

## Original Research

# Opportunistic salpingectomy versus traditional partial salpingectomy at the time of cesarean delivery: a non-inferiority randomized controlled trial

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## Abstract

**Background:** Ovarian cancer has the highest mortality of all gynecologic malignancies, however there is no proven effective screening for ovarian cancer. Evidence suggests that epithelial ovarian cancer begins in the fallopian tubes. Prophylactic bilateral total salpingectomy has been shown to reduce the risk of epithelial ovarian cancer and is now recommended to be considered at the time of sterilization procedures. There are limited well designed clinical trials that compare the safety and feasibility of total salpingectomy to that of traditional partial salpingectomy for tubal sterilization in obstetrics. We thus conducted a randomized controlled trial to assess the safety of bilateral total salpingectomy at the time of cesarean delivery. **Methods:** We conducted a non-inferiority randomized controlled trial at the Mayo Clinic, Rochester, Minnesota. Women age 21 years and older who were undergoing cesarean delivery and desired concomitant sterilization were enrolled between May 17, 2017 and July 16, 2018. Stratified randomization was performed based on number of previous cesarean deliveries and their Basal Metabolic Index, into a bilateral total salpingectomy (BTS) group and bilateral partial salpingectomy (BPS) group. All salpingectomies were performed using clamps and suture. The primary outcome was to compare the mean peri-operative hemoglobin change for both groups. Secondary objectives included sterilization completion time, postoperative length of stay, estimated blood loss, postoperative pain and adverse events. **Results:** Of the 111 women screened, 40 were enrolled and randomized. Of these, 38 underwent the assigned procedure (18 BTS, 20 BPS). No difference in Mean  $\pm$  SD hemoglobin drop between groups ( $1.4 \pm 0.7$  g/dL for the BPS group and  $1.8 \pm 1.0$  g/dL for the BTS group,  $p = 0.08$ ), however the point estimate of  $-0.4$  is very close to the non-inferiority margin of  $-0.5$ , and the CI widely exceeds the non-inferiority margin (95% CI  $-0.99, 0.17$ ). Therefore non-inferiority was not shown. Mean time to completion of sterilization procedure was significantly longer in the BTS group ( $16.3 \pm 5.6$  minutes for the BTS group vs  $5.1 \pm 1.6$  minutes for the BPS group,  $p < 0.01$ ). No significant differences for other outcome measures. **Conclusions:** Bilateral total salpingectomy is not non-inferior to traditional bilateral partial salpingectomy with regards to postoperative hemoglobin drop, and is associated with a small increase in operative time. There, however, was no difference in adverse events, postoperative length of stay and postoperative pain between the two groups. This information may be helpful when counseling patients.

**Keywords:** bilateral salpingectomy; sterilization; cesarean delivery; ovarian cancer

## 1. Introduction

Epithelial ovarian cancer has the highest mortality of all gynecologic malignancies and is the third leading cause of gynecologic malignancy after cervical and uterine cancer in the world [1]. Evidence suggests the origin of extrauterine pelvic serous carcinomas begins in the fallopian tubes, is often high grade, and is associated with poor prognosis [2]. There are no proven effective screening methods for such cancers in low risk women and symptoms are often vague and non-specific which contributes to a higher stage and grade at the time of diagnosis. In view of this, the Royal

College of Obstetricians & Gynecologists and the American College of Obstetricians and Gynecologists (ACOG) recommend considering counseling patients interested in permanent tubal sterilization about prophylactic salpingectomy as an effective method that may also prevent ovarian carcinogenesis [2–4].

The United Nations Report “Trends in Contraceptive Use Worldwide 2015” notes that 19% of women worldwide relied on tubal sterilization as a method of contraception [5]. The United States National Health Statistics Report of 2015 stated that 9.4 million (approximately 15%) of women be-



tween ages 15–44 years are currently using tubal sterilization as a method of birth control, making it the second most common contraceptive method used in the United States, following contraceptive pills [6]. There are two types of sterilization: the postpartum sterilization (performed within the first six days after delivery), and laparoscopic (or interval) sterilization. In the United States, over 50% of all sterilization procedures are performed in the postpartum period [7].

