Official title: Single or double-layer uterine closure techniques following cesarean: an ongoing debate
Document date: 07/27/2018
Clinical trial number: NCT03629028

Study design and participants

This study will be assessed cesarean delivery (CD) patients who will admit to the Obstetrics and Gynecology Clinic of the Başkent University Adana Dr. Turgut Noyan Research and Application Center between July 2018 and September 2019. Specifically, participants will be singleton pregnancy patients between 18-45 years of age who will be in gestational weeks 24-41 and had not previously received any uterine operations such as CS or myomectomy. Patients with multiple pregnancies and/or chronic inflammatory diseases such as systemic lupus erythematous, rheumatoid arthritis, and insulin-dependent diabetes mellitus will be excluded. All patients who meet the inclusion criteria will be randomized into two treatment groups (i.e., single- or double-layer closures).
This study was approved by Başkent University Institutional Review Board and Ethics Committee (Project no= KA18-71, Approval Date= 7/27/2018), and supported by Başkent University Research Fund. Patients who will agree to participate in the study will be informed about the purpose of the study before their operations, and each provided signed written consent.
Participants will be also assessed for maternal age, gravidity, parity, body mass index, smoking status, diabetes mellitus, hypertensive diseases of pregnancy, and medical history. Regardless of whether they had contractions before surgery, this study also will be determined patient CD indications, levels of cervical dilatation, and how CD will be established (i.e., elective or emergent).

Randomization and masking

A table of random numbers is used as simple randomization method for placing participants into the two treatment groups. The Research Randomizer website (https://www.randomizer.org/) was used to create this table. Before the intervention, the next envelope among a previously prepared, sealed, and number-ordered stack will be opened by a nurse for each procedure.

Surgery technique

Six operators will perform the CD operations. Access to the abdomen will be achieved via Pfannenstiel incision, while the Kerr incision technique will be applied to the uterus for all patients. Patients in the single-layer group will be received uterus closures with locking, while patients in the double-layer group will be received uterus closures with locking in the first layer, but without locking and using the Lambert style in the second layer. The decidua will be deliberately excluded during all suturations. A synthetic absorbable suture material (Vicryl 1.0, Ethicon, Somerville, NJ, USA) will be used during all uterus closures, with corner stitches will be applied to all patients. Additional suture usages and numbers will be reported only in cases of bleeding. Both uterine closure and whole operation times will be recorded by the respective operating room technicians. Finally, intravenous prophylactic antibiotics (2 g cefazolin sodium) and uterotonic medications (10 IU oxytocin) will be routinely applied during all CD procedures.

Follow-up

Postoperative follow-ups will be completed in March 2020. All participants will be called after delivery and will be invited to complete sixth-month evaluations. However, participants who will experience post-CD pregnancies, or uterine surgeries will be excluded. All remaining participants will be examined at six to nine months period after CD for niche presence in the scar region, niche measurements, scar shape, distance between niche and the external cervical os and residual myometrium thickness (RMT), and

adjacent myometrium thicknesses (AMT). The distance between the niche and external os should be measured parallel to the top of the main niche, from the most distal niche point to external os. These examinations will be conducted by two experienced sonographers who will be blinded to clinical information regarding the closure technique. Procedures will be specifically completed using a 4-10 MHz transducer (E8C-RS micro convex endocavity probe, Voluson S6, GE, Milwaukee, US), ultrasonography, and through the saline infusion sonohysterography (SIS) method. The cervix will be first cleaned with povidone iodine while the patient will be on the gynecological examination table prior to ultrasonography. The SIS process then will be progressed toward the inside of the endometrial cavity by passing from the cervical os with an intrauterine insemination cannula (intrauterine insemination catheter, Wallace Artificia Insemination Catheter, Smiths Medical International Ltd., Ashford, Kent, UK). A sterile saline solution will be applied to sufficiently distend the cavity, while ultrasonography will be conducted via transvaginal probe. At this time, the presence of a hypoechogenic area with a depth of 2mm or deeper in the CD scar region within the endometrial cavity will be accepted as a niche. Niche dimensions will be determined via 3-axis measurements for depth, length, and width. Niche shape, distance to the external cervical os, RMT, and AMT will be evaluated. During these follow-ups, patients will be also asked about their menstruation processes and any experiences of cervical pain, menstruation pain, postmenstrual bleeding (PMB) in the form of spotting, and other abnormal bleeding patterns. Those who will experience bleeding for two days or more in the form of spotting after menstruation will be defined as PMB. Participants who will use intrauterine devices after CD and/or those who could not tolerate speculum application will be examined via transvaginal ultrasonography (TV USG).

Outcomes

Primary outcomes will be considered niche presence and measurements, while secondary outcomes will be considered RMT, AMT, healing ratio, postmenstrual spotting, and dysmenorrhea.

Statistical analyses

The sample size was calculated based on a study by Di Spiezio Sardo et al. (2017) titled Risk of Cesarean Scar Defect Following Single- vs Double-Layer Uterine Closure: Systematic Review and Meta-Analysis of Randomized Controlled Trials. Their study revealed niche formation rates for single- and double-layer closure types of 25% and 43%, respectively. Based on tools available at the Power and Sample Size website (http://powerandsamplesize.com/Calculators), needed sample size was calculated at 141 for each treatment group with 90% power and 0.05 alpha error.

