit of progesterone in several clinical situations. In singleton gestations with prior preterm birth, weekly injection of intramuscular progesterone (17-alpha-hydroxy-progesterone caproate 250 mg) was recommended [79]. In Canada, the SOGC guideline strongly recommended use of vaginal micronized progesterone in a daily dose of 200 mg for prevention of spontaneous preterm birth in a singleton pregnancy [86]. In patients with a singleton gestation, short cervical length less then 20 mm before 24 weeks and no prior preterm birth, vaginal progesterone is associated with reduction in preterm birth and perinatal morbidity and mortality and “can be offered” according to the SMFM guideline [79] . Prior to these guidelines, routine cervical length screening in low-risk populations which was not common but due to the efficacy of this intervention, cervical length measurement is now routinely added to the anatomical ultrasound performed at 18 to 24 weeks of pregnancy ultrasounds to allow offering preventative treatment [78, 82–84, 86].

1.2 Rationale

Infertility and subfertility are a burden to many couples in Canada [2-4]. Investigations can reveal a structural abnormality of the female reproductive tract, known as Müllerian defects [12]. The most common defect is a uterine septum which can cause infertility, recurrent miscarriage and preterm delivery [12–24]. It can be surgically corrected with a metroplasty or uterine septum resection [12,30,34,35]. However, even after septum resection this group of patients remains at risk for infertility and adverse pregnancy outcomes [33 , 92.]. It is unknown if all or part of the risk of prematurity in this patient population is related to the underlying defect in the female reproductive tract or affected by manipulation including cervical dilation during surgery [12,30,34,35]. This study aims to explore the pregnancy outcomes of patients with infertility who underwent hysteroscopic uterine septum resection and compare these to the outcomes of patients who underwent hysteroscopic surgery for unexplained infertility.

Research Question: Is the live birth rate higher in patients who have undergone hysteroscopic uterine septum resection) compared to patients who have undergone hysteroscopic assessment with otherwise unexplained infertility?

1.3 Purpose of the Study

The purpose of this study was to determine if pregnancy outcomes are improved after hysteroscopic uterine septum resection. At inception of this project, offering hysteroscopic uterine septum resection in patients experiencing infertility was the standard of care of the treating physicians at our center. A randomized control trial was felt to be unethical. Patients with a history of unexplained infertility and a normal hysteroscopy acted as the control group.

The primary outcome was live birth rate after surgery. Secondary outcomes included pregnancy rate (defined as a positive beta hCG (β-hCG)), gestational age at delivery, presence of risk factors for preterm birth (admission to hospital for threatened preterm labour, administration of corticosteroids, and/or short cervix by TVUS), birth weight and neonatal intensive care unit (NICU) admission.

Chapter 2: Literature Review

2.1 Literature Search Strategy

The searches were conducted using electronic resources and databases available through open access online and using institutional licenses via the Health Sciences Library at Memorial University of Newfoundland. Specifically, Pubmed, the Cochrane Library, EMBASE, Google Scholar and ClinicalTrials.gov. These databases searched identifying relevant publications from 1972 until December 2021 and were limited to English language publications.

At the time of the inception of the project in 2007, the standard of care at our centre was to offer hysteroscopic septum resection to infertility patients with a uterine septum. Therefore, the literature search focused on pregnancy outcomes for postoperative hysteroscopic uterine septum resection patients and eliminated those studies involving transabdominal and laparoscopic approaches. We also eliminated reports of other experimental surgical techniques. The goal of the project was to identify post treatment outcomes on fertility and pregnancy rates. Therefore, we limited our literature review to exclude those studies that did not report postoperative pregnancy outcomes as well as case reports.

2.2 PubMed search

The initial PubMed search strategy employed inclusive terms to include pregnancy or pregnant, reproductive outcome(s), fertility, infertility, subfertility, miscarriage, live birth, premature birth, preterm birth, pre term birth, metroplast(*), septoplasty(*). See Appendix for a detailed of the search strategy.

This resulted in 263 articles. The results were reviewed individually for relevance.

2.3 Cochrane Database Search Strategy

A Cochrane database search with the search term "*metroplasty*" up to December 2021 contained 35 articles for review. Results were individually reviewed for relevance and references of selected articles were search for additional studies.

2.4 EMBASE Search

Using the database EMBASE, further searches for relevant articles were undertaken for articles up to December 2021. Similar to the PubMed search, the initial focus was on uterine septum resection or metroplasty and pregnancy outcomes and then a broader search of similar terms was employed to find articles not included in the initial search results.

Results were individually reviewed for relevance and references of the selected articles were search for additional studies. See Appendix for details of the search strategy.

2.5 Google Scholar Search Strategy

The website "Google Scholar" was also included in the literature review for articles up to December 2021. Results were individually reviewed. The search strategy included "metroplasty and pregnancy" "metroplasty and pregnancy outcomes" and "metroplasty and preterm birth". The extensive lists of results were reviewed for new and relevant articles.

2.6 ClinicalTrials.gov Search Strategy

The online database of clinical studies "ClinicalTrials.gov" was also used to identify ongoing and completed relevant studies up to December 2021. Using the search strategy "metroplasty" and "pregnancy", "metroplasty" and "preterm birth", "metroplasty" and "birth". The search was also repeated using "uterine septum" in place of metroplasty, each with “pregnancy”, “preterm birth” and “birth.” All results were reviewed individually.

2.7 Effect of a Uterine Septum on Pregnancy

2.7.1 Defining Outcome Measures

At the start of the study data collection in 2007, six published studies were used to summarize pregnancy outcomes after uterine septum resection [18,38–41,87]. Of these observational studies, four were prospective [18,39–41] and two retrospective [38,87] A potential confounder to the data for these studies is that patients included were identified because of previous adverse pregnancy outcomes or infertility. Few studies used a comparison or control group. A 2011 review by Kowalik *et al*. stated hysteroscopic septum resection in patients with recurrent miscarriage and a septate uterus was being performed in many countries to improve reproductive outcomes in patients. They cautioned this surgical treatment has been assessed in many non-controlled studies, which suggested a positive effect on pregnancy outcomes [88]. Kowalik *et al*. stated, these studies are biased due to the fact that the participants with recurrent miscarriage treated by hysteroscopic uterine septum resection served as their own controls [88]. It is unclear if many patients with a uterine septum are never identified because they do not experience infertility, pregnancy losses or preterm birth. Therefore, the baseline pregnancy rates in the study populations are likely artificially low. A control group of patients experiencing either unexplained infertility or recurrent pregnancy loss would better reflect the potential benefit in fecundability of uterine septum resection as opposed to using a patient's historical pregnancy data as her comparison.

There were no standardized outcome measurements for most of the literature. Many of the outcomes reported in these studies are dichotomous. Fortunately, this type of outcome measure is less sensitive to measurement procedures as opposed to continuous variables that would cause difference amongst study measuring techniques. For instance, pregnancy can be defined in many ways: self-reported by the patient as a positive home urine pregnancy test, confirmation at a licensed laboratory with urine or blood (serum) β-hCG levels, or a much more stringent outcome measure, documentation of pregnancy as viable on ultrasound. The latter is the most stringent for documenting a pregnancy.

Ayhan *et al.* and Saygili-Yilmaz *et al*. reported using the patients' files and obstetrical records for data collection, however they did not define how "pregnancy" was determined [38,87]. In fact, none of the studies reviewed reported their definition for documenting a pregnancy. If a study required ultrasound documentation of a viable intrauterine pregnancy (i.e., evidence of cardiac activity) this would eliminate many early pregnancy losses. This would drastically reduce the reported pregnancy rate, however not our primary outcome measure (live birth rates).

In a population of patients actively trying to achieve pregnancy we would expect a higher biochemical pregnancy rate than that generally reported. Many patients actively trying to conceive, particularly those with months or years of infertility, will regularly test for pregnancy. Some commercially available urine β-hCG tests can now report a pregnancy as early as five days before a missed menses [89]. A typical patient who is not actively trying to conceive would only test for pregnancy days or possibly weeks after a missed menses. The time difference between these two dates is up to two weeks. Many early pregnancies spontaneously abort during this time [90,91]. Therefore, allowing self-reported positive pregnancy testing in the infertility population could artificially inflate the pregnancy rate reported postoperatively in these studies. Use of a control group would help balance the baseline “pregnancy” rate in each group of participants, allowing for a more clinically relevant comparison of postoperative outcomes.

We postulate one of the many reasons why “live birth rate” is chosen as the primary outcome measure in fertility studies is to standardize the outcome measures. Overall, “live birth” is a very definitive outcome measure. As well, it is more clinically significant. When counselling couples experiencing infertility, the outcome of greatest personal importance to them would be a viable child (the “take home baby rate”). Any pregnancy (preterm, term or early miscarriage) is a welcome outcome for infertility patients but not nearly as personally important as finally having a child at home.

Another potential outcome measure of importance would be radiological confirmation that the septum is completely removed after the operative procedure. Although this has clinical significance to both the physician and patient, it is not a primary outcome used in studies for many reasons. It would be difficult to standardize this outcome in studies. A blinded radiological review of postoperative intrauterine imaging is possible. However, this would be costlier for the study, require a prospective design since it is not the standard of care, and is less relevant than a live birth or pregnancy. For these reasons we chose not to use radiologic confirmation of successful septum resection as an outcome measure in our study. It is discussed in Section 2.6.3 as part of the postoperative surveillance discussed in the articles reviewed.

Spontaneous abortion rates are difficult to standardize between studies. Criteria for a pregnancy loss will be greatly affected by how stringent the criteria were to document and confirm an early pregnancy. The loosest documentation of a pregnancy would most likely be a late menstrual period with or without a positive home urine pregnancy test. The most stringent would be documentation on ultrasound of an intrauterine gestational sac, with or without a fetal heartbeat. Many physicians settle somewhere in the middle of these two outcomes. A blood serum β-hCG would be a reasonable compromise, with possibly setting the critical value above 100 IU/mL. An ultrasound can often document a pregnancy with serum β-hCG above 1000 IU/mL and a fetal heartbeat at 5-6 weeks gestation above 5000 IU/mL. As our technology for confirming a pregnancy in home urine testing has improved, many patients can have a positive home test as low as 100 IU/mL but a very early miscarriage days later. Traditionally since these pregnancies would never have been documented on ultrasound, they would not have been recorded as a spontaneous abortion but instead an otherwise unexplained late menses. It has complicated historical comparisons between patients with primary infertility and recurrent first trimester abortions.

In the setting of a uterine septum, late first or early second trimester abortions would be expected at a higher incidence than pregnancy losses in the general population. Other uterine anomalies (e.g. a bicornuate uterus) would be more likely to have a late second trimester loss. This pattern of pregnancy loss is postulated to be caused from pregnancies implanting on the uterine septum instead of the uterine body [31, 32]. In the first month or two of pregnancy the small gestational sac can survive, but as the pregnancy grows, the blood supply in the uterine septum is insufficient, resulting in a fetal demise and subsequent spontaneous abortion [32].

Abortions, either spontaneous or induced, can be divided into first and second trimester. Typical agreed upon definitions would be any pregnancy loss before 12 weeks GA as a first trimester loss. A pregnancy loss between 12 weeks, 0 days and 19 weeks, 6 days would be considered a second trimester abortion. Another difficulty with adequate categorization would be if a patient presented at 14 weeks with a fetal demise (an inevitable abortion) but the pregnancy measured only 9 weeks on ultrasound. Should she be categorized as a first or second trimester loss?

2.7.2 Live Birth Rates

Documentation of a live birth is expected to be standardized across all studies. It is a defined term recorded in legal documents of public record via birth certificates [5]. It is assumed that all live births recorded in these studies were after 20 weeks of gestation, which is the Canadian standard for documentation of a live birth [5]. In Canada, any birth occurring before 20 weeks is deemed nonviable and would be recorded in obstetrical records as a second trimester pregnancy loss.

Although live birth is a dichotomous outcome measure that should be easily assessed, it was not a reported outcome in all the studies. Some studies instead reported a term or preterm birth; these could be presumed to be live births, although the possibility of a stillbirth still exists. To further complicate the ability to compile and standardize the data between the studies, an abortion could be any birth, live or stillborn, less than 20 weeks. However, since many consider a birth at less than 24 weeks to be previable, some births between 20 and 24 weeks could be categorized as either miscarriage or live birth. The clarity of data report as a live birth was expected to be standardized. However, since not all studies used live birth as the primary outcome measure, for the purpose of this analysis, some data were extrapolated.

Ayhan *et al.* reported abortion, preterm, term and living as their outcomes after septum resection[38]. The authors reported 30 out of 46 pregnancies (65.2%) after septum resection resulted in live births [38]. The data does not clarify how many of those were from the term (16 out of 46 pregnancies) or preterm (22 out 46), and a total of 8 pregnancies are unaccounted for [38]. No p-value was reported by the authors to assess if the outcome was statistically significant. We are left to wonder if these unaccounted births died from severe prematurity, another neonatal complication or medical condition.

Fedele and Bianchi reported 55 births from 66 pregnancies out of 102 patients after septum resection [18]. The patients were followed for 3 years postoperatively. The authors reported a cumulative probability of live birth at 36 months in two groups of patients: septate and sub-septate [18]. The cumulative probability of a live birth was 75% in the septate group and 67% in the sub-septate group, regardless of reproductive history [18]. In comparison, the baseline population rate would be 85% [1, 2]. The subseptate group of patients had a cumulative probability of live birth of 39% (primary infertility) and 62% (recurrent pregnancy loss) after uterine septum resection [18]. Conversely, in patients with a full uterine septum, the cumulative probability of live birth at 36 months was 62% (primary infertility) and 75% (previous miscarriage) [18]. Patients with a history of primary infertility had a noticeably lower but not statistically significant (p=0.06) live birth rate in the sub-septate group [18]. The authors concluded this difference could be associated to other confounding factors unrelated to the surgical procedure.