Prophylactic salpingectomy at the time of cesarean delivery is an ideal opportunity for primary prevention of epithelial ovarian cancer. With the recent ACOG committee opinion endorsing offering prophylactic salpingectomy at the time of sterilization counseling in the United States, numerous physicians have begun performing bilateral total salpingectomy (BTS) during interval sterilization in gynecologic surgery. However, BTS is still not the dominant approach for sterilization in obstetrics [8]. There are limited well designed randomized controlled trials looking at prophylactic salpingectomy at the time of cesarean delivery. Roeckner *et al.* [9] in a systemic review and metaanalysis of 3 randomized controlled trials and 8 retrospective studies, showed that salpingectomy at the time of cesarean delivery was associated with an increase in operative time without any increase in complications. Out of the three randomized controlled trials included in Roeckner *et al.*'s [9] systemic review and metaanalysis; Ganer-Herman *et al.* [10] did not performed a power calculation; Garcia *et al.* [11] was powered to assess the difference in operative times but used a bipolar vessel sealing device to perform the salpingectomies, and Subramaniam *et al.* [12] was under-powered (they needed 40 in each group but only had 27 bilateral salpingectomies and 38 bilateral tubal ligations) and the surgical providers performing the surgeries did not have any formalized training in performing total bilateral salpingectomies at the time of cesarean delivery [9–12]. Our study attempts to address these limitations noted above in the existing randomized controlled trials.

In order to assess the risk of hemorrhage and in turn the safety profile of the BTS procedure at the time of cesarean delivery, we designed a non-inferiority randomized controlled trial powered to look at the peri-operative change in hemoglobin in women undergoing concomitant sterilization at the time of cesarean delivery using the routinely available surgical clamps and sutures [13]. Our hypothesis was that patients desiring permanent contraception who undergo BTS would have equivalent surgical blood loss to those undergoing traditional bilateral partial salpingectomy (BPS) during cesarean delivery as measured by peri-operative change in hemoglobin (g/dL).

## 2. Material and methods

This was a single center, non-inferiority, two-arm randomized controlled trial. The trial was conducted between May 17, 2017 and July 16, 2018 at the Mayo Clinic

in Rochester, Minnesota and was approved by the Mayo Clinic institutional review board (17-000898). The study was registered on [ClinicalTrials.gov](https://clinicaltrials.gov), NCT03135431, on 27/04/2017.

### 2.1 Methods

Women were stratified by number of prior cesarean deliveries and Body Mass Index (BMI). Mean difference (post- vs. pre-procedure) in hemoglobin of participants undergoing cesarean non-emergent delivery with BPS via Pomeroy or Parkland method was compared to those undergoing cesarean delivery with BTS. Inclusion criteria included women 21 years of age and older who desired permanent contraception and had an obstetric indication for a cesarean delivery. Women were excluded if they needed an emergent or immediate cesarean delivery, their BMI was greater than or equal to 50 kg/m<sup>2</sup>, and or if they had a single ovary/fallopian tube.

The study coordinator approached women at their scheduled obstetric clinic visit to inform them about the trial. In addition, women who were admitted to the hospital for inpatient care, and whose cesarean delivery was not deemed an emergency, were informed of the trial by the study coordinator or one of the investigators. The informed consent was written in English; however, women who did not speak English were consented with the aid of an interpreter. After informed consent for the study was obtained, the participants were randomly assigned to either BTS or BPS using a computer based electronic dynamic allocation platform based on the Pocock-Simon algorithm according to the number of prior cesarean deliveries (first vs. repeat) and BMI (<35 vs. ≥35 kg/m<sup>2</sup>). Women who were enrolled and randomized prior to delivery underwent their assigned sterilization method regardless of the urgency of their cesarean delivery. The participants were blinded to the operative intervention at the time of the randomization, and this was later disclosed to them after their cesarean delivery.

Following enrollment, a pre-operative complete blood count (CBC) was collected from participants at the time of their preoperative labs or upon hospital admission, but not to exceed 72 hours before delivery. On admission, women were asked if they wanted to proceed with permanent contraception and consent was obtained for cesarean delivery and the assigned procedure. In the operating room, the delivering team proceeded with the cesarean delivery as indicated. Once completed, the feasibility of the participants' assigned contraceptive procedure was assessed. The start and stop time of the permanent contraceptive procedure was recorded by the nurse in the room and collected by the study coordinator. Participants assigned to BPS did so via Pomeroy or Parkland method based on the surgeon's preference. BTS was standardized using the technique described by Hall, *et al.* [14] (ACOG May 2017 Film Festival, A Novel, Safe, Low Cost Approach to Bilateral Salpingec-

tomy at Cesarean Section) using clamps and suture. This method involves using cautery to skeletonize the mesosalpinx, leaving only perforating vessels which were then suture ligated. Surgeons to be performing the bilateral total salpingectomies were first demonstrated this surgical technique via a training module and they then had to perform one proctored bilateral total salpingectomy and be checked off as competent by another competent surgeon prior to performing the bilateral total salpingectomies on their own on participants. Estimated blood loss (EBL) was calculated for the combined cesarean and sterilization procedure using visual estimation and recorded per standard practice. A post-operative CBC was collected 24 to 48 hours after the procedure.