All data were statistically analyzed using the IBM SPSS 21.0 software. Categorical measurements will be presented as frequencies and percentages, while continuous measurements will be summarized as means and standard deviations (median and range when needed). Distributions will be checked and the student's t-test was will be used for variables meeting the parametric test assumptions when comparing the continuous measurements based on groups, while the Mann Whitney U test will be used for those that will not meet the parametric test assumptions. Finally, chi-squared or Fisher's test statistics will be used to compare categorical variables. Statistical significance is set to 0.05 for all tests.

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BAŞKENT UNIVERSITY

BAŞKENT UNIVERSITY CLINICAL RESEARCHES ETHICS COMMITTEE
INFORMED CONSENT FORM FOR SCIENTIFIC RESEARCH

PLEASE READ CAREFULLY!!!

You have been invited to participate in a clinical trial for scientific research. Before accepting to take part in this study, you need to understand the purpose of the study and make your decision freely after being informed about the research. This information form has been prepared specifically for you in order to introduce this research in detail. If there are points about the research that you have not understood even though it is stated in this form, ask your doctor and ask for clear answers to your questions. You are free to join this research or not. Participation in the study is voluntarily. Once you are informed about the research, your physician will give you time before signing the form so that you can freely make your decision. Regardless of your decision, your physicians will perform their duties to ensure and maintain your full health from now on. If you agree to participate in the research, sign the form.

1. **TITLE OF PROJECT:** Single or double-layer uterine closure techniques following cesarean: an ongoing debate
2. **VOLUNTEER NUMBER**: The total number of volunteers envisaged to include the research is 282
3. **DURATION:** The period foreseen to take part in this research is 6-9 months.
4. **PURPOSE OF THE RESEARCH:** The aim of this study is to investigate the effect of single or double- layered closure of the uterine area opened during cesarean section on the formation of space in the uterine incision site in long term.
5. **TERMS OF PARTICIPATION IN THE RESEARCH:**
   a) Between the ages of 18 and 45
   b) Singleton pregnancies
   c) Women who had not previously undergone any uterine operations such as cesarean delivery or myomectomy

6. GENERAL INFORMATION ABOUT PROCEDURE

Recent studies in the literature report that, no clear difference has been found between single or double layer uterine closure during cesarean delivery. In this study, we aim to establish a clear consensus about the uterine closure and contribute to the literature. For this reason, during the cesarean operation, one of the two techniques, which are valid for the uterine closure, will be performed to you. The operation time may vary depending on the person until bleeding control is achieved. We will call you and invite to follow-up in 6 to 9 months after the cesarean delivery. In your follow-up we will ask your complaints and we will perform transvaginal ultrasonography to evaluate your cesarean scar region.

7. RESPONSIBILITIES OF THE VOLUNTEER

a. You should follow the research plan and the researcher's recommendations.

b. You should come to follow-up on the dates specified by the researcher.

c. You should inform your doctor if you become pregnant following your cesarean operation.

d. You should report any medical conditions that bother you during the investigation to your doctor (investigator).8.BENEFITS

The surgical procedure, which will be performed, may not provide any additional benefit to you as a result of this research. Our research is for scientific purposes only and is not expected to benefit you directly or change the course of your treatment. However, the results obtained from this research will contribute to the planning of the other patients who are diagnosed like you or to provide benefit to your subsequent births.

9. RISKS

This study does not consist an additional risk apart from the risks mentioned in the routine cesarean delivery informed consent form.

10. RESPONSIBILITY TO THE PARTICIPICANT

In case of any complication due to cesarean procedure, Başkent University will take the responsibility for your treatment.

11. NAME OF PRINCIPAL INVESTIGATOR

Hi, I'm Dr Şafak Yılmaz Baran, I'm the principal investigator of this study. If you have any questions, you may ask me now or later, even after the cesarean operation. You may contact with me. (Hospital phone: 03224586868/22109, personal phone: 05055830856, Address: Baskent University Adana Application and Research Center, Adana, Turkey)

12. REIMBURSEMENTS

Your participation is free. You will not be given any other money or gifts to take part in this research

13. NAME OF ORGANIZATION

This study is supported and funded by Başkent University.

14.CONFIDENTIALITY

Medical information about your operation and postoperative conditions during the research will be recorded with a unique code number and all reports will be kept confidential. The results of the research will be used for scientific purposes only. Even if the research is published, your credentials will not be given. However, if necessary, the investigators of the research, ethical committees and officials will be able to access your medical information. You can access your own medical information whenever you want.

15.EXCLUSION CRITERIA

In case of not attending the follow-up after cesarean operation in 6-9 months, or getting pregnant in the postoperative period, we will exclude you from the study. This situation will not cause any changes in your treatment and surgical procedures. However, even if you are excluded from the research, medical data about you can be used for scientific purposes.

16.RIGHT TO REFUSE OR WITHDRAW

Joining to this research is entirely up to you. You can refuse to join the research or leave the research at any stage. If you refuse to take part in the research or give up after participating, your decision will not cause any change in the treatment applied to you. Medical data related to you may be used for scientific purposes even if you withdraw or be removed by the researcher.

17.SHARING THE RESULTS

While the research is in progress, new medical information and results related to the research will be sent to you or your legal representative as soon as possible. These results may affect your desire to continue research. In this case, you may want to stop the investigation until you decide.

I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I consent voluntarily to participate as a participant in this research.

PARTICIPICANT		**SIGNATURE**
NAME		
ADDRESS		
TELEPHONE		
DATE		

INVESTIGATOR		**SIGNATURE**
NAME OF THE INVESTIGATOR		
ADDRESS		
TELEPHONE		
DATE		