

Opportunistic Salpingectomy at the time of Cesarean Delivery: A randomized controlled trial of the safety of salpingectomy vs tubal ligation

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PRÉCIS

Study Title

Opportunistic Salpingectomy at the time of Cesarean Delivery: A randomized controlled trial of the safety of salpingectomy vs. bilateral tubal ligation.

Objectives

Our primary outcome is to compare the mean difference in pre and postoperative hemoglobin between patients who receive salpingectomy vs those who have a standard bilateral tubal ligation. The secondary outcomes are to compare total time to completion, complications rates, readmission rates, reoperations rates, and length of hospital stay.

Design and Outcomes

We intend to perform a non-inferiority two-arm randomized controlled trial to evaluate the safety and feasibility of prophylactic salpingectomy at the time of a cesarean delivery as an initiative to avoid a missed opportunity in the primary prevention of ovarian cancer. Once enrolled and consented, women will be randomized using a stratified block randomization algorithm according to number of prior cesarean deliveries and BMI to either salpingectomy or bilateral tubal ligation. The data collection will include preoperative CBC, time of procedure, postoperative CBC at 24 hours, standard patient demographics, procedural complications, estimated blood loss, return to the OR, length of stay, pain scores and postoperative complications including readmission within 6 weeks.

Interventions and Duration

In the control arm, subjects will have sterilization performed via the Parkland or Pomeroy method of bilateral tubal ligation based on provider preference. In the study arm, a salpingectomy will be performed using a combination of suture ligation and cautery. The enrollment period will occur over two years and follow up will extend 6 weeks from surgery.

Sample Size and Population

The study population will included pregnant woman greater than 21 years old that have an indication for cesarean delivery and proper consent for permanent sterilization. The stratified block randomization will be according to number of prior cesarean deliveries (primary versus repeat cesarean delivery). The primary outcome is mean drop in hemoglobin. Assuming that a difference of 0.5 in the drop in hemoglobin between study arms would be considered as equivalent and assuming a common standard deviation of 1.1, the study will have 80% power to test for non-inferiority with 60 patients in each arm (120 totals). This calculation is based on a two-group 0.05 1-sided t-test of equivalent in means.

1 STUDY OBJECTIVES

1.1 Primary Objective

Identify the mean difference in pre and postoperative hemoglobin for patients undergoing salpingectomy for sterilization vs patients undergoing standard bilateral tubal ligation (BTL) via mid-segment resection of the fallopian tube at the time of cesarean delivery.

1.2 Secondary Objectives

1. Identify the time for performance of a salpingectomy vs a standard BTL at the time of cesarean delivery
2. Identify rates of procedural complications for patients undergoing salpingectomy vs a BTL at the time of cesarean delivery
3. Identify rates of readmission/take back to OR, length of stay, estimated blood loss (EBL) and pain scores in patients undergoing a standard BTL vs a salpingectomy at the time of cesarean delivery.

2 BACKGROUND AND RATIONALE

2.1 Background on Condition, Disease, or Other Primary Study Focus

Ovarian cancer has the highest mortality of all gynecologic malignancies and is the fifth leading cause of cancer death women (1). Approximately 95% of ovarian cancer arises from the epithelial cells, of which serous carcinoma is the most common subtype. Serous ovarian carcinoma can arise from the ovary itself or arise from the fallopian tube. Increasing evidence suggests the origin of extra uterine pelvic serous carcinomas arises in the fallopian tubes, especially those that are high grade and associated with poor prognosis. There are no accepted screening methods for such cancers, and symptoms of disease are vague and non-specific, which contribute to higher stage and grade at the time of diagnosis. In view of this the American College of Obstetrics and Gynecology in its Committee Opinion (ACOG) in 2015 recommended US clinicians to counsel patients about prophylactic salpingectomy as an effective method of sterilization, which may offer us a way to prevent ovarian carcinogenesis(1).

Permanent sterilization with tubal ligation as a form of contraception is the most common method used worldwide. The National Health Statistics Report of 2015 states that 9.4 million (approximately 15%) women between ages 15-44 are currently using sterilization as a method of birth control, making it the second most common contraceptive method used following contraceptive pills(2). There are several types of tubal ligation: the postpartum tubal ligation (performed within the first six days after delivery), laparoscopic (or interval) method, and hysteroscopic method. In the United States, over 50% of all sterilization procedures are performed in the postpartum period.

ACOG considers postpartum sterilization as one of the safest and most effective methods of contraception, with 10 % of women undergoing hospital deliveries opting for it (3). ACOG states that when sterilization is performed concurrently with a cesarean delivery

in comparison to postpartum sterilization, any higher risks are those attributed to the cesarean delivery itself and not to the sterilization(4). Pomeroy, modified Pomeroy, and the Parkland methods of mid segment excision are the most common techniques used for sterilization during a cesarean delivery (4). With the recent ACOG committee opinion on offering prophylactic salpingectomy at the time of sterilization counseling, numerous physicians have begun performing salpingectomy during interval sterilization but there are mixed opinions about its use for sterilization postpartum and prophylactically during a cesarean delivery especially with respect to the its safety. Not performing a prophylactic salpingectomy at the time of a cesarean delivery might present itself as a missed opportunity for prevention of ovarian cancer.