Following the participants' six week post-partum visits, their medical records were reviewed for data collection. Data abstracted included patient demographics, past medical history (including thrombophilia and history of chronic pain), obstetrical history (including placental abnormalities), pre and post-operative hemoglobin values, EBL, post-operative pain scores, postoperative narcotic use (including the amount, type of narcotic and need for patient controlled analgesia), postoperative length of stay, and adverse events. Patient pain score goals, and maximal pain scores during the first 12 hours, between 12 to 24 hours and between 24 to 48 hours after their cesarean delivery were abstracted. Pain scores were based on a Numeric Pain intensity Score of 0–10 (0 being no pain, and 10 extreme pain) [15]. Adverse events (AEs) were uncontrolled pain requiring patient controlled analgesia (PCA), symptomatic anemia requiring blood transfusion, return to the operating room (OR), loss of one or both adnexa, cesarean hysterectomy, and death. Post-operative length of stay was calculated using date of discharge minus date of surgery. All abstraction was performed by a single study coordinator who used a hard copy of the electronic data capture system (REDCap) data instrument to record information from charts and then input them into REDCap electronically. She then performed quality checks intermittently by cross-checking REDCap entries every 2–3 data points in the hardcopy abstraction tool.

The Data and Safety Monitoring Plan (DSMP) included a review of charts after the first 10 patients and then quarterly for the duration of the trial. The clinical trial was to be placed on hold if an increase in adverse events were noted. Stopping rules included greater than 20 cases of mild (increased pain scores, mild anemia) or moderate (severe anemia not requiring transfusion) adverse events; greater than 3 cases of severe adverse events (severe anemia requiring transfusion, loss of one or both ovaries); and or any life threatening adverse event (cesarean hysterectomy, return to the operating room) or death. If the above criteria for discontinuation are met, the trial was to be put on clinical hold. A Data and Safety Monitoring committee was convened to assess the causal linkage between the adverse events and the procedure. If causal linkage were established, the study

would have been permanently stopped. Participants would still have been followed, with their permission, even if the study was discontinued. If no causal linkage was established the study would have been taken off hold.

## 2.2 Statistical analysis

Due to the lack on pre-existing studies at the time this trial was started, sample size was initially calculated based on previous studies that reported a mean (SD) drop in hemoglobin of 1.32 g/dL (0.94) following a repeat cesarean delivery and 1.40 g/dL (1.2) following a first cesarean delivery [16]. Based on a review of indications of cesarean deliveries performed at the study site in 2015, we anticipated that over 75% of the cases would be repeat cesarean deliveries. As a non-inferiority study, we chose a threshold of a difference of 0.5 g/dL, approximately one-half a unit of packed cells, as a clinically important difference between BPS and BTS. Assuming that there is no difference between the study arms, a difference of upto 0.5 g/dL in the drop in hemoglobin between study arms would be considered as non-inferior, and assuming a common standard deviation of 1.1 based on previous studies of cesarean deliveries, the study would have 80% power using a *t*-test for non-inferiority with 60 participants in each arm (120 total). Although a change in hemoglobin of 0.5 g/dL is clinically considered negligible, a conservative approach was used. This calculation was based on a two-group 1-sided *t*-test with a type I error of 0.05. Approximately 1 year after our study commenced, data from a separate, retrospective study on salpingectomy at the time of cesarean delivery within the study site's community health system hospitals revealed the mean decrease in hemoglobin among women who underwent salpingectomy ( $n = 30$ ) was 1.6 g/dL (SD 0.7) and 1.8 g/dL (SD 0.9) for women who underwent BPS ( $n = 43$ ) [13]. Based on this information, we conducted a post-hoc power analysis using the same methods as before but update the common standard deviation to 0.7 instead of 1.1 and the number of accrued participants at the one-year mark of study recruitment. Based on this calculation, our study was well powered (84%) to assess our primary aim with 38 participants (18 BTS, 20 BPS). After reviewing this information with the Data Monitoring Committee (DMC) and receiving their approval we discontinued recruitment and completed the study with the accrued subjects. These calculations were conducted without knowledge of the current study findings. No interim analysis was performed. The data were descriptively summarized using means and standard deviations or medians and interquartile ranges for the continuous variables, and frequencies and percentages for the categorical variables. The primary endpoint, change (post- minus pre-procedure) in hemoglobin was calculated using a one-sided two sample *t*-test for non-inferiority. Secondary endpoints were analyzed using the two-sample *t*-test, Wilcoxon Rank Sum, Fishers exact test, and chi-square test, as appropriate. All analysis completed was conducted