Colacurci *et al.* reported 36 live births resulting from 46 pregnancies from a total of 69 patients after septum resection [39]. Four pregnancies were ongoing at study end. The authors did not specifically state how long patients were observed for postoperatively, but did report all patients were followed for at least 8 months [39]. Their primary conclusion was that uterine septum resection improved pregnancy outcomes (term and preterm births) but not the pregnancy rate in the setting of recurrent pregnancy loss [39]. However, none of their study participants had a documented live birth before the study commenced. No p-value was reported by the authors to assess if the outcome was statistically significant [39]. Of all patients, 70% of patients had a history of recurrent pregnancy loss (48 out of 69) and 30% primary infertility (21 out of 69) [39]. Postoperatively, 67% (46/69) of all patients became pregnant [39]. In total, 52% (36/69) of patients had a live birth postoperatively; 32 from the recurrent pregnancy loss group and 4 from the primary infertility group [39]. Each group had two pregnancies ongoing at the study end. Put another way, 67% (32/48) of patients with a history of recurrent pregnancy loss achieved a live birth postoperatively, compared to only 19% (4/21) of patients with a history of primary infertility [39]. Although both groups of patients had pregnancies and live births postoperatively, the dramatic increase was in the recurrent pregnancy loss group postoperatively: no live births (0%) preoperatively increasing to 67% postoperatively [39]. In comparison, there were no live births (0%) preoperatively in infertility group, increasing to only 19% postoperatively [39]. However, all the pregnancies in the primary infertility group resulted in either a live birth or were ongoing at study end. It is possible to conclude that the septum resection had little to no effect on the fertility and pregnancy outcomes of patients with a history of primary infertility. However, in the group of patients with a history of primary infertility, when they did achieve a pregnancy, the authors report no miscarriages and 1 (17%) preterm birth [39]. The sample size was small (21 patients). Perhaps the uterine septum is one of many factors leading to primary infertility is this group of patients.

Saygili-Yilmaz *et al*. reported cumulative live birth rates after septum resection when pregnancy was achieved in 3 groups of patients: primary infertility (57.7%), spontaneous abortions (81.3%) and the habitual abortion group (3-11 pregnancy losses) (79.5%) [87]. Overall, the authors documented a reduction of miscarriage rates of close to 80% compared to the preoperative pregnancy outcomes [87]. The infertility group had only 26 live births out of 193 patients (13.5%), compared to 109 live births out of 168 patients with 1 or more SA (64.9%) [87]. Since patients were excluded from the study if a known cause for infertility was identified in preoperative work up, this suggests the infertility group may have had other factors affecting fertility that were not identified. Uterine septum resection improved the live birth rate in both groups of patients but much more dramatically in patients with recurrent pregnancy losses [87].

Pabuçcu & Gomel reported 18 live births from 25 pregnancies (72%) after septum resection [40]. In total, from the 61 patients included in the study, 30% achieved a live birth postoperatively [40]. The authors did not differentiate if the live births occurred from patients with a history of recurrent pregnancy loss or primary infertility.

Mollo *et al.* reported a live birth rate of 34.1% in patients after septum resection, compared to 18.9% in their matched controls ($p<0.05$) [41]. The authors did not specifically report outcomes for the recurrent pregnancy loss group and the primary infertility group. Therefore, we do not know if patients with a history of recurrent pregnancy loss had a higher or lower chance of achieving a live birth in pregnancy post-procedure.

Nouri *et al.* [92]reported a retrospective cohort study evaluating the reproductive outcome after hysteroscopic septoplasty in 64 patients with septate uterus. The patients had primary or secondary infertility. The overall life birth rate was 49% (24/49) [92]. They concluded in patients with septate uterus and a history of infertility, hysteroscopic septoplasty was a safe and effective procedure [92].

Pang *et al.* evaluated the reproductive outcomes of 138 patients with a subseptate uterus over a 5 year period [93]. The study identified patients who did and those who did not undergo hysteroscopic resection and then and then compared their reproductive outcomes [93]. Further, they were divided into those with a history of recurrent pregnancy losses and those with no previous history of "poor reproductive outcomes." They reported pregnancy loss, preterm birth, and term delivery but not specifically live birth rates [93]. The authors concluded hysteroscopic septum resection significantly improved pregnancy outcomes in patients with a history of recurrent pregnancy losses, but did not influence reproductive outcomes in patients with no history of poor pregnancy outcomes [93].

In 2020 a cohort study led by Rikken *et al.* reported outcomes from 257 patients with a septate uterus. Patient data was collected from electronic patient files, medical records and databases within the time frame of January 2000 until August 2018 from 21 participating centres in the Netherlands, USA and UK [94]. Of these 257 patients, 151 patients underwent a septum resection and 106 patients had expectant management. Unlike previously published cohort studies comparing patients with their historical controls, outcomes were not improved in the postoperative group [94]. Live birth rates (80/151 [53.0%] compared to 76/106 [71.7 %]) were lower following surgical treatment [94]. The authors concluded in patients with a septate uterus, septum resection did not increase live birth rate compared with expectant management [94]. The data reported by Rikken *et al.* is limited because as a cohort study; it is not clear why 106 patients with a diagnosed septum were managed expectantly. In the study time period of 2000-2018, hysteroscopic septum resection was the standard of care.

In April 2021 data from the TRUST (The Randomised Uterine Septum Trial) was published. This international RCT began enrolling patients in 2010 and finished in 2018. To be eligible for enrollment, patients with a septate uterus also had to have a history of subfertility, pregnancy loss or preterm birth [95]. They were randomly allocated to septum resection (n=40) or expectant management (n=40). The primary outcome was a live birth within 12 months after randomization, defined as the birth of a living foetus beyond 24 weeks of gestational age [95]. Live birth occurred in 12 of 39 patients allocated to septum resection (31%) and in 14 of 40 patients allocated to expectant management (35%) (relative risk (RR) 0.88 (95% CI 0.47 to 1.65)) [95]. One patient who underwent septum resection was excluded from the intention-to-treat analysis because she withdrew informed consent for the study shortly after randomization [95]. They concluded this RCT provides high level evidence that in addition to the cohort data published by many of the same authors in 2020, that uterine septum resection does not demonstrate any improvements in reproductive outcomes. Although the surgery is minimally invasive and complications are rare, they questioned any rationale behind recommending surgery for these patients.

2.7.3 Pregnancy Rates

None of the studies reported a definition for "pregnancy". We can presume previous pregnancies were self-reported from patients before study participation; many of these would be medically documented but some were likely only positive home urine hCG pregnancy tests. Once patients were enrolled in the respective studies, we can presume pregnancy rates were based on a positive serum blood value as this would be the most common method of documenting a pregnancy in clinical practice.

Ayhan *et al.* reported postoperative outcomes of 46 pregnancies from 49 patients [38]. They did not specify how many of these pregnancies came from the same patient. Their data was obtained from the medical records, retrospectively, over a 20-year period. Preoperatively this same group of patients had reported 173 pregnancies, of which 155

(90%) were considered abortions [38]. It is possible that one patient in the cohort could have contributed 3 or more "pregnancies" to the data set, particularly if all were early abortions. As well, since this was historical data from a patient chart, some early pregnancies may have been not documented if they were only confirmed on a home urine hCG test that then subsequently resulted in a spontaneous abortion before seeking medical attention.

Fedele & Bianchi reported 66 pregnancies from 102 patients after septum resection [18]. In this study, patients were followed for three years postoperatively. The authors reported a cumulative pregnancy rate of 89% (the septate group) and 80% (the sub-septate group) at 36 months [18]. Eleven of the pregnancies were considered non-viable, of which one was ectopic [18]. The authors did not comment on the gestational ages of the pregnancy losses. However, they did report if the viable deliveries were before or after the 38th week of pregnancy.

Colacurci *et al.* reported 46 pregnancies from 69 patients after septum resection [39]. Forty pregnancies resulted from 48 patients with a history of pregnancy loss (83%) and 6 pregnancies resulted from 21 patients with primary infertility (29%) [39]. The authors concluded the uterine septum resection did not improve the pregnancy rate but only the pregnancy outcome [39].

Saygili-Yilmaz *et al*. followed 361 patients for 18 months postoperatively [87]. They reported 180 pregnancies in total. The authors chose to categorize the patients in three groups: primary infertility (193 patients), one or two previous spontaneous abortions (109 patients) and the habitual abortion group (three or more pregnancy losses, 59 patients) [87]. They reported cumulative pregnancy rates of 23% (primary infertility), 78.9% (spontaneous abortions) and 83% (habitual abortion) [87]. There was a significant difference in cumulative pregnancy probability among the three groups (P<0.001, log rank test). The authors concluded uterine septum resection improves obstetrical performance in patients with recurrent pregnancy losses and that surgery did not have a significant effect on the pregnancy rate [87].

Pabuçcu & Gomel followed patients for at least 8 months postoperatively (mean 11 months) [40]. They reported 25 pregnancies from 61 patients. They did not describe how a pregnancy was documented. All of their patients had previous otherwise unexplained infertility; the control group for this study was historical. Therefore, all patients appeared to have improved pregnancy rates after the operation (0% preoperative vs 41% postoperative) [40]. However, the difference between these two groups is artificially high since some infertility patients would become pregnant eventually, even without any intervention.

Mollo *et al.* followed patients with otherwise unexplained infertility, identified from three academic infertility clinics [41]. They compared patients within this group who had a septum identified, then resected, to patients in the same clinics with no identifiable cause for their infertility. Both groups were followed for 12 months with expectant management. Of the 44 patients who underwent uterine septum resection, there were 17 pregnancies (38.6%) [41]. The authors reported pregnancy rates using Kaplan Maier survival analysis. In the description of how the Kaplan Maier analysis was calculated, the authors state pregnancies were confirmed with an ultrasound after 10 weeks of amenorrhea [41]. Although the authors also reported first trimester losses in their results, requiring ultrasound dating of a pregnancy at 10 weeks' gestation appears to be the most stringent criteria used for all the studies we examined for this review.

Nouri *et al.* [92] reported a retrospective cohort study evaluating the reproductive outcome after hysteroscopic septoplasty in 64 patients with septate uterus. The patients had primary or secondary infertility. The overall pregnancy rate after hysteroscopic septoplasty was 69% (34/49) [92].

Pang *et al.* compared the reproductive outcomes of patients who did and those who did not undergo hysteroscopic septum resection [93]. They were divided into those with a history of recurrent pregnancy losses and those with no previous history of "poor reproductive outcomes" [93]. In patients with a history of recurrent pregnancy losses, the rates of pregnancy and term delivery were higher in hysteroscopic resection group compared to those did not undergo surgery ($P<0.05$) [93]. In patients who did not have a history of adverse pregnancy outcomes, there was no difference in pregnancy rate between group who did and did not have hysteroscopic septum resection [93]. The authors concluded hysteroscopic septoplasty significantly improved pregnancy outcomes in patients with a history of recurrent pregnancy losses, but did not influence reproductive outcomes in patients with no history of poor pregnancy outcomes [93].

A literature review published in 2018 by Corroenne *et al*. evaluated the effect of hysteroscopic septum resection on ART outcomes. They concluded hysteroscopic septum resection seems to improve natural conception rates in the year following surgery [96].

Rikken *et al.* reported outcomes from 257 patients with a septate uterus from 21 participating centers [94]. Pregnancy rates were higher in patients who were treated surgically (51 out of 151 [46.8%] in the septum resection group compared to 31 out of

106 [34.4 %] in the expectant management group) [94]. In the study time period of 2000-2018, hysteroscopic septum resection was the standard of care. It is not clear why 106 patients with a diagnosed septum were managed expectantly, so the cohort study design may have unrecognized selection bias.

2.7.4 Preterm Birth Rates

Preterm birth is defined as any delivery between 20 weeks 0 days and 36 weeks 6 days gestation. Preterm birth is further stratified into late preterm (32-36 weeks), very preterm (28-31 weeks) and extremely preterm (<28 weeks) with increasing neonatal mortality and morbidity [5]. Typically, an abortion would be loss of a pregnancy before 20 weeks 0 days. A first trimester abortion occurs before 12 weeks 0 days and a second trimester abortion between 12 weeks 0 days and 19 weeks 6 days. However, since the overwhelming majority of births that occur between 20 weeks 0 days and 23 weeks 6 days, would result in a non-viable birth, some studies report preterm births as only those that occur between 24 weeks 0 days and 36 weeks 6 days. To further complicate comparisons, one study in this review considered a birth preterm if it occurred before 38 weeks [18]. Colacurci *et al.* and Pabuçcu & Gomel reported a birth as preterm if it occurred before 36 weeks gestation [39,40].

Ayhan *et al*. reported 22 preterm births in their postoperative group [38]. This resulted from 46 pregnancies (48%). The same group of patients had a history of 14 preterm births from 173 previous pregnancies (8%) . The dramatic increase in preterm birth, however, is better explained by a postoperative increase in the fetal survival from 3.7% preoperatively to 65% postoperatively. If a patient became pregnant after she underwent a uterine septum resection, she had a significantly higher chance of fetal survival. By reviewing the results table and subtracting all live births from the number of pregnancies not considered abortion, 8 pregnancies remain. The eight pregnancies that were either preterm or term, but not living, were most likely deaths from prematurity. No comment is made to clarify this in the article.