2.2 Study Rationale

Opportunistic removal of bilateral fallopian tubes as a preventive procedure against development of ovarian, fallopian tube, and primary peritoneal cancers has been performed increasingly over the last five years. Surgical removal of the fallopian tubes is done during pelvic surgery for another indication, typically hysterectomy. It has also been performed in place of a tubal ligation in women desiring permanent sterilization. The procedure is offered to women who are deemed to be at average risk for ovarian cancer. Currently, women in British Columbia who undergo salpingectomies at the time of tubal sterilization are being followed as a cohort to determine the incidence of cancer in this group.(5) It is estimated that it will take fifteen years to find the definitive answer.

McAlpine et al. (2014) in a retrospective cohort study of 43,931 women in British Columbia showed that salpingectomy at the time of a hysterectomy and interval sterilization did not increase operative/perioperative risks and that it was safe and feasible(5). Recent studies have shown no increased risk in surgical morbidity when performing bilateral salpingectomies in an opportunistic manner as a replacement for sterilization procedures (6). There has been shown to be a slightly higher operating room time (approximately 10 minutes). There are no data from which to comment on ovarian reserve function after the procedure, and no data yet regarding the incidence of gynecologic malignancies in this cohort. Several practices are already offering opportunistic salpingectomies to patients who desire permanent sterilization and are being performed instead of bilateral tubal ligations.

To our knowledge to date there are no published studies that have looked at the use of prophylactic salpingectomy during a cesarean delivery. Our hypothesis is that performing bilateral salpingectomy in patients who desire permanent sterilization at the time of cesarean delivery will have equivalent surgical risk of blood loss, as measured by the drop in hemoglobin, compared to BTL at the time of cesarean delivery. The majority of women who develop ovarian cancer do not have a family history and therefore not undergoing specific surveillance. Women who are undergoing the surgical risk of a cesarean delivery and bilateral tubal ligation may gain long term benefit from a salpingectomy without an increase in their surgical risk.

A better understanding of the safety of prophylactic salpingectomy at the time of a

cesarean delivery will help us with counseling patients about the risks versus ovarian cancer preventions benefits of the procedure. It has the potential of changing and standardizing practice across the nation. We plan to register our trial in clinicaltrials.gov. We also plan to publish our study findings in a reputable journal.

3 STUDY DESIGN

We intended to perform a non-inferiority two-arm randomized controlled trial to look into the safety and feasibility of prophylactic salpingectomy at the time of a cesarean delivery, versus bilateral tubal ligation (BTL), via Parkland, or modified Pomeroy method as an initiative to avoid a missed opportunity in the primary prevention of ovarian cancer. Our primary outcome is to compare mean difference in pre and postoperative hemoglobin. The secondary outcomes are to compare total time completion, complications rates, readmission rates, reoperations rates, and length of hospital stay.

The study population will included pregnant woman greater than 21 years old that have an indication for cesarean delivery and proper consent for permanent sterilization. In the control arm (BTL), subjects will have sterilization performed via the Parkland or Pomeroy method based on provider preference. In the study arm, a salpingectomy will be performed and the entire fallopian tube will be excised using a combination of suture ligation and cautery.

The enrollment period will occur over two years and follow up will extend 6 weeks from surgery. The patients will primarily be recruited and enrolled in the clinic during their antepartum visits. However, patients who present to labor and delivery and are found to require a Cesarean delivery may be consented on admission. If an emergency cesarean delivery (alpha or beta) is required and the patient has not been consented earlier, they will not be a candidate for enrollment. The surgery will take place in the operating room on labor and delivery. Once enrolled and consented, women will be randomized using a stratified block randomization algorithm prepared by the study statistician to either salpingectomy or standard BTL stratified according to number of prior cesarean deliveries (first versus repeat) and BMI (BMI < 35, BMI > 35).

Prior to the procedure a preoperative CBC will be performed. Patients will undergo the cesarean delivery and once stable from that procedure, will progress to either salpingectomy or bilateral tubal ligation per the randomization. Time from start to conclusion of the sterilization procedure will be logged to obtain operative time. Post procedure, the type of sterilization procedure will be disclosed to the patient. A postoperative CBC will be performed the next day at least 24 hours but no later than 48 hours after the conclusion of the procedure. In addition to standard patient demographics (age, race, parity, body mass index, etc), data collection will include procedural complications, return to the OR, length of stay, and postoperative complications including readmission within 6 weeks.

The primary outcome is mean drop in hemoglobin. Previous studies have reported a mean (SD) drop in hemoglobin of 1.32 (0.94) g/dl following a repeat cesarean delivery

and 1.40 (1.2) following a first cesarean delivery (7). Based on our experience in 2015, we anticipate that over 75% of our cases will be repeat cesarean deliveries. Assuming that a difference of 0.5 in the drop in hemoglobin between study arms would be considered as equivalent and assuming a common standard deviation of 1.1, the study will have 80% power to test for non-inferiority with 60 patients in each arm (120 totals). This calculation is based on a two-group 0.05 1-sided t-test of equivalent in means.

4 SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Inclusion Criteria

Women, 21 years of age and older, who desire permanent sterility and have an obstetric indication for a cesarean delivery will be included. Patients will be consented for the cesarean delivery and sterilization procedure per standard Family Birth Center guidelines. Patient with state insurance will also require correctly completed sterilization consent paperwork.

4.2 Exclusion Criteria

Pregnant women undergoing an emergent or Beta/Alpha cesarean delivery, who are not already enrolled, will not be eligible. Women who undergo tubal ligation after vaginal delivery will not be eligible. Women with a body mass index (BMI) ≥ 50 will not be eligible. Women who have a single ovary/fallopian tube will not be eligible.

