The University of Texas Medical Branch at Galveston

Research Protocol # 21-0045

Title: Subcuticular Absorbable Staples Versus Conventional Skin Closure in Women Undergoing Cesarean Delivery: A Randomized Control Trial

Prepared by:

Brett Goldman, MD (Principal Investigator)
The University of Texas Medical Branch
301 University Blvd.
Galveston TX, 77555

Shannon Clark, MD (Faculty Sponsor)
The University of Texas Medical Branch
301 University Blvd.
Galveston TX, 77555

Sponsor: Cooper Surgical

Email: BRGoldma@UTMB.edu
Direct: Brett Goldman – (954) 263-2359

1. Introduction and Purpose:

Cesarean delivery is the most common major operating room surgery, with yearly rates increasing worldwide. Despite the high numbers of cesareans being performed, scientific evidence behind which surgical techniques are best remains uncertain. Consequently, there is significant interest in optimizing surgical techniques. Our objective is to determine if subcuticular absorbable staples improve operative time and wound cosmetics.

2. Background:

Cesarean delivery is the most common surgical procedure in the USA. Despite a concerted effort to decrease the cesarean delivery rate, it continues to hover around 30%. There is clear interest in optimizing surgical techniques. The optimal skin closure technique after cesarean delivery remains unknown. The effect of different skin closure techniques, such as suture versus staple closure, on decreasing wound morbidity and closure time, as well as improving aesthetics remains unclear. Supporting arguments for the use of either closure types remain controversial.

Randomized controlled trials comparing surgical steel staples to subcuticular sutures found no difference in wound cosmesis.[1-3] However, some studies reported increase in wound infection rates in patients who received steel staples. There are conflicting results regarding postoperative pain; one study concluded less pain with suture techniques [1], while another [3] showed the opposite. While steel staple closure is easier to perform and master than subcuticular suture closure, it requires an additional clinic visit for removal of the staples. Staple closure can also lead to the misdiagnosis of a wound infection, as it is associated with induration and erythema.

The recent introduction of absorbable subcuticular staples combines the best of both approaches. Animal studies showed absorbable subcuticular staple closure leads to less histological inflammation [4] and less wound infections compared to steel staples [5]. Clinical trials in cesarean are lacking. In a retrospective cohort study [6], this new device led to less in-hospital analgesic use compared to steel staples. Another study [7] showed that women who had skin incision closure with absorbable subcuticular staples had lower rates of wound complication compared to steel staples but similar to absorbable sutures. Both studies concluded that level 1 evidence trial is needed to further support and verify these results.

3. Concise Summary of Project:
This will be an open-label randomized controlled clinical trial. Women undergoing cesarean delivery will be randomized to have either standard wound closure with Monocryl suture or absorbable subcuticular staples placed by INSORB skin stapling device. The INSORB under the skin stapling device is FDA approved but not currently used as standard of care at UTMB. We will exclude women with intraamniotic infection, immunosuppression, active skin infection, those unlikely to be followed-up after delivery, or unable to provide consent.

Potentially eligible subjects will be informed by the obstetrical team about the study and asked for permission to contact the study personnel. Written informed consent will be obtained by person-to-person contact. The research staff will be responsible for the informed consent.

Subjects who agree to participate in the study will be randomized to one of the two groups below in a 1/1 allocation:

- Suture wound closure: absorbable sutures for closure of cesarean skin incision using Monocryl manufactured by Ethicon.
- Absorbable staple wound closure: staples will be applied as per the manufacturer's instructions (Appendix A) intraoperatively using INSORB device manufactured by Cooper Surgical.

The remainder of the subjects' care, including wound care, will be similar for both arms and will follow current standard clinical practice at the University of Texas Medical Branch (UTMB). The study period will be between 2021 and 2023. The number of subjects to be studied at UTMB will be 352. A subject will be withdrawn from the study if she wishes to discontinue participation.

4. Inclusion Criteria:

- 18-50 years of age.
- Women ≥ 24 weeks viable gestation.
- Will be undergoing cesarean delivery.