a a per protocol analysis, in that the two patients who did not undergo surgery and patient missing outcome data were excluded from the analysis. Statistical analyses were performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA) and R3.1.1 (R Foundation for Statistical Computing, Vienna, Austria).

### 3. Results

A total of 111 participants were screened and 80 eligible participants were approached, of which 40 participants were enrolled for this study between May 17, 2017 and July 16, 2018. The participants that had declined to enter study did so due to either reported lack of interest, concern for cost, concern for the risk of the BTS procedure, and/or a desire to proceed with BPS without randomization. Of the 40 participants enrolled, 38 participants were able to undergo their assigned method of sterilization, which included 18 who underwent BTS and 20 who underwent BPS (Fig. 1). Of two participants that were initially randomized to the BTS, one did not receive it as the delivering staff had not yet received formalized surgical training in the standardized surgical technique and the other participant decided to opt out of sterilization prior to their cesarean delivery. The trial ended once we achieved the desired sample size. All the participants undergoing surgery as part of this trial were followed up until their 6-week postpartum visit.

The primary outcome, change in hemoglobin pre-versus post-procedure, was not statistically higher for participants who underwent BTS versus BPS (mean difference (upper 95%):  $-0.41$  g/dL (0.07);  $p = 0.08$ ). The average decrease in hemoglobin was  $1.8$  g/dL (SD 1.0) for participants with a BTS, while those who received a BPS had an average decrease of  $1.4$  g/dL (0.7), which was below the threshold of  $0.5$  g/dL that was defined a priori as a clinically important difference between the groups, however the point estimate of  $-0.4$  is very close to the non-inferiority margin of  $-0.5$ , and the CI widely exceeds the non-inferiority margin (95% CI  $-0.99$ ,  $0.17$ ). Therefore non inferiority was not shown (Fig. 2).

At the time of randomization, there were no statistically significant demographic differences between participants randomized to BPS versus BTS. The average age of participants in the BPS group was 34.4 years compared to 32.7 years in the BTS ( $p = 0.18$ ). The median parity was two for those undergoing BPS and one and a half for those assigned BTS ( $p = 0.15$ ). Most participants were white, with some college education, and undergoing a repeat cesarean delivery (Table 1). When considering secondary endpoints, a significant difference was found in operation time for the sterilization, with BPS taking an average of 5.1 minutes (SD 1.6) to complete and BTS taking 16.3 minutes (SD 5.6) ( $p < 0.01$ , Table 2). There was no statistical difference in postoperative length of hospital stay, or pain scores in the sample (Table 2). There were no differences in the number of adverse events between the participants who underwent

**Table 1. Participant characteristics comparing women who underwent BPS and those who underwent BTS.**

	BPS (N = 20)	BTS (N = 18)
Demographics		
Age at cesarean, mean (SD)	34.4 (4.1)	32.7 (4.8)
Race, count (%)		
Hispanic and/or latino	0 (0.0)	1 (5.6)
White	20 (100.0)	17 (94.4)
Baseline BMI, mean (SD)	31.0 (7.7)	30.0 (7.1)
Married, count (%)	15 (75.0)	11 (61.1)
Education, count (%)		
At least some college	2 (10.5)	2 (11.1)
Some college, 2 year degree	5 (26.3)	11 (61.1)
4 year or professional degree	12 (63.2)	5 (27.8)
Gravidity, median (IQR)	4 (3–5)	3 (2–5)
Parity, median (IQR)	2 (1.5–3)	1.5 (1–2)
Smoking status, count (%)		
Current	3 (15.0)	5 (27.8)
Former	7 (35.0)	1 (5.6)
Never	10 (50.0)	12 (66.7)
Cesarean summaries		
Repeat cesarean, count (%)	17 (85.0)	16 (88.9)
Prior vaginal delivery, count (%)	10 (50.0)	5 (28.0)
Gestational age (weeks), mean (SD)	37.6 (2.6)	38.0 (2.4)

Note: 'n' is total number of subjects.