4.3 Study Enrollment Procedures

Women who are 21 years of age and older and desire permanent sterility who plan to have a planned cesarean delivery will be identified as early in gestation as possible. These women will be approached for possible participation in the study during their antepartum. Most subjects will be recruited and consented in the clinic setting. Women who present to the Family Birth Center and develop an indication for a non-emergent Cesarean delivery and desire permanent sterility will be approached for participation in the study. The consents are in English, but we will use interpreter to consent women who speak other languages and are interested in participation. All women must be able to provide consent themselves for study. We will keep a record of all women who are recruited for study and record the number of women who decline.

Consenting Procedure

Women will be provided information about the study in a private exam or hospital room. Questions will be addressed and time provided to consider participation. Informed consent for the study will be obtained by study coordinator or those providers listed in the IRB, excluding the surgeon who will be performing the procedure.

The consent document will be retained by the study coordinator. During the final process to re-affirm consent for the study at the time of planned cesarean delivery, if

the patient then chooses to reverse her decision to participate, her wishes will be respected. If a patient consents to the study and then becomes ineligible (screen failure) this will be communicated with her both prior to and after the cesarean delivery.

Study Risks

The risks of a bilateral tubal ligation include bleeding from the surgical site that may require further surgery including removal of the ovary. The bleeding may also be severe enough to require a blood transfusion. The other risks include a risk of sterilization failure where one of every 100 cases results in a pregnancy for which 50% of those pregnancy results in a pregnancy in the tubes that may require further treatment. Other risks include infection and damage to surrounding organs. There may be an increased risk of pain during menses with a bilateral tubal ligation.

The risks of bilateral salpingectomy are similar to those of a bilateral tubal ligation. There may be an increased risk of bleeding compared to a bilateral tubal ligation because all of the tube is removed and therefore increased risk of need for removal of ovary and blood transfusion compared to a bilateral tubal ligation. Additionally there may be a decrease failure rate as all of the tube is removed.

There may be other risks of bilateral salpingectomy following cesarean section that are currently unknown.

5 STUDY INTERVENTIONS

5.1 Interventions, Administration, and Duration

Interventions will consist of randomization for patients desiring permanent sterilization at the time of cesarean delivery. Randomization will be to either salpingectomy or to the standard BTL arm.

The administration of the intervention will be done immediately after cesarean delivery in patients who have already been consented and enrolled in the study.

There are no medications involved in the study.

5.2 Handling of Study Interventions

There are no drugs or lifestyle/behavioral interventions in the study.

The intervention being investigated is the safety of salpingectomy as a form of sterilization vs BTL at the time of Cesarean delivery. Patients meeting enrollment criteria are those who desire permanent sterilization, are correctly consented, and are planning a repeat cesarean delivery. They will be blinded to the operative intervention at the time of

enrollment and randomization; after the surgery, it will be disclosed to them the procedure they had performed.

To investigate differences in mean hemoglobin, preoperative hemoglobin and postoperative hemoglobin will be obtained for all study participants.

To investigate the differences in operative time for the different surgical procedures being studied, all surgeries will be timed beginning at the initiation of the sterilization procedure being performed (i.e., once the cesarean delivery has been completed, and just prior to starting either the tubal ligation or salpingectomy procedure).

5.3 Concomitant Interventions

There are no medication interventions in the trial.

5.3.1 Required Interventions: If required, iron replacement for blood loss anemia and/or transfusion of blood products may be administered as standard of care.

5.3.2 Prohibited Interventions: Individuals undergoing emergency (alpha) cesarean and beta C-sections who have not previously been enrolled will not be approached for participation in this study.

5.4 Adherence Assessment

Adherence to the study regimen will be ascertained as the number of participants enrolled in the study that actually complete the procedure to which they are randomized. The study is powered for 60 patients in each arm to detect a difference in postoperative hemoglobin.

Patients will be given the right to decline either procedure if they decline permanent sterilization and voice this request prior to their planned cesarean delivery or prior to sterilization procedure.

We will incorporate into our analysis any patients who decline permanent sterilization after being enrolled in the study.

6 STUDY PROCEDURES

Patients will be screened to be eligible in the study if they :

- 1) Desire permanent sterilization
- 2) Are scheduled for a Cesarean delivery (no emergency/'alpha' deliveries)
- 3) Are equal to or greater than 21 years of age
- 4) Have a BMI < 50

5) Have both ovaries/fallopian tubes

Patients may be screened for eligibility antenatally in the obstetrics clinic or at the time of presentation to the Family Birth Center for a non-emergent Cesarean delivery. If they meet eligibility, they will have the option to enroll in the study. A preoperative hemoglobin will be done at admission to the Family Birth center for delivery. If the patient is screened and enrolled at the time of admission to the birth center, a preoperative hemoglobin will be obtained prior to the planned cesarean delivery. All patients enrolled will have a postoperative hemoglobin obtained between 24 hours and 48 hours after the cesarean delivery and concomitant intervention procedure. Patients will be scheduled for a standard 6 weeks postpartum follow- up visit which will be reviewed. Patients who enroll in the study and then subsequently decline any form of permanent sterilization will be noted in the analysis of the results and discussed accordingly.