Fedele & Bianchi chose to categorize a birth as preterm if it occurred before 38 weeks [18]. In their study, 10 out of 55 births were preterm (18%). The focus of the study was reproductive prognosis, but the authors focused on pregnancy rates and live births. The authors do not discuss prematurity as it related to prognosis [18]. We do not know the outcome, short term, or long term, of the premature births from this study. For patients affected by a premature birth, the survival and morbidity are certainly important factors.

Colacurci *et al.* chose to categorize a birth as preterm if it occurred before 36 weeks and resulted in a live birth [39]. In their study, five live births occurred before 36 weeks (11% of all pregnancies). Using their results tables, 6 pregnancies resulted in miscarriage and the remainder were either reported as "term" or "ongoing". Unfortunately, we cannot be certain if there were any deliveries before 36 weeks that did not result in a live birth. This type of delivery could have been categorized as a miscarriage in the results. Due to the small population size, it is most likely that there simply were not any deliveries between 12 weeks and 36 weeks that did not result in a live birth.

Saygili-Yilmaz *et al*. reported 34 preterm births from 180 pregnancies (19%) [87]. Eighteen of the premature births survived (53%). The authors did not define the date range of a preterm birth. The dramatic fetal loss rate of 47% of preterm births underscores the clinical relevance of prematurity [18]. We do not know how many of these premature births were stillborn, how long some survived or if they were pre-viable, very premature, or extremely premature. It is emotional to lose a pregnancy at any gestation. The cost to medically manage a premature birth would increase greatly in the very premature and extremely premature group.

Pabuçcu & Gomel reported preterm live births less than 36 weeks [40]. In their cohort of 61 patients, they reported 5 preterm deliveries from 18 live births (28%). We do not know if there were any deliveries before 36 weeks that were not live births, but it is possible due to the small study size there were none. By examining the results table, the remainder of the pregnancies were either reported as spontaneous abortions or term live births.

Mollo *et al.* reported 3 preterm births from 17 pregnancies in their cohort of 44 patients (17.6%) [41]. Their control group of 132 patients had only 1 preterm birth in 27 pregnancies (3.7%). The difference was not statistically significant, likely due to the small sample size. The authors did not define preterm birth. Most likely they used the common definition of any birth from 20 weeks 0 days to 36 weeks 6 days.

Pang *et al.* compared the reproductive outcomes of patients who did and those who did not undergo hysteroscopic septum resection [93]. They were divided into those with a history of recurrent pregnancy losses and those with no previous history of "poor reproductive outcomes" [93]. In patients with a history of recurrent pregnancy losses, the incidence of another pregnancy loss or preterm delivery was higher in group who did no undergo surgical correction, compared to those who did (P<0.05) [93]. In patients who did not have a history of adverse pregnancy outcomes, there was no difference in preterm delivery between group who did and did not have hysteroscopic septum resection [93].

Rikken *et al.* reported preterm birth rates were higher in the septum resection group (26/151 [29.2%]) compared to those patients managed expectantly (13/106 [16.7 %]) [94]. The authors concluded in patients with a septate uterus, septum resection did not decrease the rates of pregnancy loss or preterm birth, compared with expectant management [94]. As mentioned earlier, it is unclear why so many patients were managed expectantly during this period when hysteroscopic septum resection was the standard of care [33].

Prematurity can have significant morbidity and mortality [54, 55]. It has a high societal cost from short term and long-term medical expenses [58]. It is unfortunate that the studies in this review did not use the same definitions for preterm birth so we cannot compare the outcomes. As well, we cannot directly comment on the number of deaths from prematurity or the hospital costs from very premature and extremely premature births. Both parents, clinicians and the society as a whole can be greatly affected by premature births, particularly those occurring before 34 weeks [57]. Larger cohorts would be needed to adequately capture this proportion of patients affected.

2.7.5 Gestational Age

The gestational age of a delivery is reported in weeks and days. It is a matter of governmental record for live birth certificates and registration of stillbirths. There are several standards employed for dating a pregnancy, either from last menstrual period (the traditional), ultrasound dating or as is the case with assisted reproduction technologies, precise dating with embryo transfer dates [97]. Many, but not all, pregnancies that use dating from last menstrual period have confirmation with ultrasound dating. The accuracy of ultrasound dating evolved over time as the technology improved. Ultrasound image quality has vastly improved over the last few decades. However, the range of error in ultrasound dating remains as high as three weeks for late third trimester pregnancies and as low as three days for early first trimester pregnancies [98,99]. Early transvaginal ultrasound is also more precise than transabdominal imaging [98,99]. Not all patients have an early ultrasound but many in the infertility population would. After trying to conceive for months or year, it is common practice in the infertility clinics to perform an early ultrasound to reassure patients of a viable pregnancy. If we can fairly assume that the overwhelming majority of infertility patients have at a minimum a confirmation ultrasound by 12 weeks, the range in error for dating should be no more than 5-7 days, depending on the technology used at the time.

An advantage of using gestational age at delivery as an outcome is that it is a continuous variable. As discussed in Section 2.5.4, a premature birth at 28 weeks has significantly greater morbidity and mortality than a birth at 36 weeks. Due to the small sample sizes, the number of births in the extremely preterm, very preterm, moderate, and late preterm is little or none. Counselling by pediatricians to parents is drastically different for an extremely preterm birth as opposed to a late preterm birth. Counselling by a gynecologist to weigh the pros and cons of surgical septum resection would also be affected if a successful surgery was more likely to result in a late preterm birth as opposed to an abortion or extremely preterm birth.

None of the studies reported gestational age as an outcome in weeks and days. Fedele & Bianchi did not report gestational age as a continuous outcome, but in their table of results they dichotomize births with a gestational age of less than 38 weeks or greater than and equal to 38 weeks [18]. In their series, 10 out of 55 births (18%) occurred before 38 weeks. Colacurci *et al.* mentioned gestational age only in reporting live births under 36 weeks (5 births out of 46, 10.8%) [39]. Saygili-Yilmaz *et al*. made no mention of gestational age in their results, but since only half of preterm births survived, mortality and likely morbidity was high [87]. Most likely many of the preterm births were extremely preterm or very preterm. Pabuçcu & Gomel also do no report a gestational age [40]. They do report births before 36 weeks. All preterm births in their series were live births, but we do not know how many survived the neonatal period. It is also possible that the authors categorized stillborn extremely preterm births as a spontaneous abortion. Mollo *et al.* and Ayhan *et al.* make no comment in their results about gestational ages [38,41].

2.8 Surgical Procedures

Some of the studies included in this review reported a detailed description of their operative techniques. The prospective studies were able to control which surgeons performed the procedure, which would standardize skill level of the surgeon and specific operative techniques [39–41]. The retrospective studies could not control the study design as closely, but since this procedure is rare, it is quite possible each institution had only a handful of surgeons who perform this surgery. Unless the available technology at the hospitals changed, we hope the procedures performed in each retrospective cohort were similar.

2.8.1 Indication for Surgery

Ayhan *et al.* reviewed 20 years of charts from one hospital [38]. They studied patient files and obstetrical records. The authors used descriptions in the operative reports and radiology reports of hysterosalpingograms to classify the Mullerian defect [38]. The indication for uterine septum resection was symmetric uterine anomaly, confirmed with hysteroscopy or hysterosalpingogram and exclusion of bicornuate uterus with laparoscopy. As well, the patients had to have a history of late recurrent abortion or preterm delivery to be eligible for surgery [38].

Fedele & Bianchi evaluated patients referred to one infertility clinic [18]. All patients had a history of recurrent pregnancy loss or infertility. All patients had evidence on hysterosalpingogram and ultrasound of a uterine septum. As well, if the patient had primary infertility she underwent a laparoscopy to rule out endometriosis [18]. Patients and their partners also had an extensive workup to look for any other causes for infertility before they underwent the uterine septum resection.

Colacurci *et al.* included all patients identified with a uterine septum from one infertility clinic [39]. The cohort included patients who underwent uterine septum resection at the same hospital over a four-year period. Most patients had a history of 3 or more abortions (48 out of 69 patients, 70%); the remaining 21 patients had a history of infertility [39].

Saygili-Yilmaz *et al*. used retrospective data from one infertility clinic over a ten-year period [87]. All patients had a history of recurrent pregnancy loss or infertility. All patients had a preoperative work up for causes of infertility and were excluded if another cause was identified. As well, all patients had a preoperative hysterosalpingogram and laparoscopy [87].

Pabuçcu & Gomel performed a prospective observational study of 61 patients [40]. The authors identified patients from the same infertility clinic over a nine-year period. They reported an extensive preoperative work up for other causes of infertility [40]. They excluded patients with endometriosis and over the age of 35 [40]. All patients had a preoperative hysterosalpingogram.

Mollo *et al.* prospectively followed forty-four patients with a uterine septum resection and matched each patient to three infertility patients (132 patients) from the same clinic [41]. The authors identified their patients using three infertility clinics. The study was done over a six-year period. Patients were limited by age (18-35 years) and body mass index (18-28 kg/m^2) [41]. All patients underwent investigations for causes of infertility and were only included in the study if they were deemed to be normogonadotrophic normoovulatory. Immunological and infectious causes were also excluded.

Corroenne *et al*. evaluated the effect of hysteroscopic septum resection on ART outcomes. They concluded hysteroscopic septum resection seems to improve natural conception rates in the year following surgery [96]. Overall, they recommended hysteroscopic septum incision for patients undergoing assisted reproductive technologies [96].

The cohort study reported by Rikken *et al.* reported outcomes from 257 patients with a septate uterus [94]. Of these, 106 patients had expectant management. Patient data was collected from electronic patient files, medical records and databases within the study time frame [94]. It is not reported how many of the 106 patients with a diagnosed septum did not meet criteria for surgery or chose to be managed expectantly.

2.8.2 Operative Technique

Ayhan *et al.* did not describe the operative technique used [38]. The study is a 20-year retrospective review, so it is quite possible the surgery changed over time with the introduction of new technologies. The authors reported the patients in the study had no surgical complications [38]. All patients had surgery at the same hospital.

Fedele & Bianchi provided a detailed description of the operative technique used in their study [18]. All patients were in the proliferative phase of their menstrual cycle and treated preoperatively with danazol. Three different surgical techniques were reported: microscissors, argon laser and urologic resectoscope. The number of surgeons used was not stated.

Colacurci *et al.* reported all surgeries were performed using a resectoscope [39]. Slightly less than half of patients (46%) had surgery in the proliferative phase of their menstrual cycle [39]. 28 patients (41%) were pre-treated with a gonadotrophin releasing hormone analogue [39]. All surgeries were under general anesthetic with the same loop electrode and using similar currents (50-70 Watts) [39]. To rule out other confounding pathology, all infertility patients also had laparoscopy. The authors did not comment on how many different surgeons were used. They reported no intraoperative complications.

Saygili-Yilmaz *et al*. analyzed 361 patient charts who underwent uterine septum resection at the same institution [87]. The number of surgeons included in the study was not reported. All patients were given the same preoperative treatment of danazol 600 mg daily for six weeks [87]. All patients received perioperative antibiotics. All procedures were done under general anesthetic. The same model of hysteroscope was used for all procedures and all surgeons used a loop electrode with similar currents (50-70 watts). A detailed description of the operative technique to remove the septum is included. This suggests only a small number of surgeons were used for the analysis. Most likely this is due to only a few surgeons at the hospital being trained in this procedure. Although this was a retrospective analysis, the standardized procedure with preoperative treatment indicates the technique does not appear to have changed much over the ten year span of the data collected.

Pabuçcu & Gomel reported a standardized operative technique [40]. All patients had a concurrent laparoscopy to identify any other causes for infertility. The same model of hysteroscope was used in all cases. The procedure was performed with a cutting knife electrode at similar power (50-70 watts) [40]. Although the number of surgeons included in the study results was not reported, the detailed description of the procedure included in the article suggests most likely only a few surgeons were involved.

The surgeons in Mollo *et al.*'s article scheduled surgery in the proliferative phase [41]. A diagnostic laparoscopy was performed in all patients. The number of surgeons included was not reported, but the authors describe all surgeons as "experienced hysteroscopists with similar skill levels". The same model of hysteroscope was used in all cases. A monopolar knife was used at 60-80 watt current [41]. The authors describe the procedure in detail, again allowing us to presume the procedure was only performed by a few different surgeons.

2.8.3 Postoperative Surveillance

Ayhan *et al.* reported that all patients were followed postoperatively for evidence of cervical incompetence in pregnancy [38]. Since this was a retrospective review spanning two decades, we must assume it was an established standard of care at that institution to follow this type of patient in pregnancy. The patients were monitored with ultrasound and pelvic examinations. One third of patients underwent a cervical cerclage in pregnancy [38].

In the cohort reported by Fedele & Bianchi, about one quarter of patients received postoperative estrogen and progesterone [18]. As well, approximately one quarter of patients had an IUD inserted postoperatively [18]. In the late secretory phase of the next menstrual cycle patients underwent a transabdominal ultrasound. They also had another hysteroscopy in the next proliferative cycle. A residual notch was found in 37 out of 102 patients (36%) and these patients had a repeat procedure [18]. In pregnancy, patients with evidence of cervical incompetence on hysterosalpingogram were treated with a cerclage.

Colacurci *et al.* reported all patients underwent a postoperative hysterosalpingogram or hysteroscopy to assess the uterine cavity [39]. The majority of patients (85%) had a residual notch less than 1 centimeter [39] . Two patients (3%) eventually underwent a second surgery to remove the residual notch [39] . There were no postoperative complications. Thirteen patients (28% of pregnancies) underwent a cervical cerclage in pregnancy [39] . Indications for cerclage included a history of 3 or more miscarriages, a history of a preterm birth before 30 weeks or evidence on hysterosalpingogram of an incompetent cervix in the current pregnancy [39] .