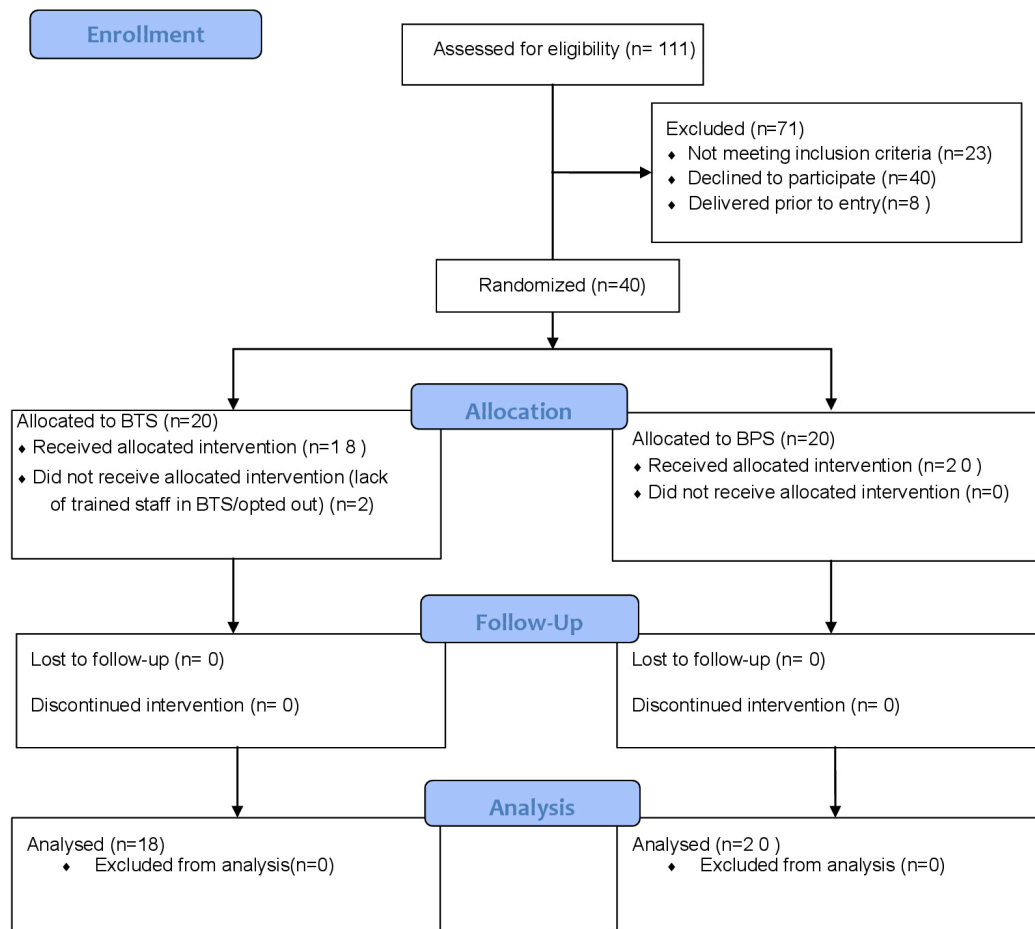
BPS versus those who underwent BTS. One participant in the BTS group required transfusion of 1 unit of blood for symptomatic anemia two days post-delivery. The participant's operative report did not mention any source of hemorrhage and an appropriate rise in her hemoglobin was appreciated post transfusion. She was discharged home on post-operative day three. One participant in the BPS group experienced an uncontrolled pain requiring PCA use. It was undetermined if her increased post-operative pain was related to her BPS.

### 4. Discussion

Our study failed to show non-inferiority of BTS to BPS at the time of cesarean delivery with regards to perioperative hemoglobin change in the participants of this study. While there is potential benefit to BTS in reducing future epithelial ovarian cancer risk at the time of cesarean delivery, our study does not show that BTS is as safe as BPS from a perioperative hemoglobin change standpoint. With regards to the time to completion of the sterilization procedure, our study shows that BTS took an average 16.3 minutes to complete (SD 5.6) S in comparison to BPS which took 5.1 minutes (SD 1.6). There was no difference in adverse events, postoperative length of stay and postoperative pain between the two groups.