6.1 Schedule of Evaluations

Assessment	Antepartum Screening Enrollment	Delivery/ Sterilization Visit 1	24-hours PP Visit 2	Follow-up: 6 Week PP
Informed Consent Form	X	*X		
Demographics	X	X		
Medical History	X	X		X
Hematology		X	X	
Inclusion/Exclusion Criteria	X	*X		
Randomization		X		
Adverse Events		X	X	X

*Patients who are screened and enrolled at the time of admission to L&D will have demographic, medical history, current medications, and vital signs reviewed/collected at the time informed consent is obtained. Patients who are screened and enrolled antenatally will at the time of admission for their planned cesarean delivery.

6.2 Description of Evaluations

6.2.1 Screening Evaluation

Screening

Patients may enroll in the study any time they are determined to meet eligibility requirements (please refer to inclusion criteria in section 4.1), and before they undergo cesarean delivery.

6.2.2 Enrollment, Baseline, and/or Randomization

Enrollment

Patients will be considered for enrollment if they meet inclusion criteria (please refer to section 4.1). If a patient expresses a desire to undergo permanent sterilization to her provider at any time and will undergo a cesarean delivery then she is eligible for enrollment and the study coordinator will be contacted to introduce the study and obtain informed consent.

In the event the study coordinator is not available for consent (i.e., middle of the night, spontaneous onset of labor in a patient planning repeat cesarean for delivery), then an obstetrical provider listed in the IRB will be able to obtain consent for enrollment. The delivering provider will not obtain consent.

Randomization

- Initiation of study intervention relative to randomization: When patients have been enrolled in the study they will be randomized. The Dynamic Allocation System will be used for electronic randomization based on the stratification criteria. Outcome of randomization (arm) will be communicated to the surgical team prior to surgery and to the participant following surgery.
- After cesarean delivery has been performed and the surgeon feels it is safe to proceed with surgical sterilization procedure identified from randomization (salpingectomy vs BTL), the start and stop time of the surgical procedure will be recorded by the circulating RN or other obstetrical provider on a case report form. Total time of the procedure, in minutes, will be recorded.

Follow-up Visits (abstracted from the Electronic Medical Record)

- Visit 1 (24 hours post operatively)
 - Vital signs
 - Physical exam
 - Medications
 - Hemoglobin
 - Adverse events
- Visit 2: Scheduled post-partum exam 6 weeks post procedure.
 - Vital signs
 - Physical exam
 - Medications
 - Adverse events

Completion/Final Evaluation

Final visit will be at the patient's postpartum exam. Any untoward events from after the first 24 hours from the procedure to that time will be reviewed (i.e., blood transfusion, readmission to hospital, etc.). If the participant receives post-partum care at a local clinic, not Mayo Clinic Rochester, the study coordinator will call the participant to collect final evaluation data, using an IRB-approved telephone script.

Patients who decide to withdraw from the study will also be interviewed and reasons for this will be discussed and potential reasons explored.

7 SAFETY ASSESSMENTS

7.1 Specification of Safety Parameters

All patients will be closely monitored both intra and post operatively for bleeding that is in excess of normal cesarean delivery estimated blood loss (EBL). If vital signs are deranged in any fashion this will prompt laboratory and clinical assessment that meets standard of care irrespective of study participation (for example, HR >120, SBP <90>160, DBP <50>90, temp >38.0 C, RR >22<8).

Hemoglobin values that are < or equal to 7.0 g/dL will warrant transfusion; also, if patients have hemoglobin values that are above this threshold but active ongoing bleeding is suspected clinically, then preparations may also be made for transfusion. In no way will standard of care post operatively at RMH be compromised based on study inclusion.

7.2 Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

To our knowledge, there has not been a randomized controlled trial investigating the safety of salpingectomy compared to tubal ligation at the time of cesarean delivery in women desiring permanent sterilization. A study performed retrospectively in 2014 of over 40,000 women in Canada showed that when performed at the time of hysterectomy, salpingectomies did not increase operative risks and was feasible(5). The concern with performing a salpingectomy post-delivery is that the uterus and its blood vessels are quite enlarged. A salpingectomy removes more of the tissue along the mesosalpinx which can be associated with quite large vessels. This theoretically may increase the risk of disrupting these large vessels which may lead to excessive blood loss, need for blood and further surgery that may lead to the loss of the adnexa and or uterus. However, the sterilization will only take place if the patient is clinically stable for the procedure.

Danis et al recently published data on a cohort of 16 patients undergoing a salpingectomy after a vaginal delivery through an umbilical incision matched with 64 controls undergoing a BTL through a similar incision.(6) No increased risk of bleeding or complications was noted in the study group. This suggests that salpingectomy as a method of sterilization in a recently pregnancy-enlarged uterus may be equivocal in safety to the standard BTL.

After each set of 20 patients are enrolled, the study team will evaluate the operative reports of enrolled patients for evidence of adverse events.

7.3 Adverse Events and Serious Adverse Events

Adverse Event: Is defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporarily associated with the use of a medical treatment or procedure that may or may not be considered related to the

medical treatment or procedure.

Adverse events are classified according to their severity.

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

- Increased pain score
- Mild anemia

Grade 2: Moderate; minimal, local or noninvasive intervention indicated

- Severe anemia not requiring transfusion

Grade 3: Severe or medically significant but not immediately life-threatening hospitalization or prolongation of hospitalization indicated; disabling limiting self-care.

- Severe anemia requiring transfusion
- Loss of one or both adnexa

Grade 4: Life threatening consequences; urgent intervention needed

- Requiring Cesarean hysterectomy
- Return to operating room

Grade 5: Death related to AE

Adverse outcomes are also problems/events that in the opinion of the principal investigator may have adversely affected the rights, safety, or welfare of the subjects or others, or substantially compromised the research data.