Saygili-Yilmaz *et al*. reported that all patients had a hysterosalpingogram two months after the surgery [87]. If there was evidence of a residual notch greater than one centimeter, the patient had a repeat surgery (number not reported). All patients were followed for at least 18 months for pregnancy outcomes.

Pabuçcu & Gomel saw all patients on postoperative day one [40]. All patients returned for a two-month postoperative visit and underwent a hysterosalpingogram. Fourteen patients (20%) also had a postoperative hysteroscopy [40]. Five patients (8%) had a repeat surgery due to a residual fundal notch [40]. The patients were followed for pregnancy outcomes for at least 6 months (up to 24 months) postoperatively.

Mollo *et al.* performed a repeat hysteroscopy and ultrasound one month postoperatively [41]. Once a normal cavity was confirmed, patients were followed for 12 months after the procedure. No repeat uterine septum resections were reported.

2.9 Neonatal Morbidity

Indicators for neonatal morbidity include birth weight, APGAR scores, antenatal steroid administration, NICU admissions, neonatal (0 to 28 days of life) mortality and infant (up to 1 year) mortality. These outcomes were not a focus of any of the studies reviewed. Fedele & Bianchi reported the incidence of low birthweight (<2500 g) [18]. This occurred in three of 55 pregnancies (5.5%) [18]. Saygili-Yilmaz *et al*. reported rates of miscarriage, preterm delivery, term delivery and live births [87]. From this data set we can extrapolate 16 deliveries were not live births. If this was interpreted that all non-live births were premature, then 47% of preterm births did not survive. This would indicate a significant morbidity and mortality from prematurity. At best, at least 16 of all 151 preterm and term deliveries were not live births. Therefore, the stillbirth rate is at least 11%.

In the cohort study reported by Rikken *et al.* the only outcome that improved was fetal malpresentation at birth [94]. Fetal malpresentation was reduced in the postoperative group (17/151 patients who underwent septum resection (19.1%) versus 27/106 patients who had expectant management (34.6%) [94]. Fetal malpresentation can lead to operative delivery and fetal trauma [100, 101].

2.10 Systematic Reviews

An updated Cochrane review was published in 2017 by Rikken *et al* with the objective "to determine whether hysteroscopic septum resection in patients of reproductive age with a septate uterus improves live birth rates and to assess the safety of this procedure." [94]. The search strategy for Cochrane reviews is extensive, including MEDLINE, Embase, PubMed, conference abstracts, unpublished dissertations and theses, CINAHL database and Google. They identified no randomised controlled trials for inclusion in the review [94]. They concluded that although hysteroscopic septum resection in patients of reproductive age with a septate uterus is performed worldwide to improve reproductive outcomes, at present, there is no evidence to support this surgical intervention [94].

> *"Women with a septate uterus are at increased risk for subfertility, recurrent miscarriage, and preterm birth. Restoration of the anatomy of the uterus by hysteroscopic septum resection is an established intervention. This treatment has been assessed mainly in retrospective cohort studies, which suggested a positive effect on pregnancy outcomes. The major flaw in these studies is the before/after design, which will always favour the tested intervention."* [94]

Other systematic reviews came to similar conclusions. The Spanish Infertility SWOT Group (SISG) in 2018 concluded that although Hysteroscopic septum resection is worldwide considered as a standard procedure in patients with a septate uterus, currently no level 1 published evidence supports uterine resection in patients with septate uterus [102]. They advised well-designed randomized controlled trials are required to confirm the clinical benefits and cost-effectiveness of this procedure [102].

A systematic review in 2020 by De Franciscis *et al.* reviewed 164 published studies, of which only six met the inclusion criteria. They reported they found very few randomized clinical trials and case-control studies were available due to ethical constraints [103]. From these 6 accepted studies were 221 patients who had undergone hysteroscopic septum resection [103]. The authors reported a live birth rate of 50% from a clinical pregnancy rate of 73% [103]. In patients who experienced recurrent miscarriages, at least half successfully had a live birth postoperatively [103]. There were few surgical and obstetric complications.

2.11 Comparison of Study Results from Literature Review

Table 1: Summary of Results from Comparison Studies

Author (year)	Study Design & Number of Participants	Results
Ayhan *et al.* [37] (1992)	*Retrospective clinical analysis* 102 patients	30 out of 46 pregnancies (65.2%) after septum resection resulted in live births Of these, 22 out 46 were preterm (47.8%)
Saygili-Yilmaz *et al* [85] (2003)	*Retrospective cohort* 361 Patient The infertility group had 193 and 168 patients with 1 or more SA	A total of 180 (49.8%) pregnancies were achieved after uterine septum resection during the follow-up period of 18 months. Of the 180 pregnancies 117 (57.2%) reached to term and 34 (18.8%) ended in preterm delivery and the remaining 29 (16%) resulted in abortion. Of the preterm babies 18 (52.9%) were able to live. We obtained 135 (75%) live babies totally. Cumulative live birth rates after septum resection when pregnancy was achieved in 3 groups of patients: 1-primary infertility (57.7%), 2-spontaneous abortions (81.3%) and 3-habitual abortion group (3-11 pregnancy losses) (79.5%). The infertility group had only 26 live births out of 193 patients (13.5%), compared to 109 live births out of 168 patients with 1 or more SA (64.9%)
Fedele and Bianchi [18] (1995)	*Retrospective cohort* 102 patients	55 births from 66 pregnancies The cumulative probability of a live birth was 75% in the septate group and 67% in the sub-septate group
Colacurci *et al.* [38] (1996)	*Retrospective cohort* 69 patients	36 live births resulting from 46 pregnancies (78.2 %) from a total of 69 patients (52.2 %)
Pabuçcu & Gomel [40] (2004)	*Retrospective cohort* 61 patients	18 live births from 25 pregnancies (72%) from a total of 61 patients (29.5 %)
Mollo *et al.* [41] (2008)	*Prospective controlled trial* 44 patients compared to 132 controls	live birth rate of 34.1% in patients after septum resection, compared to 18.9% in their matched controls ($p<0.05$)

Nouri *et al.* [92] (2010)	*Retrospective cohort study* 64 patients	The overall life birth rate was 49% (24/49). The overall pregnancy rate after hysteroscopic septoplasty was 69% (34/49)
Pang *et al.* [93] (2011)	*Prospective cohort* 138 patients Group A: Recurrent Spontaneous Abortion (RSA) 78 Group B: no history of poor outcomes 60	In group A, the pregnancy rate was higher in the group who underwent hysteroscopic septum resection, 80.4% (37/46) compared to expectant management, 56.3% (18/32). Of these, 73.0% ended in term deliveries, compared to only 22.2% in the control group, ($P < 0.05$). In group B, there was no difference in the pregnancy rate, incidence of spontaneous abortion, or preterm or term delivery. The incidence of spontaneous abortion and preterm delivery was higher in control group than in the intervention group ($P < 0.05$). In patients without a history of poor reproductive outcome, there was no difference in pregnancy rate, incidence of RSA, or preterm or term delivery between the control and intervention groups.
Rikken *et al.* [94] (2021)	*Cohort study* 257 patients: 151 patients underwent a septum resection and 106 patients had expectant management	Live birth rates (80/151 [53.0%] compared to 76/106 [71.7 %]) were lower following surgical treatment. Pregnancy rates were higher, (51/151 [46.8%] compared to 31/106 [34.4 %]). Preterm birth rates were higher (26/151 [29.2%] compared to 13/106 [16.7 %])
TRUST [95] (2018)	*Randomized Control Trial* 80 patients (40 each group)	Live birth occurred in 12 of 39 patients allocated to septum resection (31%) and in 14 of 40 patients allocated to expectant management (35%) (relative risk (RR) 0.88 (95% CI 0.47 to 1.65)).

2.12 Going Forward

It is likely that many patients with Mullerian anomalies can have normal reproductive outcomes and hence are never identified. With improved diagnostic accuracy of ultrasound, we are likely to see an increase incidence in diagnosis of these defects. We do not believe it is possible to predict which patients will have adverse pregnancy outcomes and infertility with the isolated finding of a uterine septum.

The effect of a uterine septum on fertility and pregnancy is likely not limited to the physical space occupied by the septum in the uterine cavity. Pabuçcu & Gomel noted in their article improved outcomes for uterine septum resection in both the infertility and recurrent pregnancy loss populations [40]. The authors commented in their discussion there may be unknown and unproven physiologic explanations for this difference [40]. Fedele & Bianchi reported different endometrial linings for patients with a uterine septum [18]. They postulated there were ultrastructural alterations, reduced ciliated cell ratios and irregular distributions of glandular ostia. The authors theorized that these factors contributed to primary infertility in this group of patients [18].

As gynecologic surgeons moved away from a transabdominal approach to hysteroscopy for septum resection the morbidity of the surgery decreased. Uterine septum resection is now most often an out-patient day procedure with a quick recovery and return to fertility. The results from the TRUST study bring doubt to physicians recommending surgical excision of a uterine septum. However, study sizes are small and recruitment in a multi center study still took 8 years. Further randomized control trials, including patients with and without traditional morbidity from a uterine septum (such as recurrent pregnancy loss and preterm birth) is warranted.

Chapter 3: Methods

3.1 Data Procurement

At the time the study was undertaken, the standard of care for patients diagnosed with a uterine septum and experiencing infertility or subfertility at Newfoundland and Labrador Fertility Services was a uterine septum resection. Therefore, the investigators did not feel it was ethical to randomize patients for surgery or expectant management. Surgery was offered to all patients. The study design chosen was an ambi-directional cohort study. Initial data retrieval began in the fall of 2007 and continued until the spring of 2012. All patients were followed from surgery for at least one year to monitor pregnancy outcomes.

No patients were contacted directly. The data was extracted from the Newfoundland and Labrador Fertility Services chart (including nursing notes from phone conversations), the antenatal record, the hospital chart, the hospital electronic record (including laboratory tests and visit history), the database of diagnostic imaging done in the province (for evidence of obstetrical ultrasounds) and occasionally contacting the referring Obstetrician Gynecologist if the patient resided outside of the Avalon peninsula and might have sought prenatal care at hospitals and health care facilities whose electronic records are not shared with our local health board.

3.2 Sample

3.2.1 Inclusion and Exclusion Criteria

This cohort study included all patients who had a uterine septum resection performed by one of two surgeons at Health Sciences Center from October 2003 to June 2011. The patients had previously been referred to Newfoundland and Labrador Fertility Services. Reasons for referral included recurrent pregnancy loss, primary infertility, secondary infertility or diagnosis of a uterine septum by an Obstetrician Gynaecologist who did not perform septum resections.

The control group consisted of patients referred to Newfoundland and Labrador Fertility Services who underwent diagnostic hysteroscopy as part of their fertility work-up and were confirmed to have a normal uterine cavity, without any evidence of Mullerian anomalies, polyps or fibroids [12]. Their presenting complaint could be recurrent pregnancy loss, primary or secondary infertility.

Patient records were reviewed postoperatively until a documented pregnancy or until study closure. Only the first documented pregnancy after surgery was included for study analysis.

Patients with multiple gestations were excluded due to known increased risk of pregnancy loss and preterm birth.

3.2.2 Sample Size

The sample size for the study was calculated using previously published results of pregnancy outcomes [39–41]. The primary outcome was live birth rate. A 20% improvement in live birth rate, from a baseline of 20% to 40%, was deemed to be clinically relevant. A 1:4 intervention to control ratio was used to increase the power of the study as we were limited by the number of intervention patients available. Setting two-sided alpha at 5% and the power at 80% we calculated a sample size of 53 uterine septum resection patients with a control group of 212 patients.

3.3 Data Management

The cohort for this study was identified using the surgical billing records from Newfoundland and Labrador Fertility Services. This allowed capture of all patients who had a uterine septum resection at the Health Sciences Centre in St John's, Newfoundland. These two surgeons were the only two infertility specialists in the province and the only surgeons trained in uterine septum resection at the time of the study. The surgical billing records for the same surgeons and over the same time period were then used to identify the control group. For every patient identified as a uterine septum resection, the next four patients who underwent a diagnostic hysteroscopy for unexplained infertility by the same surgeons were enrolled as control patients. This allowed identification of a control group with similar desire for pregnancy and a similar timeline and follow-up period.

Data collected included surgery date, procedure, surgeon, and the results of the first postoperative pregnancy. Demographic information and previous pregnancy history were also recorded (Table 2).