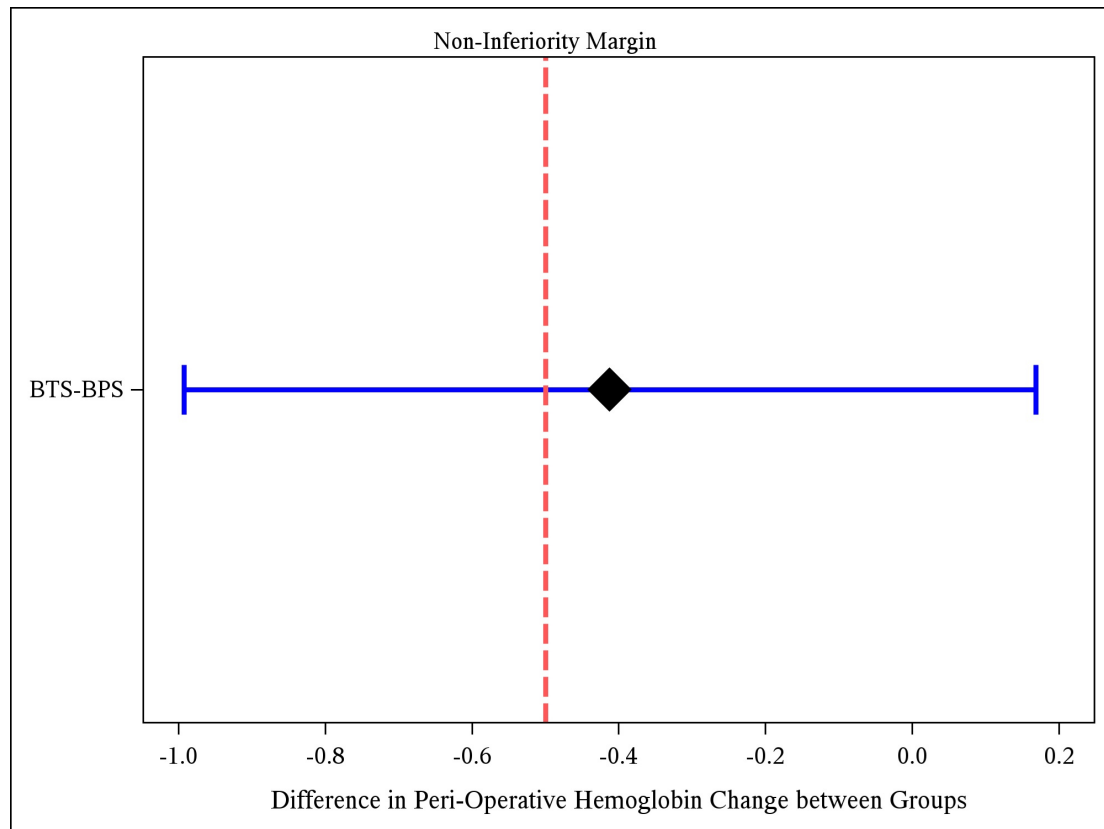
# CONSORT 2010 Flow Diagram



**Fig. 1. Flow diagram of cases randomized to BPS and BTS (Note: ‘n’ is total number of subjects).**

Pregnancy is associated with significant venous engorgement [17] and this is evident at the time of a cesarean delivery. These venous vessels can be closely associated with the fallopian tubes and accidental injury to which can lead to significant hemorrhage. This risk of injury is often a concern when performing sterilization at the time of cesarean delivery and may theoretically be increased with BTS when compared to BPS at the time of a cesarean delivery due to the complete removal of the fallopian tubes with the BTS procedure. Our study shows that BTS may not be as safe as BPS from a perioperative hemoglobin change standpoint, however like existing studies have shown this hemoglobin drop did not lead to an increase in adverse events (uncontrolled pain requiring patient controlled analgesia, symptomatic anemia requiring blood transfusion, return to the operating room, loss of one or both adnexa, cesarean hysterectomy, and death) and postoperative length of stay between the two groups. Roeckner *et al.* (2020)