Given that a cesarean delivery will have also been performed prior to the tubal surgery, it will be difficult to distinguish if adverse events or serious adverse events are the direct result of the cesarean or the salpingectomies. Detailed review of the operative note will provide clarification as to which portion of the procedure is thought to have contributed to any adverse events.

7.4 Reporting Procedures

Patients enrolled in the trial will be monitored post-operatively according to standard of care in the hospital inpatient unit. Once the patient is discharged from the hospital, a routine postpartum visit will be ordered at 6 weeks. In the interim, any study patient returning to the hospital will be reported to the principal investigator and prompt a chart review.

The specimens from the sterilization procedures will be sent to pathology and undergo evaluation per protocol. Results will be reported back to the surgeon performing the procedure when completed.

7.5 Follow-up for Adverse Events

Adverse events will be followed immediately per standard of care for all surgical patients while in the immediate inpatient postoperative period and also if outpatient follow up is required. If a patient presents to an outside hospital for evaluation of a complication that is thought to be due to the procedure performed in the study, this will be captured in the 6 week post procedure follow up by speaking directly with the patient or the patient's representative and requesting a copy of the care provided at the outside hospital.

7.6 Safety Monitoring

A data safety monitoring plan (DSMP) will be filed as an attachment to the protocol. The primary elements of which include the following:

- Review of charts after the first 10 patients and then at least quarterly thereafter.
- Placement of study on hold if a trend in adverse events are noted.

7.7 Reporting Procedures

At each contact with the subject, the study team must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event section of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic, laboratory or procedure results should be recorded in the source document.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been ultimately determined that the study treatment or participation is not the probable cause. Serious adverse events that are still ongoing at the end of the study period must be followed up, to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be at least possibly related to the study treatment or study participation should be recorded and reported immediately.

7.8 Follow-up for Adverse Events

All unresolved adverse events should be followed by the principal investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the coordinator or principal investigator should instruct each subject to report, any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study.

8 INTERVENTION DISCONTINUATION

Criteria for Discontinuation of Study or Early Stopping include:

1. More than 20 cases Grade 1 or 2 adverse events
2. More than 3 cases of Grade 3 adverse events
3. Any case of Grade 4 or Grade 5 adverse events

If the above criteria for discontinuation are met, the study will be put on clinical hold. A Data Monitoring and Safety committee will be convened to assess the causal linkage between the adverse events and the procedure. If causal linkage is established, the study will be permanently stopped. If no causal linkage is established the study will be taken off hold. Participants will continue to be followed, with their permission, even if the study is discontinued.

The study may be discontinued at any time by the IRB, the OHRP, the FDA, or other government agencies as part of their duties to ensure that research participants are protected.

Safety data on any subject discontinued due to an AE or SAE will be collected. Subjects will be given appropriate care under medical supervision until the symptoms of any AE resolve or the subject's condition becomes stable.

Subjects may withdraw voluntarily from participation in the study at any time and for any reason.

9 STATISTICAL CONSIDERATIONS

9.1 General Design Issues

The null hypothesis in this non-inferiority trial is that the mean difference in pre and postoperative hemoglobin of patients undergoing salpingectomy will be lower than that for patients undergoing BTL at the time of cesarean delivery by at least 0.5 g/dl. The alternative hypothesis to be proven is that this difference will be no lower than 0.5 g/dl.

A non-inferiority trial was chosen as the study aims to compare a less commonly performed procedure with a known and accepted standard. We want to show that the less common procedure is at as safe as the standard. Patients will be randomly assigned to salpingectomy or BTL at enrollment.

Primary hypothesis: The alternative hypothesis to be tested is that the mean difference in pre and postoperative hemoglobin of patients undergoing salpingectomy will be no lower than those that undergoing BTL at the time of cesarean delivery.

Primary variable: Mean hemoglobin change

9.2 Sample Size and Randomization

The primary outcome is mean drop in hemoglobin. Previous studies have reported a

mean (SD) drop in hemoglobin of 1.32 (0.94) g/dl following a repeat cesarean delivery and 1.40 (1.2) following a first cesarean delivery (7). Based on our experience in 2015, we anticipate that over 75% of our cases will be repeat cesarean deliveries. Assuming that a difference of 0.5 in the drop in hemoglobin between study arms would be considered as equivalent and assuming a common standard deviation of 1.1, the study will have 80% power to test for non-inferiority with 60 patients in each arm (120 total). This calculation is based on a two-group 0.05 1-sided t-test of equivalent in means.

9.2.1 Treatment Assignment Procedures

Once enrolled and consented, women will be randomized using a stratified block randomization algorithm prepared by the study statistician to either standard BTL or salpingectomy stratified according to number of prior cesarean deliveries (first versus repeat), and BMI (BMI < 35, BMI > 35).

9.3 Interim analyses and Stopping Rules

No interim analysis is planned.

The study will be stopped or placed on clinical hold if the number of adverse events exceeds the thresholds detailed in section 8.

9.4 Outcomes

9.4.1 Primary outcome

The primary outcome is mean change in preoperative to postoperative hemoglobin. These values will be collected from the patient's chart. The preoperative hemoglobin will be performed on the day of surgery. The postoperative hemoglobin will be performed the morning after surgery at least 24 hours but no greater than 48 hours after the procedure.