Table 2: Data Procurement

Type of Data	Unit or Coding in Statistical Software
Maternal age	In years at time of surgery
BMI	kg/m2
Surgeon	Surgeon A or Surgeon B
Surgery date	day/month/year
Surgical procedure	Any combination of: • Hysteroscopy only • Laparoscopy only • Laparoscopy and dye insufflation • Hysteroscopy and dilation and curettage • Uterine septum resection • Laparoscopy with any of adhesionolysis, excision of

	endometriosis, removal of ovarian or paratubal cyst)
Past pregnancy history	• spontaneous abortion • preterm delivery • term delivery • ectopic pregnancy
Length of infertility	Years, as reported by the patient
History of cerclage	Yes or No
First pregnancy postoperatively:	
Date delivered	Day/Month/Year
Length of gestation	Days
If delivery was preterm < 37 weeks gestation	Yes or No
Pregnancy Outcome	• spontaneous abortion, • ectopic, • preterm birth, • term birth
Mode Of Delivery	• spontaneous vaginal birth • operative vaginal birth, • caesarean delivery

Cervical monitoring by ultrasound	Weeks
Shortest cervical length recorded	cm
Short cervix less than 2.5 cm	Yes or No
Composite score of risk factors for preterm delivery (any of antenatal admission, received steroids, short cervix on ultrasound)	Yes or No
Birth Weight	Grams
APGAR scores at 1 and 5 minutes of life	Scored as 0-10
APGAR score less than 7	Yes or No
Neonatal admission to NICU	Yes or No
Stillbirth	Yes or No
Neonatal death	Yes or No
Cerclage	Yes or No

3.4 Data Analysis

Clinically, the most relevant outcome is a healthy, term infant. Indices of this are pregnancy rates, live birth rates, gestational age at delivery and incidence of preterm birth. For the current study, the primary outcome was live birth after surgery. Secondary outcomes were pregnancy rates after surgery (any evidence of pregnancy, including positive serum beta-human chorionic gonadotrophin (β-hCG), evidence of pregnancy on ultrasound), gestational age at delivery, preterm birth before 37 weeks, preterm birth before 34 weeks (clinically a more worrisome outcome for the infant), as well as markers of morbidity (risk factors for preterm birth, admission to NICU, birth weight, APGAR scores).

3.4.1 Data Analysis

3.4.1.1 Analysis of the primary outcome

The primary outcome was live birth after surgery. This is a dichotomous outcome (yes/no) and clinically relatively easy to determine since a live birth is a matter of legislative record in the province (registration of live birth). This outcome should be easy to find in the patient records through a chart review and should not be at risk of observer bias.

3.4.1.2 Analysis of secondary maternal outcomes

The secondary maternal outcomes included a variety of dichotomous and continuous variables. Some of the outcomes could be affected by observer bias or difficult to clearly establish from the patient's records. Maternal age in years, for instance, can clearly be established as all patients would have a date of birth recorded in the chart and a clear date for surgery and delivery of a pregnancy. We chose not to include months for this variable and used whole years only. Fertility outcomes are certainly affected by age, worsening with increasing age, but we did not feel that the data precision required age in months with the goal to show that both the intervention group and control groups were of similar ages in years. If this study had been of a pediatric population, documentation of age in years and months could make a significant change in the precision of the data but in our population the main goal was to determine if the majority of patients were in the peak fertility range (for instance age 20-32 years), later fertility range (age 32-35 years) or advanced fertile age (age 35 and over).

The body mass index (BMI) is recorded in kilograms per meter squared (kg/m^2). Although weight is measured at appointments, it is quite possible that some or many of the recorded patient heights were self-reported by the patients and not measured in a standardized fashion. We do not believe this will limit the study, however, since although most people will overestimate their height (and therefore underestimate their BMI), both the invention group and control group were treated in the same fashion. The purpose of recording a BMI was to show the groups were similar in this characteristic since it is established the elevated BMI and markedly low BMI can affect fertility and pregnancy outcomes.

The surgery data recorded included the surgeon who performed the procedure (dichotomous outcome clearly identified in the chart; Surgeon as 1=A and 2=B), date of surgical procedure in day/month/year (a finite outcome clearly identified in the chart), and surgical procedure the patient underwent (coded in a combination of hysteroscopy, laparoscopy, dye insufflation, dilation and curettage, metroplasty and other (any of adhesionolysis, removal of ovarian or paratubal cyst)).

The surgical technique between the two surgeons is quite similar. The surgical procedure would be clearly documented in the patient's chart and would also be required to be clearly defined for physician billing purposes. Each operative report was reviewed to appropriately categorize the surgical procedure. Not all patients underwent laparoscopy but those with a diagnosis of endometriosis were excluded from the study. Patients had to have "unexplained infertility" to be included in the control group.

3.4.2 Analysis of infant data

3.4.2.1 APGAR score

The Apgar score is an assessment tool for the immediate condition of a neonate at birth. The scoring system, marked out of 10, was published by Dr. Virginia Apgar in

1953 [104]. It is usually recorded at 1 and 5 minutes of life. Although this scoring system is widely used, it is a subjective test. The score is assigned by a health care professional at birth (any one of pediatrician/neonatologist, nurse, pediatric resident or respiratory therapist present at delivery). There is inter-observer variability, but a score of 7 or greater is generally considered to be normal [104]. The dichotomous variable used for our analysis was APGAR < 7 (yes or no). As well, this outcome was measured and recorded by an individual outside of the study. The score is a part of the neonate's chart, independently assigned and unrelated to this study, so the data gathered should not be biased for one group or the other.

3.4.2.2 Admission to NICU

Admission to the Neonatal Intensive Care Unit (NICU) contributes a significant cost to a birth as well as potential morbidity to the child. Hospital acquired infections in the NICU are more common than neonates who are "rooming in" with the mothers in private postpartum care beds.

Scott *et al.* reported for the Canadian Institute for Health Information that in 2002 to 2003, the average cost for Canadian hospitals per NICU admission was $9,700 [105]. In that same year, the average cost per newborn stay was $795 for babies of normal birth weight delivered vaginally without a NICU admission [105]. Fallah *et al.* reported babies born before 37 weeks had an odds ratio of 13.7 (p<0.0001) for admission to NICU [100].

Fallah *et al.* also reported an increased risk of admission to NICU when term neonates were delivered by C-Section (OR 2.7, $p<0.0001$) [100]. Shaulov, Belisle and Duhan reported average NICU length of stays of 10 days [101]. In their analysis of healthcare costs for the province of Quebec's publicly funded IVF program, they reported a total cost for NICU stays for babies conceived through IVF of $4.8 million in 2011 to 2012 alone [101].

The decision to admit a newborn to the NICU is typically under the attending pediatrician or neonatologist. It is possible that a neonate in a certain clinical condition at one hospital would be transferred to the NICU whereas at another hospital, he or she would remain under close supervision in the postpartum ward. Fortunately, there is only one NICU in the province. There are only 5 attending physicians responsible for this unit. Therefore, it is assumed that the decision to admit a child to NICU remained similar throughout the study period.

3.4.2.3 Respiratory Complications

The decision to intubate a newborn can be an urgent and critical decision. Intubation and mechanical ventilation infer risk to the neonate, such as injury and post-extubation airway obstruction [106]. This is a clinical decision, often made by the attending neonatologist as well respiratory therapist. However, since the number of neonatologists and respiratory therapists at our hospital is small, we believe this reduced the inter-patient variability of the clinical decision making. The incidence was low, and the data gathered retrospectively from the infant's chart, so we do not anticipate any bias from one group of subjects to the other.

3.4.2.4 Birth Weight

The weight of the child at birth is a strong indicator of fetal status. It is measured on calibrated scales in the birthing unit and recorded in kilograms. This outcome is a finite value documented in the birth record and should not be subject to any inter-observer variability.

3.5 Statistical Analysis

Data were analyzed using the statistical software SPSS 27 (IBM Corporation, Armonk, New York). Demographic data were reported using descriptive statistics. Testing for normality of continuous data was done using the Shapiro-Wilk test. Q-Q plots were also created. Normally distributed continuous variables were compared using Student's *t* test. Non-normally distributed continuous variables were compared using the Mann-Whitney U test. Categorical variables were compared using Chi-squared test, or Fisher's exact test (if at least 25% of cells contained numbers less than 5).

Multiple logistic regression was used to analyze the live birth rate in relation to several potential confounders. Regarding sample size for multiple logistic regression, a general rule is that the number of subjects should be 5 to 10 times the number of variables in the multiple logistic regression model. The potential confounders that were analyzed included: chief complaint (recurrent pregnancy loss, primary infertility or secondary infertility); surgeon (surgeon 1 or surgeon 2); gravity (0-9); parity (0-2); nulliparity (yes or no); previous preterm birth (yes or no); previous full-term birth (yes or no); previous miscarriage (yes or no).

The multiple logistic regression model was run using the backwards stepwise selection method. The variables included in the model were selected based on biological plausibility to affect live birth rate or pregnancy rate. For the univariate and multivariate analyses, a p-value less than 0.05 for the primary outcome was considered significant.; and for the secondary outcomes a p value less than 0.01 was considered statistically significant.

3.6 Confidentiality and Ethics

Subjects were identified using surgical billing records. Data were extracted from patient charts by the lead researcher. The patient's names and demographic data were available to the lead researcher. Once a subject was identified, data were then recorded in a confidential manner and each subject was assigned a random, non-identifying 3-digit subject number. Once the data were recorded in SPSS, the patient charts were no longer used for any further study purpose. All data were recorded and analyzed in SPSS using the anonymous subject number. The original paper copies of the recorded data were kept in a locked office. The computer used to analyze the non-identifying data in SPSS is password protected, the study files on the computer were password protected and the laptop was kept in a locked office.

Study approval was granted by the Human Investigation Committee at Memorial University (Reference # 10.161, Appendix C).

Chapter 4: Results

4.1 Sample

All patients who underwent a metroplasty resection at the Health Sciences Center from October 2003 until June 2011 were reviewed. The indication for surgery varied, including patients with recurrent pregnancy loss, primary and secondary infertility. However, in order to be included in this analysis, the patients could not have any other additional reasons for their subfertility, such as endometriosis, anovulation, or male factor. This resulted in 50 intervention patients.

These intervention patients were then matched with patients undergoing a hysteroscopy for unexplained infertility. The control group included patients with recurrent pregnancy loss, primary and secondary infertility. In order to be included in this analysis, the patients in the control group could not have any other reasons identified for their subfertility, such as endometriosis, anovulation, male factor.

The 50 intervention patients were matched with 189 patients undergoing a hysteroscopy for unexplained infertility (total 239 patients). The study design for 1:4 intervention to control would have required 212 matched controls for the metroplasty patients; unfortunately, only 189 patients with unexplained infertility were identified during that time frame. The study was underpowered for the sample size calculation of 53 intervention patients matched with 212 control patients. This is due to a lack of eligible patients during the eight-year study time period.

4.2 Patient Demographics

The demographic characteristics of the 239 patients are summarized in Table 3. A key difference noted between the two groups is the stated ‘chief complaint’ for patients. Due to the pathophysiology of a uterine septum, and the possibility of a pregnancy implanting on the septum and leading to early pregnancy loss, it is not unexpected that the uterine septum group had a significantly higher proportion of patients with recurrent pregnancy loss compared to primary and secondary infertility.

Table 3: Patient Demographics

	Uterine Septum Resection N=50	Unexplained Infertility N=189	p-value
Age at surgery (years)	33.4 [4.7]$^{\sigma}$	33.9 [4.1]$^{\sigma}$	0.46$^{\tau}$ 0.54$^{\Sigma}$
BMI (kg/m^2)	28.7 [5.7]$^{\sigma}$	27.1 [5.6]$^{\sigma}$	0.084$^{\tau}$ 0.054$^{\Sigma}$
Years trying to conceive	4.57 [2.9]$^{\sigma}$	4.04 [2.9]$^{\sigma}$	0.17$^{\mu}$ <0.001$^{\Sigma}$
Chief complaint			
RPL*	22 (44.0)$^{\psi}$	12 (6.3)$^{\psi}$	
1◦ infertility	16 (32.0)$^{\psi}$	106 (56.1)$^{\psi}$	<0.0001$^{\chi}$
2◦ infertility	12 (24.0)$^{\psi}$	71 (37.6)$^{\psi}$	
Surgeon			
A	31 (62.0)$^{\psi}$	107 (56.6)$^{\psi}$	0.49$^{\varphi}$
B	19 (38.0)$^{\psi}$	82 (43.4)$^{\psi}$	
Previous preterm birth	2 (4.0)$^{\psi}$	4 (2.1)$^{\psi}$	0.45$^{\varphi}$
Previous full-term birth	8 (16.0)$^{\psi}$	45 (23.8)$^{\psi}$	0.34$^{\varphi}$

Variables are reported in mean [standard deviation]$^{\sigma}$ or mean (percentage)$^{\psi}$
*** RPL = recurrent pregnancy loss**
τ: Student's t test
φ: Fisher's exact test
χ: Chi squared test
σ: Standard deviation
ψ: Percentage
Σ: Shapiro-Wilk
μ: Mann-Whitney Test

Of note, there was no difference in history of previous preterm birth between the two groups, (4.0% compared with 2.1 %, p=0.45). As well, there was no difference between the two groups in the history of a previous full-term birth. (16.0% vs 23.8 %. p=0.34). However, there was a difference between the groups in the reported history of a previous spontaneous abortion (58.0% vs 28.6%, p<0.0001). This is consistent with the patient population as it would be expected that patients with an unresected uterine septum have a higher chance of miscarriage than patients with a normal uterine cavity.

Testing of normality of data was done using the Shapiro-Wilk test. Years trying to conceive was not normally distributed so groups were compared using the Mann Whitney U test (U=4045, p=0.17). This most likely occurred due to outliers in the groups. Many patients will seek fertility investigations and treatment after 1 year. In our study population, one patient reported 18 years of trying to conceive. The length of infertility in the two groups were not statistically significant so the outliers should not have skewed the results.

4.3 Effect of Surgery on Live Birth Rate

There were 89 live births reported from the 119 pregnancies of the 239 patients in this study. The primary outcome, live birth after surgery, is reported in Table 4. Confirming my hypothesis, there was a significantly greater percentage of live births

(52%) following septum resection compared to expectant management (33%), RR=1.56 [1.12-2.18], p = 0.015, Chi squared test). A subgroup analysis was performed using the patient's reproductive history of recurrent pregnancy loss, primary or secondary infertility, demonstrating differences in the live birth rates depending on the patient's preoperative fertility history, as reported in Table 4 (p=0.001, Chi squared test).