[9] in a recent systematic review and metaanalysis of salpingectomy at the time of cesarean delivery showed that bilateral salpingectomy at the time of cesarean delivery was not associated with an increased rate of surgical complications. Most of the other existing literature on BTS at the time of cesarean delivery are retrospective studies. Ferrari *et al.* (2019) [18], in a retrospective study of 528 pregnant women undergoing BTS (n = 245), BPS (n = 239) and other permanent sterilization methods (n = 48) at the time of cesarean delivery showed no difference in EBL and postoperative complications (5.3% in the BTS group vs. 2.5% in the BPS group;  $p = 0.11$ ) between the groups. Powell *et al.* (2017) [19], in a retrospective study of 206 salpingectomies performed at the time of cesarean delivery, showed a similar median blood loss between BTS and BPS at cesarean delivery. Shinar *et al.* (2017) [20] in another retrospective study comparing BTS (n = 50) to BPS (n = 99) at the time of cesarean delivery, found no difference in estimated



**Fig. 2. Non inferiority plot for the difference in perioperative hemoglobin change between BTS and BPS.** The dotted red line denotes the non inferiority margin of 0.5 g/dL, The rhombus is the point estimate of  $-0.4$  g/dL between the two study groups which is very close to the non-inferiority margin of  $-0.5$ , and the CI widely exceeds the non-inferiority margin (95% CI  $-0.99, 0.17$ ). Therefore non inferiority was not shown between the two groups.

blood loss and other complications within 1-month postpartum. At our institution, Parikh *et al.* (2019) [13], in a retrospective study in the larger Mayo Clinic Health System comparing BTS ( $n = 41$ ) and BPS ( $n = 48$ ) at the time of cesarean delivery and showed that the mean difference in pre and postop hemoglobin of  $0.18$  g/dL (95% CI  $-0.51, 0.17$ ) however the confidence interval did also cross their non inferiority margin on  $0.5$  g/dL. There are three randomized controlled trial in literature comparing BTS and BPS at the time of cesarean delivery, however they are limited by their study designs. Ganer-Herman *et al.* (2017) [10] looked at the effect BTS on ovarian reserve (22 women underwent BTS and 24 underwent BPS). They did not find any difference in ovarian reserve and complications between both groups, however they did not performed a power calculation to be able to determine if their findings were statistically significant. Garcia *et al.* (2018) [11] in another randomized controlled trial looked at the difference in operative times in 19 women undergoing BTS and 18 undergoing BPS at the time of cesarean delivery. They found no difference in operative times between both the groups, however they used a bipolar vessel sealing device to perform the salpingectomies which could have impacted their findings. Subramaniam *et al.* (2018) [12] also looked at

the difference in operative times between the BTS group and BPS group at the time of cesarean delivery, however they were under-powered, as they required 40 in each group but they only had 27 participants in the BTS group and 38 participants in the BPS group. Also, the surgical providers performing the surgeries did not have any formalized training before doing the procedures. There is some conflicting evidence with regards to the feasibility of BTS at the time of cesarean delivery. Subramaniam *et al.* (2018) [12] showed that BTS could only be completed successfully in 68% cases (27 if the 40 women enrolled), however, Garcia *et al.* (2018) [11] showed that BTS could be completed in 95% (19 out of 20 patients enrolled for BTS). In our study, all patients ( $n = 18$ ) for which BTS were attempted were able to have a BTS without any failures of the procedure.

There are many strengths to our study. Firstly, our study is unique in that it attempts to address the limitations of the existing randomized controlled trials in literature that compare BTS and BPS at the times of cesarean delivery. Our study is adequately powered to assess the difference in mean drop in hemoglobin between the two procedures, and we provided formalized surgical training to the surgeons in the standardized surgical technique used to perform the salpingectomy. We used instruments and suture