9.4.2 Secondary outcomes

1. Time in minutes in performance of BTL vs salpingectomy: Start time and stop time will be articulated by the surgeon and recorded by the circulating RN or other obstetrical provider on a case report form. Total time will be calculated
2. EBL in ml as documented in the operative report.
3. Complications as documented in the operative report and medical record
4. Pain scores as documented in patient chart

9.5 Data Analyses

A 1-sided 95% confidence interval will be constructed for the difference between study arms in the mean drop in hemoglobin. In addition, the reduction in hemoglobin will be analyzed using a one-sided T-test using a change of .5g/dL. Secondary endpoints will be analyzed using two-sided T-test testing for a difference between the two study arms or a Chi-square test as appropriate. Statistical significance will be determined using a p-value of 0.05.

10 DATA COLLECTION AND QUALITY ASSURANCE

10.1 Data Collection Forms

Case Report forms will be used to collect data from the patient's chart. The Case Report forms will be maintained by the study coordinator.

10.2 Data Management

All data will be manually abstracted from the electronic medical records and the Case Report Forms and then recorded in the Redcap database by the study coordinator, Principal Investigator and Co-Investigators.

Only necessary research team members will have access to the data for data entry or analysis. All data collection and analysis will be performed behind the Mayo firewall.

10.3 Quality Assurance

10.3.1 Training

The Family Birthing Center supervising providers and the chief residents performing the procedure will have prior training in the techniques used to perform both salpingectomy and BTL. Any provider who has not previously performed a salpingectomy at a Cesarean delivery will be required to review a training module and be proctored during the completion of their first procedure.

10.3.2 Monitoring

The study coordinator, Principal and Co- Investigators will perform all data entry. The principal investigator or designee co-investigator will independently collect data on every 20th patient, and a comparison of data points will be performed for quality assurance.

11 PARTICIPANT RIGHTS AND CONFIDENTIALITY

11.1 Institutional Review Board (IRB) Review

This protocol and the informed consent document and any subsequent modifications will be reviewed and approved by the Mayo Clinic IRB responsible for oversight of the study.

11.2 Informed Consent Forms

A signed consent form will be obtained from each participant. For participants who cannot consent for themselves, such as those with a legal guardian (e.g. person with power of attorney), this individual must sign the consent form. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy will be given to each participant or legal guardian and

this fact will be documented in the participant's record. Special provisions will be made for special populations such as interpreters for non-English speakers. Patients with state insurance will also require correctly completed sterilization consent paperwork.

11.3 Participant Confidentiality

Any data, specimens, forms, reports, video recordings, and other records that leave the site will be identified only by a participant identification number (Participant ID, PID) to maintain confidentiality. All records will be kept in a locked file cabinet. All computer entry and networking programs will be done using PIDs only. Information will not be released without written permission of the participant, except as necessary for monitoring by IRB, the FDA, and the OHRP.

11.4 Study Discontinuation

The study may be discontinued at any time by the IRB, the OHRP, the FDA, or other government agencies as part of their duties to ensure that research participants are protected.

12 ETHICAL CONSIDERATIONS

This study is to be conducted according to United States government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted local Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study. The decision of the IRB concerning the conduct of the study will be made in writing to the sponsor-investigator before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the Approved IRB consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject or the subject's legally authorized representative, and the individual obtaining the informed consent.

This study involves a vulnerable population, namely pregnant women. All criteria as specified in "Special categories of research: Pregnant women, human fetuses, and neonates" delineated by the Mayo Clinic Office for Human Research Protection have been met to perform research involving pregnant women.

13 COMMITTEES

1. Independent Data Monitoring and Safety Committee: An independent Data Monitoring and Safety Committee will be established by the Obstetrics and Gynecology Department Research Chair if the threshold of adverse events is exceeded. Otherwise a Data Safety Monitoring plan is attached.

14 **PUBLICATION OF RESEARCH FINDINGS**

This study will be registered to ClinicalTrials.gov prior to subject enrollment in the trial. The primary results will be posted to ClinicalTrials.gov within 12 months of final data collection. We also plan to publish our study findings in a reputable journal within 12 months of completion of the study participant accrual.

15 **REFERENCES**

1. Salpingectomy for ovarian cancer prevention. Committee Opinion No. 620. American College of Obstetricians and Gynecologists. *Obstet Gynecol* 2015;125:279–81.
2. Daniels K, Daugherty J, Jones J, Mosher W. Current contraceptive use and variation by selected characteristics among women aged 15–44: United States, 2011–2013. National health statistics reports; no 86. Hyattsville, MD: National Center for Health Statistics. 2015.
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4. Benefits and risks of sterilization. Practice Bulletin No. 133. American College of Obstetricians and Gynecologists. *Obstet Gynecol* 2013;121:392–404.
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6. Danis RB, Della Badia CR, Richard SD. Postpartum Sterilization: Could Bilateral Salpingectomy Replace Tubal Ligation? *Journal of Minimally Invasive Gynecology* .Nov-Dec 2015: Vol 22 Issue 6 Supplement
7. Bodur S, Ismet G, Ozkan O, Babayigit M. Safety of uneventful cesarean section in terms of hemorrhage. *Int J Clin Exp Med* 2015;(8(11))21653-21658



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RESEARCH PARTICIPANT CONSENT AND PRIVACY AUTHORIZATION FORM

Study Title: Opportunistic salpingectomy at the time of cesarean delivery: A randomized controlled trial of the safety of salpingectomy vs tubal ligation

IRB#: 17-000898

Principal Investigator: Dr. Vanessa Torbenson and Colleagues

Please read this information carefully. It tells you important things about this research study. A member of our research team will talk to you about taking part in this research study. If you have questions at any time, please ask us.