5. Exclusion Criteria:

- Patient unwilling or unable to provide consent.
- No or very limited prenatal care or a non-resident patient who is unlikely to follow-up after delivery.
- Immunosuppressed subjects: i.e., taking systemic immunosuppressant or steroids (e.g. transplant subjects; not including steroids for lung maturity), HIV with CD4 <200, or other.

- Decision not to have skin closure (e.g. secondary wound closure, mesh closure).
- Current skin infection.
- Coagulopathy.
- High likelihood of additional surgical procedure beyond planned cesarean with our without tubal ligation (e.g. scheduled hysterectomy, unplanned tubal ligation, bowel or adnexal surgery).
- Incarcerated individuals.
- Intraamniotic infection.
- Subjects participating on other treatment trials or studies that would interfere with the current study's primary outcome.

6. Study Procedures:

6.1 Screening Recruitment and Consenting:
Under the direction of the PI, trained research staff will be available 24/7 to screen and consent subjects. Subjects will be enrolled at the time of admission to labor and delivery (L&D) for delivery or thereafter when decision for cesarean section is made. Medical records of all potential subjects will be reviewed and those who satisfy eligibility criteria will be approached and written informed consent obtained. Potential subjects with whom there is no treating relationship, the permission of the treating provider will be obtained prior to approaching subjects to participate in the study. A screening log will be used to track all subjects approached for the study. Women will be randomized in the operating room when the decision is made to proceed with skin closure and they continue to be eligible.

Recruitment: We will offer the trial to all pregnant subjects admitted to L&D and who meet our eligibility criteria. Whenever practical and feasible, information about our research project will be made available to subjects prior to labor. Once the inclusion criteria for our study are met, the clinical team will inform the subject about the study and ask her authorization to contact one of the study personnel. We will not consent subjects who appear not to be able to evaluate their options (such as recent intravenous narcotics). This strategy is currently followed in other approved OB/GYN studies with similar recruitment timing and has been well received among participants without concerns or complaints. Once the inclusion criteria for our study are met, the clinical team will inform the subject about the study and ask her authorization to contact one of the study personnel.

Consenting process: Written consent will be obtained by direct person-to-person contact. The research staff will be responsible for the informed consent. Written consent will be obtained. The consent form will be thoroughly reviewed with the

subjects prior to signing. Details of participation as well as risks and benefits will be discussed with the patient. Questions will be invited and just prior to signing, the research staff will ask questions of the subject to ensure her complete understanding of the study and her voluntary willing participation. Subjects will be informed that their decision about participating in the study will in no way affect the care they will receive. Research team members will be available for any further discussion or questions/concerns expressed by the patient. For non-English speaking subjects, informed consent will be provided in their primary language (Spanish). A certified translator will review the consent with them which will be provided in their own language .The research data collected will not be used for clinical diagnosis or treatment purposes. Subjects will be reassured that participation in the study is voluntary and will not interfere with diagnose or treatment of her condition. The subjects will receive the same care and expertise as any other patient treated in our unit.

6.2 Randomization

A confidential computer-generated simple randomization scheme will be prepared and provided on an ongoing basis to our research staff. A randomization log with group assignment, patient name and medical record number will be used to track the randomization process.

6.3. Study visits/Follow-up

Two maternal follow-up study visits will be scheduled to ascertain outcomes at the same time as routine clinical visits (~7 days postoperative & ~ 6 weeks postpartum visit). These visits are standard postpartum visits at UTMB. The standard procedure in our postpartum care unit is that the providers will schedule the postpartum visit before the patient leaves the hospital. Our research staff will document the time and dates of the postpartum appointments in the datasheet in order to confirm follow up. The subject will be informed of the appointment and will be given a phone number for any questions and concerns regarding the study (contact information will be in the consents). Subject participation will end after their 6 week post partum visit.

At the visits, the research staff or trained provider will obtain relevant outcomes described in section 6.7. We will also review the electronic medical record for the relevant outcomes. We will have research staff at every obstetrical clinic available during regular hours. If the subject does not present at the visits, or the survey was not completed during the visit, every effort will be made to contact her by phone and outcomes further ascertained. If greater than 30 days have passed from the last scheduled visit and the subject could not be reached, she will be designated as lost to follow-up.