Table 4: Live birth after surgery

	Uterine Septum Resection		Unexplained Infertility		p-value	Relative Risk	95% CI
	N	(%)	N	(%)			
Live Birth	26 (50)	52.0	63 (189)	33.3	0.015$^{\chi}$	1.56	1.12-2.18
Subgroup Analysis:							
RPL*	10 (22)	45.5	4 (12)	33.3	0.49$^{\chi}$	1.36	0.54-3.43
1◦ infertility	8 (16)	50.0	36 (106)	34.0	0.21$^{\chi}$	1.47	0.84-2.57
2◦ infertility	8 (12)	66.7	23 (71)	32.4	0.023$^{\chi}$	2.06	1.22-3.47

χ: Chi squared test
***RPL = recurrent pregnancy loss**
CI = Confidence Interval

4.4 Effect of Surgery on Pregnancy Rate

There were 119 recorded pregnancies during the study. One of the secondary outcomes, pregnancy rate after surgery is shown in Table 5. There was a significantly greater percentage of pregnancies (72%) following septum resection compared to expectant management (41%), RR=1.74 [1.38-2.21], $p < 0.001$, Chi squared test.

Table 5: Obstetrical Outcomes After Surgery By Gestational Age

	Uterine Septum Resection		Unexplained Infertility		p-value	Relative Risk	95% CI
	N	(%)	N	(%)			
Any Pregnancy	37	72.0	82	41.2	<0.001$^{\chi}$	1.74	1.38-2.21
Of Patients Who Achieve Pregnancy							
Delivery <12 weeks	10	20.0	16	19.5	0.58$^{\varphi}$		
Delivery 12+0 to 19+6	1	2.7	3	3.7			
Delivery 20+0 to 23+6	0	-	0	-			
Delivery 24+0 to 31+6	3	8.1	2	2.4			
Delivery 32+0 to 34+6	0	-	1	1.2			
Delivery 35+0 to 36+6	1	2.7	2	2.4			
Delivery 37+0 onwards	22	59.4	58	70.7			

χ: Chi squared test
φ: Fisher's exact test
CI = Confidence Interval

The obstetrical outcome and mode of delivery were also summarized (Table 6). Excluding spontaneous abortions and ectopic pregnancies, the three modes of delivery (spontaneous vaginal birth, operative vaginal birth, and Cesarean section) were compared. The groups were not significantly different in mode of birth (p=0.56, Chi squared test).

Table 6: Obstetrical Outcomes After Surgery By Mode of Delivery/Pregnancy Loss

	Uterine Septum Resection		Unexplained Infertility		p-value
	N	(%)	N	(%)	
Pregnancy	37	72.0	82	41.2	<0.001$^{\chi}$
Spontaneous Abortion	10	20.0	14	7.4	0.13$^{\chi}$
Ectopic	0	0	3	1.6	0.55$^{\varphi}$
Of All Live Births:					
Spontaneous Vaginal Delivery	15	30.0	28	14.8	0.56$^{\varphi}$
Operative Vaginal Delivery	2	4.0	7	3.7	
Cesarean Section	9	18.0	27	14.3	

χ: Chi squared test
φ: Fisher's exact test

4.5 Effect of Surgery on Preterm Birth Rate

There were 89 live births reported from the 119 pregnancies of the 239 patients in this study. Of these, 9 were recorded as preterm (24+0 to 36+6 weeks gestational age), (7.6%). Data was recorded from birth records of gestational ages at delivery. One patient was excluded from the analysis of preterm birth rate due to an iatrogenic preterm birth identified by the lead researcher (induced preterm delivery due to pre-eclampsia). From 37 pregnancies, there were 4 spontaneous preterm births from the septum resection group (10.8 %) compared to 5 spontaneous preterm births from 82 pregnancies (6.1 %) from the control group, as reported in Table 7. The groups were not significantly different in rates of preterm birth (p=0.37, Fisher's exact test). Subgroups analysis for late preterm birth (35+0 to 36+6 weeks), moderately preterm birth (32+0 to 34+6 weeks) and very preterm birth (24+0 to 31+6 weeks) was performed. The groups were not statistically significant (p=0.17, Fisher's exact test).

Table 7: Preterm Birth After Surgery, By Gestational Age

	Uterine Septum Resection	Unexplained Infertility	p-value
	N (37) (%)	N (82) (%)	
Delivery 24+0 to 36+6	4 (10.8)	5 (6.1)	0.37 φ
Delivery 24+0 to 31+6	3 (8.1)	2 (2.4)	
Delivery 32+0 to 34+6	0	1 (1.2)	0.17φ
Delivery 35+0 to 36+6	1 (2.7)	2 (2.4)	

φ: Fisher's exact test

4.6 Effect of Surgery on Maternal and Neonatal Morbidity

4.6.1 Antepartum Maternal Morbidity

Obstetric morbidity can also include antepartum complications, such as administration of medication, admission to hospital and even increased frequency of pelvic examinations and transvaginal ultrasounds. We defined several common antepartum outcomes as obstetrical morbidity for the purpose of this study. These were: cervical length less than 2.50 cm by TVUS, any antepartum admission to hospital for threatened preterm labour, any identification of a diagnosis in the obstetric record of "threatened preterm labour", administration of antenatal corticosteroids to the mother for fetal lung maturation or administration of any tocolytic to stop uterine contractions (Table 8).

Table 8: Antepartum Maternal Morbidity For Pregnancies >24 weeks Gestation

	Uterine Septum Resection	Unexplained Infertility	p-value	Relative Risk	95% CI
	N (27) (%)	N (65) (%)			
Antenatal admission to hospital	7 (25.9)	5 (7.7)	0.018^{χ}	3.37	1.17-9.69
Administration of Steroids	6 (22.2)	3 (4.6)	0.019^{φ}	4.81	1.30-17.87
Administration of tocolytics	1 (3.7)	0 (0)	0.29^{φ}		
Composite risk of preterm birth	8 (29.6)	7 (10.8)	0.035^{χ}	2.75	1.11-6.83

χ: Chi squared test
φ: Fisher's exact test
CI= Confidence Interval

Due to the small study and rarity of some of these outcomes, a composite score was given if any occurred. Overall, 8 of the 27 patients from the uterine septum resection group were identified with a risk factor for preterm birth and 7 of 63 patients from the control group (29.6% vs 11.1%, p=0.035). This outcome does not reach statistical significance based on our definition of statistical significance for secondary outcomes.

4.6.2 Neonatal Morbidity

Neonatal morbidity is as an important secondary outcome. As obstetrical care providers, gestational age at delivery is clinically relevant, as reported in Table 9. The indicators for neonatal morbidity include APGAR score at 1 and 5 minutes of life, admission to NICU, admission to NICU for more than 24 hours, and neonatal death (death in the first 28 days of life), as reported in Table 10.

Neonatal morbidity was not recorded for any previable birth. We defined viability as 24 weeks gestation for this study. From the 87 potentially viable live births, 26 were from the septum resection group (30%) and 61 from the control group (70%). There were no significant differences between the groups with short-term morbidity (1 and 5-minute APGAR scores) or intermediate morbidity (admission to NICU, admission to NICU for more than 24 hours).

There was only 1 death in the study which was from the control group. The neonate was preterm and died from complications due to extreme prematurity. There were no stillbirths in either group.

4.6.2.1 Gestational Age and Birth Weight at Delivery

Clinically it was felt that gestational age and birth weight were important secondary outcomes for neonatal morbidity. As continuous variables, it would be easier to compare the two study groups even with a small sample size.

Excluding the 30 pregnancies that were considered nonviable (either ectopic or delivered before 24 weeks), the gestational age at delivery was also recorded as a marker for morbidity. Of the 89 live births, the mean gestational age at delivery was 268 +/- 20.6 days for the septum resection group compared to 274 +/- 16.8 days for the control group. Using the Mann-Whitney U test, this difference was not statistically significant (U=1231, p=0.10), as reported in Table 9.

Of the 89 live births, the mean birth weight was 3378 +/- 175.5 grams for the septum resection group compared to 3401 +/- 85.2 grams for the control group. Using the Mann-Whitney U test, this difference was not statistically significant (U= 3183, p=0.65), as reported in Table 9.

Table 9: Gestational Age and Birth Weight of all Viable Births

	Uterine Septum Resection	Unexplained Infertility	
	Mean [Std. Deviation]	Mean [Std. Deviation]	p-value
Gestational Age (days)	268 [20.6]	274 [16.8]	0.10$^{\mu}$ <0.001$^{\Sigma}$
Birth Weight (grams)	3378 [175.5]	3401 [85.2]	0.65$^{\mu}$ <0.001$^{\Sigma}$

μ: Mann-Whitney Test
Σ: Shapiro-Wilk

4.6.2.2 Composite Score for Neonatal Morbidity

Due to the low incidence of outcomes, a composite score for neonatal morbidity was created by the group to include any of: APGAR score less than 7 at 5 minutes, admission to NICU for greater than 24 hours, neonatal death and stillbirth, as reported in Table 10.

Table 10: Neonatal morbidity

	Uterine Septum Resection	Unexplained Infertility	p-value	Relative Risk	95% CI
	N (%)	N (%)			
APGAR <7 at 1 minute	5(19.2)	6 (9.8)	0.20$^{\chi}$		
APGAR <7 at 5 minutes	0	2 (3.3)	0.49$^{\varphi}$		
Admission to NICU	3 (11.5)	4 (6.6)	0.34$^{\varphi}$		
Admission to NICU >24 hours	3 (11.5)	3 (4.9)	0.24$^{\varphi}$		
Stillbirth	0	0	-		
Neonatal death	0	1 (1.6)	0.70$^{\varphi}$		
Composite neonatal morbidity	3 (11.5)	4 (6.5)	0.029$^{\varphi}$	1.81	0.44-7.56

χ: Chi squared test
φ: Fisher's exact test
CI= Confidence Interval

The incidence of neonatal morbidity using a composite score was still low in both groups and did not reach statistical significance between the two groups. Three births from the septum resection group and 4 from the control group (11.5% vs 6.5%) experienced neonatal morbidity (p=0.029).

4.7 Logistic Regression Evaluating Outcomes of Interest

4.7.1 Live Birth After Surgery

Logistic regression analysis was performed for our primary outcome (live birth) comparing the uterine septum resection group (SR) with the control group (DH). The regression analysis was performed using the backward conditional method to step-wise exclude variables p>0.10 until a final model was reached. Variables included in the initial analysis were: subject age at the time of surgery, body mass index (BMI) at the time of surgery, length of infertility at enrollment into the fertility clinic and obstetric history (nulliparity, history of preterm birth, history of full-term birth, history of miscarriage, previous live birth) as reported in Table 11.

Table 11: Logistic Regression Analysis of all Variable Comparing Uterine Septum Resection to Diagnostic Hysteroscopy on Live Birth Rates – Initial Model

Outcome	Adjusted OR	P-value	95 % CI	
			Lower	Upper
Septum resection group	2.30	0.028	1.09	4.83
Age at surgery	0.96	0.30	0.90	1.04
Body Mass Index	0.97	0.36	0.92	1.03
Years trying to conceive	0.82	0.002	0.72	0.93
Nulliparity	1.10	0.89	0.32	3.80
Previous preterm birth	3.48	0.48	0.11	113.26
Previous term birth	1.41	0.82	0.080	24.86
Previous miscarriage	1.34	0.60	0.45	3.99
Previous live birth	0.72	0.79	0.062	8.28

The final model demonstrated the study group (SR or DH, p=0.016) and years trying to conceive (p=0.001) were significant variables to predict live birth after surgery, as reported in Table 12.

Table 12: Logistic Regression Analysis Comparing Uterine Septum Resection to Diagnostic Hysteroscopy on Live Birth Rates - Final Model

Outcome	Adjusted OR	P-value	95 % CI	
			Lower	Upper
Septum resection group	2.35	0.016	1.17	4.74
Years trying to conceive	0.81	0.001	0.72	0.92

4.7.1.1 Subject BMI

There was no body mass index recorded for 25 of the 239 patients. When the regression analysis for live birth after surgery was repeated excluding the 25 patients with a missing BMI value, the primary outcome remained the same. The study group (SR or DH, p=0.016) and years trying to conceive (p<0.001) remained significant in predicting live birth after surgery, as reported in Table 13.

Table 13: Logistic Regression Comparing Uterine Septum Resection to Diagnostic Hysteroscopy on Live Birth Rates for patients with a known BMI – Final Model

Outcome	Adjusted OR	P-value	95 % CI	
			Lower	Upper
Septum resection group	2.35	0.016	1.17	4.74
Years trying to conceive	0.81	<0.001	0.72	0.92

4.7.2 Pregnancy After Surgery

Logistic regression was performed comparing patients with a uterine septum resection with the control group, using pregnancy rates after surgery as the primary outcome. The same variables of interest as reported in Table 10 were included. The study group ($p<0.001$) and years trying to conceive ($p=0.005$) remained significant variables to predict live birth after surgery, as reported in Table 14.

Table 14: Logistic Regression Comparing Uterine Septum Resection to Diagnostic Hysteroscopy on Pregnancy Rates – Final Model

Outcome	Adjusted OR	P-value	95 % CI	
			Lower	Upper
Septum resection group	3.78	<0.0001	1.80	7.93
Years trying to conceive	0.86	0.005	0.77	0.96

4.7.3 Preterm Birth (less than 37 weeks)

Logistic regression was performed comparing patients with a uterine septum resection with the control group, using spontaneous preterm birth as the primary outcome (live birth before 37+0 weeks' gestation). The analysis was limited to those patients who achieved a pregnancy of potential viability (at least 24 weeks gestation). None of the variables were statistically significant.