Take your time to decide. Feel free to discuss the study with your family, friends, and healthcare provider before you make your decision.

To help you decide if you want to take part in this study, you should know:

- Taking part in this study is completely voluntary.
- You can choose not to participate.
- You are free to change your mind at any time if you choose to participate.
- Your decision won't cause any penalties or loss of benefits to which you're otherwise entitled.
- Your decision will not change the access to medical care you get at Mayo Clinic now or in the future if you choose not to participate or discontinue your participation.

For purposes of this form, Mayo Clinic refers to Mayo Clinic in Arizona, Florida, and Rochester, Minnesota; Mayo Clinic Health System; and all owned and affiliated clinics, hospitals, and entities.

If you decide to take part in this research study, you will sign this consent form to show that you want to take part. We will give you a copy of this form to keep. A copy of this form will be put in your medical record.



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CONTACT INFORMATION

You can contact ...	At ...	If you have questions about ...
<p>Principal Investigator: Dr. Vanessa Torbenson</p> <p>Study Team Contact: Marnie Wetzstein, RN Study Coordinator</p>	<p>Phone: (507) 266-9873</p> <p>Phone: (507) 266-4813</p> <p>Institution Name and Address: Mayo Clinic 200 First St SW Rochester, MN 55905</p>	<ul style="list-style-type: none"> ▪ Study tests and procedures ▪ Research-related injuries or emergencies ▪ Any research-related concerns or complaints ▪ Withdrawing from the research study ▪ Materials you receive ▪ Research-related appointments
<p>Mayo Clinic Institutional Review Board (IRB)</p>	<p>Phone: (507) 266-4000</p> <p>Toll-Free: (866) 273-4681</p>	<ul style="list-style-type: none"> ▪ Rights of a research participant
<p>Research Subject Advocate (The RSA is independent of the Study Team)</p>	<p>Phone: (507) 266-9372</p> <p>Toll-Free: (866) 273-4681</p> <p>E-mail: researchsubjectadvocate@mayo.edu</p>	<ul style="list-style-type: none"> ▪ Rights of a research participant ▪ Any research-related concerns or complaints ▪ Use of your Protected Health Information ▪ Stopping your authorization to use your Protected Health Information
<p>Research Billing</p>	<p>Rochester, MN: (507) 266-5670</p>	<ul style="list-style-type: none"> ▪ Billing or insurance related to this research study



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Other Information:

A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. Law. This Website will not include information that can identify you. At most, the Website will include a summary of the results. You can search this Website at any time.

1. Why are you being asked to take part in this research study?

You are being asked to take part in this research study because you have requested to have a permanent sterilization procedure performed at the time of your cesarean delivery.

The plan is to have 120 women take part in this study at Mayo Clinic.

2. Why is this research study being done?

The purpose of this study is to compare the safety of performing a bilateral tubal ligation vs bilateral salpingectomy, two procedures performed for permanent sterilization, at the time of cesarean delivery. We want to examine if performing bilateral salpingectomy at the time of cesarean delivery poses any greater risk for blood loss, as compared to a bilateral tubal ligation.

Bilateral tubal ligation is the typical procedure performed at the time of cesarean delivery. In this procedure, a portion of the fallopian tubes is removed. The remaining ends are no longer connected, therefore, do not allow for sperm to travel to the egg for fertilization. During a bilateral salpingectomy, the entire fallopian tube is removed. Both of these procedures are highly effective in preventing pregnancy. Currently, at Mayo Clinic, only bilateral tubal ligations are routinely performed at the time of cesarean delivery.

Potentially both of these procedures may provide a long-term health benefit for some women. Research studies have suggested that women who have had a bilateral tubal ligation are at a decreased risk for some types of ovarian cancer. Recent research suggests that bilateral salpingectomy may provide even greater risk-reduction for ovarian cancer.



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3. Information you should know

Who is Funding the Study?

Mayo Clinic is funding this study.

4. How long will you be in this research study?

You will be in this study from the time your cesarean section begins, until your post-partum obstetrical visit, which occurs approximately 6 weeks after delivery.

5. What will happen to you while you are in this research study?

If you are eligible for the study, you will be asked to participate in the following:

- We will assign you by chance (like a coin toss) to the bilateral tubal ligation group or the bilateral salpingectomy group. You and the Principal Investigator can't choose your study group. You will have an equal chance of being assigned to either group.
- A blood sample to measure your preoperative hemoglobin level will be drawn upon arrival to the Family Birth Center. A second blood sample will be drawn approximately 24 hours after surgery, to assess your postoperative hemoglobin level. If required, iron replacement for blood loss anemia and/or transfusion of blood products may be administered as standard of care.
- We will collect follow-up information about your health from you and your medical record up to approximately six weeks after the birth of your baby. Information you're your 6-week post-partum examination, including physical exam, vital signs, and list of current medications, will also be collected.



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6. What are the possible risks or discomforts from being in this research study?

The known risks of a bilateral tubal ligation include:

- Bleeding from the surgical site that may require further surgery, including removal of the ovary
- Blood loss during surgery that requires a need for blood products
- Sterilization failure. One of every 100 sterilization cases results in a pregnancy, 50% of these pregnancies occurs in the fallopian tubes, requiring further treatment.
- Infection and damage to surrounding organs
- Increased risk of pain during menses

The risks of bilateral salpingectomy are similar to those of a bilateral tubal ligation. There may be an increased risk of bleeding, and thus need for removal of an ovary or blood products, as compared to a bilateral tubal ligation. However there may be a decrease in sterilization failure rate as all of the tube is removed. There may be other risks of bilateral salpingectomy following cesarean section that are currently unknown.