6.4. Baseline Procedures

Routine post-cesarean care will be according to the subjects' clinical providers. Trained and experienced research staff will be responsible for all research data abstraction. The PI will review and validate the data. Data on these forms devoid of personal identifiers will be securely stored in our perinatal research division offices.

6.5. Device Dispensation

Initial receipt of stapler and materials from the sponsor will be kept in a locked research room with limited access. Receipt of the devices will be documented. Once the study is approved; the devices will be maintained in Labor and Delivery in a locked area ready for access after patient is randomized. This is similar to our other L&D studies where materials/devices are needed. Clinical staff will be trained by the sponsor as an inservice and a log will be created to document training before initiation of recruitment.

6.6 Withdrawals

Subjects who withdraw from the study after randomization will be excluded from further follow-up. Outcomes will be reported by intent to treat fashion. Those who withdraw prior to ascertaining of the primary outcome and refuse further data collection will be accounted for by randomizing an equal number of additional subjects and will not be included in the analysis. Patients will be reassured that participation in the study is voluntary and they are able to withdraw at any time if they wish.

6.6. Primary Outcome

OR Case time in minutes

6.7. Secondary Outcomes

- Need of in hospital analgesics
- Composite wound complication.
    - Defined as presence of any of the following within 30 days from surgery: **Wound infection**: Presence of either superficial or deep incisional surgical site infections described as cellulitis/erythema and induration around the incision or purulent discharge from the incision site, with or without fever, such as necrotizing fasciitis (diagnosed based on necrotizing wound infection). **Wound hematoma, seroma, or breakdown alone.**

- Endometritis, wound infection (including necrotizing fasciitis), other infections including abscess, septic thrombosis, pneumonia, pyelonephritis and breast infection.
- Maternal Death.
- Puerperal fever: temperature >100.4^{o}F after first 24 hours or ≥101^{o}F any time.
- Postpartum antibiotic use.
- Wound hematoma or seroma.
- Wound dehiscence.
- Use of resources: hospital stay, postpartum clinic or emergency room visit within 30 days of delivery, need for imaging or other invasive procedures.
- Adverse events: allergic reactions (anaphylaxis, angioedema, skin rashes including Stevens Johnson and Toxic Epidermal Necrolysis).
- Bluebelle Wound Healing Questionnaire for assessment of surgical-site infection/wound complications in closed primary wounds during wound check visit on POD 5-10 days standard visit, which will be completed by the patient
- Analog pain scale ranging from 0-10 on postoperative days 1 to 3 as well as at wound check visit, this is a standard question that nurses as during the post partum period while in the hospital and clinic/nursing visits. The numerical score will be recorded from the patient's chart.
- Wound cosmesis on POD 5-10 visit postpartum visits: A digital photograph of the incision will be obtained on wound check visit POD 5-10 days and 4-6 weeks postoperative. Each photograph will be evaluated according to objective criteria (width, elevation, color, marks, and general appearance) by independent blinded research staff using the Stony Brook Scar Evaluation Scale
- Satisfaction a questionnaire POD 2-3 (before discharge) and at wound check visit (Appendix B).

7. Sources of Research Material:

Electronic Medical chart/records, questionnaires, photographs.

8. Potential Risks:

8.1. Study Risks

Adverse effects (rare events overall <2%) include irritation, redness, itchiness, discomfort, infection, and allergic reaction. Subjects will be closely monitored for all side effects. For side effects/adverse events, patients will be treated with standard medical care to address their symptoms. The arm that they are enrolled in will not influence treatment.

8.2. Randomization Risk

Since wound closure will be randomized, it is possible that the patient may be in a group with higher adverse outcomes.

8.3. Loss of Confidentiality

Any time information is collected there is a potential risk for loss of confidentiality. Every effort will be made to keep patient's information confidential; however, this cannot be guaranteed.