**Table 2. Summaries of primary and secondary outcomes comparing women who underwent BPS and those who underwent BTS.**

Hemoglobin (g/dL), mean (SD)	BPS (N = 20)	BTS (N = 18)	p-Value
Pre cesarean, mean (SD)	11.5 (1.0)	11.3 (1.1)	0.52 <sup>1</sup>
Post cesarean, mean (SD)	10.0 (0.8)	9.3 (1.5)*	0.06 <sup>1</sup>
Reduction (pre-post), mean (SD)	1.4 (0.7)	1.8 (1.0)*	0.08 <sup>2</sup>
Secondary endpoints			
Operation time (mins), mean (SD)	5.1 (1.6)	16.3 (5.6)	<0.01 <sup>1</sup>
Estimated blood loss (mL), mean (SD)	833 (105.5)	842 (84.5)	0.77 <sup>1</sup>
EBL by group, count (%)			0.79 <sup>3</sup>
<800 mL	11 (55)	11 (61)	
800 mL	3 (15)	1 (5.6)	
>800 mL	6 (30)	6 (33.3)	
AEs <sup>a</sup> , Mean (SD)	0.10 (0.31)	0.22 (0.43)	0.31 <sup>1</sup>
Post-operative length of stay, median IQR	3 (3, 4)	3 (3, 4)	0.91 <sup>4</sup>
Highest pain score, mean (SD)			
First 12 hours	5.2 (2.5)	5.1 (1.9)	0.89 <sup>1</sup>
First 12 to 24 hours	5.8 (2.3)	5.7 (2.2)	0.93 <sup>1</sup>
First 24 to 48 hours	6.9 (1.6)	6.8 (1.5)	0.90 <sup>1</sup>

Note:

\*Summaries reflect 17 of the 18 patients. One patient was missing the post cesarean hemoglobin.

<sup>a</sup>Adverse Events.

<sup>1</sup>Two sample *t*-test.

<sup>2</sup>One sided *T*-test for non-inferiority.

<sup>3</sup>Fishers exact test.

<sup>4</sup>Wilcoxon Two-Sample test.

'n' is total number of subjects.

that are generally available in all operative rooms without using costly disposable vessel sealing devices. However, our use of suture and clamps may have contributed to the increase in operative time with the BTS group when compared to the BPS group. We anticipate that as surgeons get more experienced with performing BTS at the time of cesarean delivery this difference in operative time will decrease. Alternatively, a vessel sealing device can also be used to perform at BTS to save time, keeping in mind the potential increase in the cost of performing the procedure. We were able to quantitatively assess the risk of bleeding with BTS at the time of cesarean delivery in a randomized controlled trial. We understand that a large population study is likely a better study design to assess the safety and peri-operative complications associated with BTS at the time of cesarean delivery, however we feel that our study is a well-designed randomized controlled trial that contributes to the existing literature.

One limitation of our study is the post ad hoc analysis and small sample size; however, we are adequately powered. Post-hoc power calculations are not ideal and we had originally powered the clinical trial without a source. When information became available, we estimated the power again without evaluating our findings to date to see if that

new information would impact our power/sample size. Another limitation was the exclusion of women with a BMI greater than 50 kg/m<sup>2</sup>. Ten percent of the women screened were unable to participate in the study due to their pre-pregnancy BMI. As obese women with BMI greater than 50 kg/m<sup>2</sup> represent an increasing proportion of our obstetric population, the findings of this study may not apply to this group. Performing BTS in women with a BMI greater than or equal to 50 kg/m<sup>2</sup> may be more difficult and decreased access to the entire fallopian tube may increase the risks. Special attention should be paid in further studies with this specific group.

## 5. Conclusions

In conclusion, BTS is not non-inferior to traditional bilateral partial salpingectomy with regards to postoperative hemoglobin drop, however, there was no difference in adverse events, postoperative length of stay and post-operative pain between the two groups. BTS is associated with a small increase in operative time which may improve as surgeons gain more experience with the procedure. We recognize the potential benefit of bilateral total salpingectomy in reducing the risks of epithelial ovarian cancer, and the findings of our study may be helpful when counseling

patients allowing them to make a better informed decision when choosing between BTS versus traditional BPS at the time of cesarean delivery. Future research should focus in evaluating the risk of BTS in women with a BMI of  $\geq 50$ .

## Author contributions

RR study protocol development, recruitment, final manuscript writing and review; EYRC study protocol development, recruitment, final manuscript writing and review; ACT study protocol development, recruitment, final manuscript writing and review; MLD study protocol development, recruitment, final manuscript review; KDT recruitment, final manuscript review; LLE recruitment, final manuscript review; MMW recruitment, data collection, final manuscript review; MAH data analysis, and final manuscript review; MEB data analysis and final manuscript review; VET study protocol development, recruitment, final manuscript writing and review.

## Ethics approval and consent to participate

This clinical trial study protocol was approved by the Mayo Clinic Institutional Review Board (17-000898) and is in accordance with the guidelines laid by the Declaration of Helsinki. A written informed consent was obtained from all participants prior to their enrollment in this trial.

## Acknowledgment

Not applicable.

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## Conflict of interest

The authors declare no conflict of interest.

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