The risks of drawing blood include pain, bruising, lightheadedness, and/or fainting, or rarely, infection at the site of the needle stick.

As with all research, there is a chance that confidentiality could be compromised; however, we take precautions to minimize this risk.

7. Are there reasons you might leave this research study early?

You may decide to stop at any time. You should tell the study team if you decide to stop. In addition, the Principal Investigator or Mayo Clinic may stop you from taking part in this study at any time:

- if it is in your best interest,
- if you do not follow the study procedures,
- if the study is stopped.



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If you leave this research study early, or are withdrawn from the study, no more information about you will be collected; however, information already collected about you in the study may continue to be used.

We will tell you about any new information that may affect your willingness to stay in the research study.

8. What if you are injured from your participation in this research study?

Where to get help:

If you think you have suffered a research-related injury, you should promptly notify the Principal Investigator listed in the Contact Information at the beginning of this form. Mayo Clinic will offer care for research-related injuries, including first aid, emergency treatment and follow-up care as needed.

Who will pay for the treatment of research related injuries:

Care for research-related injuries will be billed in the ordinary manner to you or your insurance. You will be responsible for all treatment costs not covered by your insurance, including deductibles, co-payments and coinsurance.

9. What are the possible benefits from being in this research study?

Other pregnant women undergoing permanent sterilization following cesarean section may benefit in the future from what we learn in this research study.

10. What alternative do you have if you choose not to participate in this research study?

You don't have to be in this study to receive treatment for your condition. You can undergo a bilateral tubal ligation as planned at the time of your delivery. Talk to the Principal Investigator or your provider if you have any questions about any of these treatments or procedures.



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11. What tests or procedures will you need to pay for if you take part in this research study?

You won't need to pay for tests and procedures which are done just for this research study. These tests and procedures are:

- Blood draws to assess hemoglobin levels before and after surgery

However, you and/or your insurance will need to pay for all other tests and procedures that you would have as part of your clinical care. These tests and procedures are:

- Surgical procedure (bilateral tubal ligation or bilateral salpingectomy)
- Postoperative obstetrical care

You will also be responsible for any co-payments and deductibles.

If you have billing or insurance questions call Research Billing at the telephone number provided in the Contact Information section of this form.

12. Will you be paid for taking part in this research study?

You will not be paid for participating in this study.

13. How will your privacy and the confidentiality of your records be protected?

Mayo Clinic is committed to protecting the confidentiality of information obtained about you in connection with this research study. The data for this study will be evaluated on password protected computers on the Mayo Clinic campus. This data will only be accessible to study personnel.

During this research, information about your health will be collected. Under Federal law called the Privacy Rule, health information is private. However, there are exceptions to this rule, and you should know who may be able to see, use and share your health information for research and why they may need to do so. Information about you and your health cannot be used in this research study without your written permission. If you sign this form, it will provide that permission.



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Health information may be collected about you from:

- Past, present and future medical records.
- Research procedures, including research office visits, tests, interviews and questionnaires.

Why will this information be used and/or given to others?

- To do the research.
- To report the results.
- To see if the research was done correctly.

If the results of this study are made public, information that identifies you will not be used.

Who may use or share your health information?

- Mayo Clinic research staff involved in this study.

With whom may your health information be shared?

- The Mayo Clinic Institutional Review Board that oversees the research.
- Other Mayo Clinic physicians involved in your clinical care.
- Federal and State agencies (such as the Food and Drug Administration, the Department of Health and Human Services, the National Institutes of Health and other United States agencies) or government agencies in other countries that oversee or review research.
- A group that oversees the data (study information) and safety of this research.

Is your health information protected after it has been shared with others?

Mayo Clinic asks anyone who receives your health information from us to protect your privacy; however, once your information is shared outside Mayo Clinic, we cannot promise that it will remain private and it may no longer be protected by the Privacy Rule.

Your Privacy Rights

You do not have to sign this form, but if you do not, you cannot take part in this research study.

If you cancel your permission to use or share your health information, your participation in this study will end and no more information about you will be collected; however, information already collected about you in the study may continue to be used.

If you choose not to take part or if you withdraw from this study, it will not harm your relationship with your own doctors or with Mayo Clinic.



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You can cancel your permission to use or share your health information at any time by sending a letter to the address below:

Mayo Clinic
Office for Human Research Protection
ATTN: Notice of Revocation of Authorization
200 1st Street SW
Rochester, MN 55905

Alternatively, you may cancel your permission by emailing the Mayo Clinic Research Subject Advocate at: researchsubjectadvocate@mayo.edu

Please be sure to include in your letter or email:

- The name of the Principal Investigator,
- The study IRB number and /or study name, and
- Your contact information.

Your permission lasts until the end of this study, unless you cancel it. Because research is an ongoing process, we cannot give you an exact date when the study will end.



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ENROLLMENT AND PERMISSION SIGNATURES

Your signature documents your permission to take part in this research.

Printed Name / / : AM/PM
Date Time

Signature

Person Obtaining Consent

- I have explained the research study to the participant.
I have answered all questions about this research study to the best of my ability.

Printed Name / / : AM/PM
Date Time

Signature