9. Subject Safety and Data Monitoring

The PI and research staff will be responsible for monitoring the safety of this study. A report to the IRB will be submitted according to its policy if adverse events (AEs) or serious adverse events (SAEs) occur, and any changes in the protocol as a result of these events. No interim analysis will be planned and there will be no study-specific criteria to halt the study. Since, Monocryl and INSORB absorbable stables are deemed safe and available for use according to the FDA, there are no safety and minimal toxicity concern.

The research staff will ensure all aspects of data quality including monitoring for adherence to consent procedures, inclusion and exclusion criteria, valid abstraction, correct entry, timeliness and responsiveness to data queries.

Data collection will take the form of excel data entry and will be identified with a participant ID number. Data will be collected and stored with the participant ID code only. The master enrollment log linking patient identifiers with study ID numbers will be kept in a password-protected database on the Ob/Gyn Department's internal server separate from the data. Several data collection forms will be used. Data on these forms devoid of personal identifiers will be securely stored at our perinatal research division. The research staff will be available to monitor the data and correct any discrepancies based on source documents if needed. The principal investigator and research staff will monitor the study accrual rate, study attrition including withdrawals/dropouts, and any changes in risk/benefit bi-annually.

Each subject will be provided contact information to reach study staff. Additionally, the consent form provides instructions and a mechanism of contact for subjects to reach the primary investigator and also provides contact information for the subject to contact the IRB directly. Any significant concerns or complaints or requests for study information would be directed from the study staff to the study coordinator and study PI. Any complaints or adverse events gleaned from these contacts would be reported to the IRB (per IRB policy) and to the sponsor.

10. Procedures to Maintain Confidentiality

Each patient will be assigned a study number with personal identifiable information deleted or removed. Subjects' information will be de-identified and tagged with a number. Data will be collected and stored on a UTMB password-protected computer in a locked room.

The data collected will be kept on a password-secured UTMB computer. An encrypted USB flash drive will be used to transfer data. The data will be linked to the subject by subject's MRN number. This identifier is needed to access and analyze demographic data. During analysis of the data, all identifiers will be deleted.

11. Potential Benefits

A potential benefit is that the novel stapler device leads to shorter operating room time, better aesthetic outcomes, improved patient satisfaction, and less pain. We also hope that this novel stapler will ultimately reduce SSI rates and maternal health costs.

12. Statistical Approach

Analysis will be performed by intent to treat. For this analysis, normality will be tested using Shapiro-Wilk method. Between-group differences in continuous variables will be assessed using Student t test or Man-Whitney rank sum test and results will be given as mean, standard deviation, or median range as appropriate. Categorical variables will be assessed using the Pearson chi-square test or Fisher exact test as appropriate. For dichotomous endpoints, relative risk (RR) and 95% CI values will be calculated. $P < 0.05$ will be considered significant. The analysis will be performed after study completion.