4.7.4 Preterm Birth (less than 34 weeks)

Logistic regression was then performed using early preterm birth as the primary outcome (live birth before 34+0 weeks' gestation). None of the variables were statistically significant secondary outcomes, as reported in Table 15.

Table 15: Logistic Regression Comparing Uterine Septum Resection to Diagnostic Hysteroscopy on Preterm Birth (<34 weeks) – Final Model

Outcome	Adjusted OR	P-value	95 % CI	
			Lower	Upper
Previous preterm birth	19.25	0.049	1.01	367.21

Chapter 5: Discussion

Infertility is a common medical condition, affecting approximately 1 in 7 couples. Although the incidence appears to be increasing as many patients delay childbearing to pursue further education and establish their career, infertility is not a recent medical condition. Guttmacher's publication on data from 1940-1950s continues to be the basis of the Reproduction Endocrinology and Infertility communities' knowledge of the prevalence of infertility [6]. Despite advances in assisted reproductive technologies and IVF, infertility remains for many couples.

A thorough investigation of couples is often warranted. Of all medically recognized pregnancies (a positive β-hCG), approximately 1 in 4 will end in early pregnancy loss. Although Mullerian anomalies are relatively rare, an important step in investigations for infertility is evaluation of the uterine cavity [13].

At the time this study was started, it was larger than previously published studies [18,38,41]. This study covered almost one decade of patients from a tertiary care fertility center. Using hospital records and provincial data over this long period allowed an extensive collection of possible pregnancy and birth outcomes, with few patients lost to follow up. This study demonstrated that treatment of the septum improves live birth rate and pregnancy rates in patients with a history of recurrent pregnancy loss or infertility.

5.1 Study Outcomes

This study suggests that treatment of the septum may improve live birth rates and pregnancy rates, in patients with a history of recurrent pregnancy losses and/or those with primary or secondary infertility. Obstetric history is an important predictive factor for outcomes in future pregnancies. Patients with a previous preterm birth are often monitored differently in subsequent pregnancies to reduce infant morbidity and mortality. This difference in obstetrical care could create some confounding to the outcomes from the cohort study design. Therefore, it was felt to be an important variable from the outset with the study design to record whether or not the patients included in either cohort reported a history of a preterm or full-term birth.

5.1.1 Live Birth Rates after Uterine Septum Resection

The results of this study are consistent with the previously published prospective and retrospective cohorts in the literature review [37-40, 85, 89, 90]. The live birth rate was 52.0% (26 live births from 50 patients) in the postoperative septum resection cohort compared to 33.3% in the control group (63 live births from 189 patients, p=0.015, Table 4). Colacurci *et al.* had a study population of 69 patients with no previous live births [39]. Postoperatively, 52% (36/69) had a live birth. Saygili-Yilmaz *et al.* reported a live birth rate of 13.5% in the primary infertility group and 64.9% in the previous pregnancy loss group [87]. Pabuçcu and Gomel reported a live birth rate of 30% [40]. Mollo *et al.* reported a live birth rate of 34.1% [41]. Nouri *et al.* reported a live birth rate of 49% [92]. Pang *et al.* did not explicitly report live birth rates, but did report term and preterm births (46/76, 60.5%) [93]. Rikken *et al.* reported lower live birth rates after surgery,53.0 % (80/151) compared to 71.7% (76/106) who chose expectant management [94].

The only published randomized control trial did not find a significant difference in live births after surgery. In the TRUST study published by Rikken *et al.* live birth occurred in 12 of 39 patients allocated to septum resection (31%) and in 14 of 40 patients allocated to expectant management (35%) (relative risk (RR) 0.88 (95% CI 0.47 to 1.65) [95]. Live birth had to occur within 12 months after randomization, or if the patient became pregnant within 12 months, the pregnancy was followed to completion [95]. Twelve months of follow up is consistent with the previously published cohorts and our study design [37-40, 85, 89, 90]. However, patients in our cohort were followed for at least 12 months postoperatively, so this may partially explain our higher live birth and pregnancy rates. The surgical technique in this RCT was not standardized but 69% of patients underwent a diagnostic control hysteroscopy 6-8 weeks after surgery to assess the results of the septum resection [95]. Our study cohort included only two surgeons and it is possible their surgical technique resulted in higher live birth rates and pregnancy rates. It is also possible that our cohort inadvertently excluded patients with small uterine septa that current ultrasound technology would have diagnosed. The TRUST study cohort [95], which is more recent, may have included patients which smaller and less clinically relevant uterine septa. The patients with small uterine septa are perhaps are less likely to have improved obstetrical outcomes postoperatively.

Some studies in our literature review reported live births as a proportion of pregnancies instead of the total cohort. Ayhan et al. reported a live birth rate of 30 out of 46 pregnancies (65.2%) [38]. Fedele and Bianchi reported a cumulative live birth rate of 39% in patients with previous primary infertility and 67% in patients with recurrent pregnancy loss [18]. In our study cohort, 26 live births came from 39 pregnancies (66.7%, Table 3, Table 5), which is also consistent with the previous publications.

The study was powered to find an absolute difference of 20% in the live birth rate. We calculated a need of 53 treated patients for our sample size and were only able to identify and include 50. We were only able to match the uterine septum resection patients with 189 control subjects, instead of 192 control patients required from the power analysis. The study, therefore, was inadequately powered. Despite this, multiple logistic regression analysis did demonstrate a significant improvement in live birth rate between the septum resection group and the control group ($p=0.016$, Table 12).

5.1.2 Pregnancy Rates after Uterine Septum Resection

A secondary outcome of importance was pregnancy rate after uterine septum resection. In our study cohort, 119 pregnancies were documented. A total of 37 of 50 patients from the uterine septum resection group (72.0%) and 82 of 189 patients from the control group (41.2%), $p<0.0001$ (Table 6). Multiple logistic regression analysis demonstrated a significant improvement in the pregnancy rate in the septum resection group compared to the control group (p<0.001, Table 14).

Ayhan et al. reported pregnancy rates of 46 out of 49 patients (93.9%) [38]. However, this data was collected retrospectively over 20 years and 1 patient could contribute more than 1 pregnancy to the study cohort, so it is not a true “pregnancy rate”. As well, preoperatively this cohort had a pregnancy rate of 90%. Fedele and Bianchi reported a pregnancy rate of 80-89% over 36 months [18]. Colacurci *et al.* reported an overall pregnancy rate of 66.7% from 69 patients [39]. Nouri *et al.* reported a pregnancy rate after hysteroscopic septoplasty of 69% (34/49) [92]. Pang *et al.* **r**eported a pregnancy rate was higher in the recurrent spontaneous abortion group who underwent hysteroscopic septum resection, 80.4% (37/46) compared to expectant management, 56.3% (18/32) [93]. In patients with no prior poor reproductive history, there was no difference in the pregnancy rates [93]. Rikken *et al.* reported **p**regnancy rates were higher in the surgery group, (51/151 [46.8%] compared to 31/106 [34.4 %]) who chose expectant management [94]. The TRUST study reported a pregnancy rate of 56% in the surgery group compared to 48% in the control group (RR 1.2 [0.77-1.2]) [95].

Our results are generally consistent, although our pregnancy rates were higher than all except Pang *et al.* [93]. Our control included all patients who presented to the fertility clinic for investigations who then underwent a diagnostic hysteroscopy for unexplained infertility, regardless of their obstetrical history. We also believe we lost few patients to follow up due to our province wide EMR. The cohort for Colacurci *et al.* had a study population with no previous live births [39]. Saygili-Yilmaz *et al.* reported a lower pregnancy rate than many of the other studies in our review [87]. From 361 patients, only

49.9% achieved pregnancy postoperatively [87]. Pabuçcu and Gomel reported a pregnancy rate of 41.0% [40]. Mollo *et al.* reported a pregnancy birth rate of 38.6% [41]. These lower pregnancy rates than found in our study is likely due to the short time patients were followed in the Saygili-Yilmaz *et al.* cohort (only 18 months) [87], Pabuçcu and Gomel followed patients for "at least" 8 months postoperatively (mean 11 months) [40], Mollo *et al.* for 12 months postoperatively [41]. Rikken *et al.* [94] and the TRUST study [95] followed for 12 months after randomization, whereas our study group were followed for "At least 12 months" up until the study end time.

5.1.3 Preterm Birth Rate after Uterine Septum Resection

Preterm birth affects approximately 8% of births [43]. Of the 119 pregnancies in our total study cohorts, we reported 9 preterm births (7.6%) (Table 7). Four preterm births were from the uterine septum resection group (10.8%) compared to 5 from the control group (6.1%) (Table 7).

Most studies included in our review had significantly higher preterm birth rates. Ayhan *et al.* reported 22 preterm births from 46 pregnancies (45%) postoperatively [38]. Mollo *et al.* reported 3 preterm births from 17 pregnancies (17.6%) compared to a lower preterm birth rate of 3.7% in their control group [41]. Saygili-Yilmaz *et al.* reported 34 preterm births from 190 pregnancies (19%) [87]. However, only 53% of these babies survived which leaves the reader to assume many were extremely premature births.

Several studies included in the literature review chose to define preterm differently than our study. Fedele & Bianchi reported 10 preterm births from 55 pregnancies (18%), using before 38 weeks as the definition for preterm [18]. Colacurci *et al.* reported 5 preterm births (11%) but defined preterm as before 36 weeks [39]. Pabuçcu & Gomel also defined preterm at before 36 weeks [40]. They reported a preterm birth in 5 of 18 live births (28%) [40].

Pang *et al.* **r**eported a significant lower preterm birth rate in patients who underwent hysteroscopic septum resection 5.4% vs 27.8% ($P<0.05$) in the cohort of patients with a history of recurrent spontaneous abortion [93]. In patients with no prior poor reproductive history, there was no difference in the preterm birth rates [93]. Rikken *et al.* reported preterm birth rates were higher in the surgery group, 29.2% (26/151) compared to 16.7 % (13/106) in the expectant management group [94]. The TRUST study reported a preterm birth rate of 13% in the surgery group compared to 10% in the control group (RR 1.3 [0.37-4.4]) [95].

Patients with a history cervical instrumentation and excisional procedures are also at higher risk of preterm birth [48–50,52–54]. Our study cohort and comparison group were chosen to control for known risk factors, as all patients had at least a hysteroscopy to be included in the analysis.

In our study cohort, 2 of the 50 patients from the uterine septum resection group (4%) and 4 of the 189 patients from the control group (2.1%) had a history of preterm birth (Table 2). This is below the population average but was not a significant difference between the groups ($p=0.45$).

Ayhan *et al.* had a preoperative preterm birth rate of 8% (14 of 173 pregnancies). Postoperatively the rapid increase in preterm birth to 45% is better represented by an increase in fetal survival from 3.7% to 65% [38].The relative risk of a preterm birth when pregnant in this cohort was high, but the procedure markedly increased the fetal survival rate. Infant morbidity was not reported [38].

The incidence of preterm birth in our control group is similar to the population average. It is difficult to comment on why our septum resection group had a much lower rate of preterm birth than any of the studies included in the literature review. This could be changes in obstetric practices over the last decade to reduce preterm birth, such as close cervical length monitoring or less aggressive instrumentation and surgical technique by our two study surgeons. Multiple logistic regression analysis did not demonstrate a significant difference in live birth rates before 37 weeks or 34 weeks between the septum resection group and the control group.

5.1.4 Maternal Morbidity after Uterine Septum Resection

5.1.4.1 Obstetric Operative Delivery

Obstetric operative delivery (cesarean section, forceps) can create morbidity for patients. This could be an important factor in preoperative counselling for fertility patients considering uterine septum resection.

We did not anticipate an increased morbidity at delivery for patients with a uterine septum resection. It is possible patients with a uterine septum may have decrease obstetric morbidity for delivery since the congenital uterine anomaly is believed to cause weakening of the cervix and could possibly improve spontaneous delivery rate. A uterine septum that is not completely resected could increase the rate of fetal malpresentation (e.g. breech presentation) which would increase the rate of elective caesarean section. As reported in recorded Table 4, there was not a significant risk of operative delivery for patients in the uterine septum resection group for caesarean section (p=0.41) or forceps delivery (p=0.72). This is consistent with data published in the TRUST study, which reported no differences in mode of delivery (caesarean section or spontaneous birth) in the two groups (RR=1.9 [0.88-5.0]) [95].

5.1.4.2 Operative Treatment of Pregnancy Loss

We were unable to obtain from the data set if patients experiencing ectopic pregnancy or early pregnancy loss were subject to further surgery such as laparoscopy, laparotomy or dilation and curettage. Some ectopic pregnancies may have been medically managed or surgically managed, but this information is not available. However, there were only 3 ectopic pregnancies in the entire data set, all from the unexplained infertility group and this was not significant (p=0.55, as reported in Table 6). We do not know if patients with miscarriage had expectant, medical management, or surgical treatment.

There were 10 miscarriages in the uterine septum resection group and 15 in the unexplained infertility group. There could be trauma to the uterus and cervix if operative treatment was required with a dilation and curettage, but this is not known. However, the groups did not have a significant difference in miscarriage (p=0.13, as reported in Table 6).