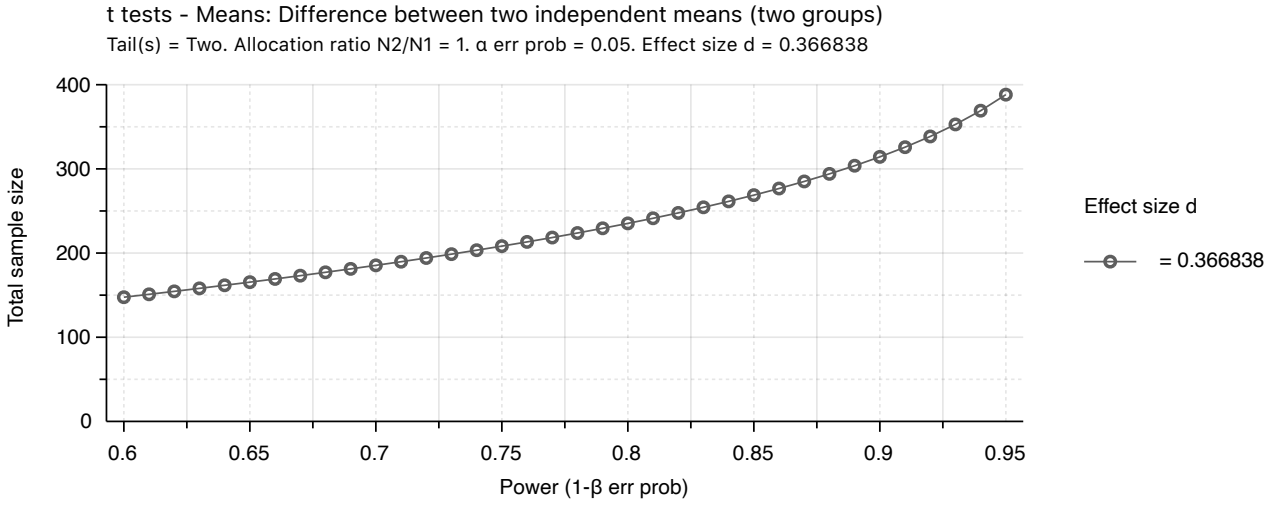
Sample size was calculated based on the determination of superiority. The primary outcome is operative time in minutes. Based on our institution's usual operating time for a routine cesarean section, the mean of operative time in patients undergoing incision closure with sutures was 55.46 with a standard deviation of 13.63 mins. We estimated that the absorbable staples would lead to a decrease in time by 5 mins. If we calculate the sample size based on 90% power to confirm superiority and an alpha of 0.05, we estimate we would need a total of 316 patients. Assuming a 10% loss to follow-up, we plan to enroll a total sample size of 352 (176/group). STATA 16 (Dallas, TX) will be used for statistical computations. This trial will be registered with Clinical Trials Register (Clinicaltrials.gov), before recruitment is initiated and after IRB approval.

Below is the sample size calculation protocol:

T tests - Means: Difference between two independent means (two groups)

Analysis: A priori: Compute required sample size

Input:	Tail(s)	=	Two
	Effect size d	=	0.3668379
	α err prob	=	0.05
	Power (1-β err prob)	=	0.9
	Allocation ratio N2/N1	=	1
Output:	Noncentrality parameter δ	=	3.2605266
	Critical t	=	1.9675477
	Df	=	314
	Sample size group 1	=	158
	Sample size group 2	=	158
	Total sample size	=	316
	Actual power	=	0.9015744



REFERENCES

1. Frishman GN, Schwartz T, Hogan JW (1997) Closure of Pfannenstiel skin incisions. Staples versus subcuticular suture. J Reprod Med 42(10):627–630
2. Gaertner I, Burkhardt T, Beinder E. Scar appearance of different skin and subcutaneous tissue closure techniques in caesarean section: a randomized study. Eur J Obstet Gynecol Reprod Biol. 2008 May;138(1):29-33.
3. Rousseau JA, Girard K, Turcot-Lemay L, Thomas N (2009) A randomized study comparing skin closure in cesarean sections: staples vs subcuticular sutures. Am J Obstet Gynecol 200 (3):265 e261–e264
4. Fick JL, Novo RE, Kirchhof N (2005) Comparison of gross and histologic tissue responses of skin incisions closed by use of absorbable subcuticular staples, cutaneous metal staples, and polyglactin 910 suture in pigs. Am J Vet Res 66(11):1975–1984
5. Pineros-Fernandez A, Salopek LS, Rodeheaver PF, Drake DB, Edlich RF, Rodeheaver GT (2006) A revolutionary advance in skin closure compared to current methods. J Long Term EV Med Implants 16(1):19–27.
6. Nitsche J, Howell C, Howell T. Skin closure with subcuticular absorbable staples after cesarean section is associated with decreased analgesic use. Arch Gynecol Obstet. 2012 Apr;285(4):979-83. doi: 10.1007/s00404-011-2121-5. Epub 2011 Oct 30. PMID: 22037686.
7. Schrufer-Poland TL, Ruiz MP, Kassar S, Tomassian C, Algren SD, Yeast JD. Incidence of wound complications in cesarean deliveries following closure with absorbable subcuticular staples versus conventional skin closure techniques. Eur J Obstet Gynecol Reprod Biol. 2016 Nov;206:53-56. doi: 10.1016/j.ejogrb.2016.07.501. Epub 2016 Aug 3. PMID: 27632411.