5.1.4.3 Antepartum Maternal Morbidity

We defined several common antepartum outcomes as obstetrical morbidity for the purpose of this study, as reported in Table 8. None of the studies in our literature review reported outcomes on maternal morbidity. This was a secondary outcome in our study that was identified in the initial study planning as clinically relevant. The statistically significant increased rate of obstetrical morbidity from the study group could be explained by several factors. Patients in the uterine septum resection group were thought to be at increased risk of preterm birth, based on many published results from our literature review [18,38,40,41,87]. Saygili-Yilmaz *et al.* reported a fetal survival of only 53% in live births [87]. Patients with a history cervical instrumentation and excisional procedures are also at felt to be higher risk for preterm birth and pregnancy complications [48–50,52–54]. Due to these studies, it is expected that the patients in the uterine septum resection cohort were more likely to be considered high risk once they were pregnant. Therefore, they likely had closer clinical monitoring, more appointments and ultrasounds and were then more likely to be identified for other markers of antepartum maternal morbidity.

5.1.5 Neonatal Morbidity after Uterine Septum Resection

Neonatal morbidity was not reported in the studies included for our literature review but was identified during the study planning as important secondary outcomes. There were no significant differences between the groups with short-term morbidity (1 and 5-minute APGAR scores), intermediate morbidity (admission to NICU, admission to NICU for more than 24 hours) (Table 10). This is likely because the study was underpowered for secondary outcomes.

There was only 1 death in the study which was from the control group. The neonate was born preterm, and cause of death was extreme prematurity. There were no stillbirths in either group. This is likely due in part to the small sample size as the rate of stillbirth in Canada is between 0.5 and 1% [43].

5.1.5.1 Gestational Age at Delivery

Clinically it was felt that gestational age was an important secondary outcome for neonatal morbidity. As a continuous variable it would be easier to compare the two study groups even with a small sample size. As well, it would be clinically relevant for counselling patients preoperatively for expected pregnancy outcomes. The different rates in preterm birth and term birth are clinically relevant, but it may be easier to counsel patients on “real life” outcomes if they were presented outcomes using an everyday metric like “days”. Couples can relate to the difference of a baby being born 4 days earlier vs 3 weeks premature, when comparing the two study groups. As reported in Table 7, the difference in length of pregnancy between the groups was six days, but this did not reach statistical significance.

The uterine septum resection group delivered on average less than 1 week earlier than the control group. The non-significant difference in gestational ages at delivery should be very useful to counsel patients if they decided to proceed with a uterine septum resection as well as to be reassured that the postoperative pregnancy length is similar to the matched controls.

5.1.5.2 Composite Score for Neonatal Morbidity

The incidence of neonatal morbidity was low in both groups. Due to the low incidence of outcomes, a composite score for neonatal morbidity was created, as reported in Table 9 The studies comparison studies in the literature review did not report neonatal outcomes. The study was underpowered to analyze these secondary outcomes.

If the six patients with a history of preterm birth are excluded from this analysis (2 from the study group and 4 from the control group), only 1 other patient experienced neonatal morbidity that could not be explained by previous obstetrical history. This patient was in the uterine septum resection group. Due to the low incidence, causality cannot be implied from the uterine septum or the surgical resection.

5.2 Limitations of the Study

Although this study cohort spanned almost 8 years of records at our institution, only 239 patients met the inclusion criteria to be included in the analysis. The power calculation to demonstrate a 20% improvement in live birth rates for the sample size required was only 53 study patients matched with 212 controls (alpha 5%, beta 80%). However, this required a study timeline of close to 1 decade, and even then, we were unable to reach the calculated sample size. The study was underpowered to evaluate secondary outcomes. We were unable to do subgroup analyses based on the indication for referral to Newfoundland and Labrador Fertility Services (e.g., primary infertility, secondary infertility, or recurrent pregnancy loss).

We are not aware of any significant changes to the surgical technique of either study surgeon during that time based on operative reports. Small changes of operative technique could have occurred over the study period. Likewise, other fertility therapies are constantly being developed that could affect the overall pregnancy rates and preterm birth rates for both groups. It is possible one of these advancements in therapy could have favoured one group over the other, although it is not expected.

As the tertiary care center for the entire province, it is assumed that an overwhelming majority of patients undergoing fertility investigations and treatments would have presented to the study physicians, but it is not known. Some patients, particularly from further outside the metropolitan area, may have chosen to fly out of province for treatment. If these patients were paying for care privately (for instance private-pay IVF), they most likely would have only done so after the fertility clinic had ensured a normal uterine cavity. It is possible, although unlikely, that these unknown patients would have affected the control group outcomes. After identifying a cause for infertility, patients may have self-referred to a local gynecologist for treatment to be covered under their provincial health care and save expenses.

All cohort studies are limited by the data available. Although extensive effort was made to seek missing chart data from patients who delivered outside of the Avalon peninsula, some data could not be obtained. It is not known is this could have affected the outcomes of this small study sample, but Logistic regression analysis did not reveal and obvious confounding (for instance with missing BMI data). Smoking status was not recorded. Since all of the extracted data is anonymized for confidentiality, we are unable to feasibility go back to extract the data from patient charts.

The treatment group of patients were all operated on by one of two REI surgeons. Although this reduced variability in the study outcomes as the surgical techniques were quite similar and reproducible, it could limit the application of the study conclusions to other centers whose surgeons have different operative techniques for uterine septum resection.

5.3 Dissemination of the Work

Our goal is to share the data documented in this cohort throughout the Canadian Obstetrics and Gynecology community and with fertility treatment centers worldwide. The work has been presented in abstract form at a national conference and locally as part of the Memorial University Dept of Obstetrics and Gynecology Research Day forum. Our next goal is publication of an article in a dedicated Fertility journal.

5.4 Conclusions

Patients who undergo septum resection have higher pregnancy and live birth rates, compared to patients with unexplained infertility or recurrent pregnancy loss and normal uterine contours. This information can be used to counsel patients found to have uterine septa.

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Appendices

A. Definitions (for the lay person)

Antenatal Corticosteroids: *an intramuscular injection given to the mother in the third trimester to accelerate the lung maturation of the fetus, reduce rates of neonatal death, respiratory distress syndrome, intraventricular hemorrhage and early neonatal infection*.

Cerclage: *a cervical suture for treatment of cervical insufficiency, to prevent second trimester pregnancy loss (after 12 weeks) or preterm birth.*

Cervical Length: *the distance measure on ultrasound, either transabdominally or transvaginally, from the internal os to the external os of the cervix.*

Fecundability: *ability to achieve pregnancy per menstrual cycle*

Fecundity: *ability to achieve live birth per menstrual cycle*

Fibroid: *a benign growth or tumour in the uterus that can distort the endometrial cavity*

Gestational Age: *the length of a pregnancy, reported in weeks and days, generally from the start of the patient's last menstrual period to the current date. The calculation* *assumes a 28-day menstrual cycle with ovulation on day 14 and gestational length of 280 days. The gestational age of a pregnancy can be corrected by dating ultrasound measurements and menstrual patterns. In IVF cycles with frozen embryos, an adjusted date is used based of the age of the embryo at transfer.*

Hysterosalpingogram (HSG): *a radiological procedure to investigate the shape of the uterine cavity and the shape and patency of the fallopian tubes.*

Live Birth: *the complete expulsion or extraction of a product of human conception, after 20 week's gestation, which breathes, or shows any other evidence of life such as beating of the heart, pulsation of the umbilical cord, or definite movement of voluntary muscles, whether or not the umbilical cord has been cut or the placenta is attached.*

Metroplasty: *surgical removal of the uterine septum*

Morbidity: *the state of being symptomatic or unhealthy from a disease or condition*

Neonatal Period: *the first 28 days of life*

Neonatal Intensive Care Unit (NICU): *an intensive care unit specializing in the care of ill or premature newborn infants.*

Preterm Birth: *the birth of a baby at less than 37 weeks' gestational age*

Spontaneous Abortion: *pregnancy loss at less than 20 weeks' gestation in the absence of medical or surgical measures to terminate the pregnancy*

Therapeutic Abortion: *the purposeful ending of a pregnancy, by medical or surgical means*

Threatened Preterm Labour (TPTL): *the progression of cervical dilatation or ripening of the cervix caused by regular uterine contractions occurring before 37 weeks of pregnancy*

Transvaginal Ultrasonography (TVUS): *a type of pelvic ultrasound used to examine female reproductive organs via the vagina. An internal examination with the ultrasound probe.*

Uterine Septum: *a form of a congenital malformation where the uterine cavity is partitioned by a longitudinal septum; the outside of the uterus fundus maintains a normal shape.*

B. Literature search strategy

PubMed Search Strategy

The initial PubMed search strategy employed the inclusive terms to include pregnancy or pregnant, reproductive outcome(s), fertility, infertility, subfertility, miscarriage, live birth, premature birth, preterm birth, pre term birth, metroplat(*), septoplasty(*)

> *"Pregnancy"[Mesh] OR pregnan*[tiab] OR "reproductive outcome*"[tiab] OR "Fertility"[Mesh] OR "Infertility"[Mesh] OR fertility[tiab] OR infertil*[tiab] OR subfertil*[tiab] OR miscarriage*[tiab] OR "live birth*"[tiab] OR "Premature Birth"[Mesh] OR "premature birth*"[tiab] OR "preterm birth*"[tiab] OR "pre term birth*"[tiab]) AND (metroplast*[ti] OR septoplast*[ti] OR (("uterine septum"[ti] OR "septate uter*"[ti] OR "subseptate uter*"[ti] OR "arcuate uter*"[ti] OR "hysteroscopic sept*"[ti]) AND (resect*[tiab] OR transect*[tiab] OR hysteroscop*[tiab]))) AND "English"[la]*

EMBASE Search Strategy

The initial EMBASE search was done using the following terms:

'uterine septum' *AND* ***'pregnancy'****/exp/mj AND [female]/lim AND [adult]/lim AND [humans]/lim AND [english]/lim AND [abstracts]/lim AND [1995-2021]/py.*

This database search yielded five articles. Two of these articles were relevant to this review, however they had been previously identified in the PubMed search [33,66].

A second search was then done as follows:

'metroplasty' *AND* ***'pregnancy'****/exp/mj AND [female]/lim AND [adult]/lim AND [humans]/lim AND [english]/lim AND [abstracts]/lim AND [1995-2021]/py.*

This yielded 7 articles. Two of these articles were unique and relevant to this review [16,32].

To ensure articles describing postoperative effects of metroplasty on the secondary outcome (preterm birth) were included in the EMBASE search, the search was repeated with the following two further search strategies:

'metroplasty' *AND* ***'preterm'*** *AND [female]/lim AND [adult]/lim AND [humans]/lim AND [english]/lim AND [abstracts]/lim AND [1995-2021]/py.*

This yielded 10 articles. Unfortunately, none of the unique articles were relevant to this study.

'uterine septum' *AND* ***'preterm'*** *AND [female]/lim AND [adult]/lim AND [humans]/lim AND [english]/lim AND [abstracts]/lim AND [1995-2021]/py.*

This yielded 39 articles. The results were reviewed individually for relevance.

MEMORIAL UNIVERSITY

Faculty of Medicine

Human Investigation Committee
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95 Bonaventure Avenue
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Tel: 709 777 6974 Fax: 709 777 8776
hic@mun.ca www.med.mun.ca/hic

October 1, 2010

Dr. Karen Splinter
OBGYN
Health Science Centre

Dear Dr. Splinter:

Reference # 10.161

Re: "Effect of uterine septum repair on pregnancy outcomes"

Your application received an expedited review by a Sub-Committee of the Human Investigation Committee and **full approval** was granted effective **September 29, 2010.**

This approval will lapse on **September 28, 2011**. It is your responsibility to ensure that the Ethics Renewal form is forwarded to the HIC office prior to the renewal date. *The information provided in this form must be* ***current to the time of submission*** *and submitted to the HIC* ***not less than 30 nor more than 45 days*** *of the anniversary of your approval date.* The Ethics Renewal form can be downloaded from the HIC website http://www.med.mun.ca/hic/downloads/Annual%20Update%20Form.doc

The Human Investigation Committee advises THAT IF YOU DO NOT return the completed Ethics Renewal form prior to date of renewal:

- *Your ethics approval will lapse*
- *You will be required to stop research activity immediately*
- *You may not be permitted to restart the study until you reapply for and receive approval to undertake the study again*

Lapse in ethics approval may result in interruption or termination of funding

It is your responsibility to seek the necessary approval from Eastern Health, other hospital boards and/or organizations as appropriate.

Modifications of the protocol/consent are not permitted without prior approval from the Human Investigation Committee. Implementing changes in the protocol/consent without HIC approval may result in the approval of your research study being revoked, necessitating cessation of all related research activity. Request for modification to the protocol/consent must be outlined on an amendment form (available on the HIC website) and submitted to the HIC for review.
This research ethics board (the HIC) has reviewed and approved the research protocol and

documentation as noted above for the study which is to be conducted by you as the qualified investigator named above at the specified site. This approval and the views of this Research Ethics Board have been documented in writing. In addition, please be advised that the Human Investigation Committee currently operates according to *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans*; *ICH Guidance E6: Good Clinical Practice* and applicable laws and regulations. The membership of this research ethics board is constituted in compliance with the membership requirements for research ethics boards as defined by *Health Canada Food and Drug Regulations Division 5; Part C*

Notwithstanding the approval of the HIC, the primary responsibility for the ethical conduct of the investigation remains with you.

We wish you every success with your study.

Sincerely,

[redacted]

Co-Chairs
Human Investigation Committee

C VP Research c/o Office of Research, MUN
VP Research c/o Patient Research Centre, Eastern Health
HIC meeting date: October 14, 2010