Research title: A study of uterine closure techniques in cesarean section

Research Director: Takashi Murakami

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Research protocol following ethical guidelines for medical research involving human subjects

■**Approval has been obtained from the head of the relevant clinical department or department head**
(Name of department head: Takashi Murakami)

Please check the applicable guidelines

■Ethical guidelines for medical research involving human subjects

□Ethical guidelines for human genome/gene analysis research

□Others outside the scope of application (Reason:)

Please check additional obligations (select from below)

□Interventional research (unapproved/inapplicable research on drugs/medical devices, or research with designs such as blinding or allocation) that involves invasiveness (excluding minor invasiveness)

□This is an interventional study that involves minor invasion.

■No invasive or minor invasive intervention studies

□Observational studies involving invasion or minor invasion

□ Observational and non-invasive research (no additional obligations)

② Research implementation structure (select from below)

■Single center research

Affiliation, name, and role of the principal investigator

Takashi Murakami; Professor, Department of Obstetrics and Gynecology, Shiga University of Medical Science; Supervision of research

Affiliation, name, and role of the co-researcher

Shiga University of Medical Science, Department of Obstetrics and Gynecology

Associate Professor; Shunichiro Tsuji; Research planning, implementation and consideration

Assistant professor; Katsura Daisuke; Research execution,
Person in charge of personnel information management

Assistant professor; Shinsuke Tokoro; Research execution

Assistant professor; Tetsuro Hanada; Research execution

Clinical Fellow; Yuri Nobuta; Research execution

Clinical Fellow; Akiko Nakamura; Research execution

Clinical Fellow; Makiko Kasahara; Research execution

Clinical Fellow; Takako Hoshiyama; Research execution

Research collaborator:

Department of Obstetrics and Gynecology Secretary; Akemi Yamamoto; In charge of the assignment

③ Purpose and significance of the research (including the background for starting this research)

[Background]

Cesarean scar syndrome (CSS) refers to a condition that causes abnormal uterine bleeding, dysmenorrhea, chronic pelvic pain, and infertility after a cesarean section). Although this syndrome is not yet included in the glossary of the Japanese Society of Obstetrics and Gynecology, secondary infertility due to CSS has become a clinical concern as the rate of cesarean section has increased in recent years.

We clarified the current situation in a nationwide survey conducted through a subcommittee of the Japan Society of Obstetrics and Gynecology (1). Further, we demonstrated the efficacy of hysteroscopic surgery against CSS (2). However, the procedure for preventing the onset of CSS has not yet been established.

A contributing factor for the onset of CSS is the presence of a cesarean scar defect (CSD) that occurs after suturing the lower part of the uterus during a cesarean section. However, the optimal suture method to prevent the formation of a CSD is still debated. According to previous reports, a two-layer suture is superior to single-layer sutures, and an un-lock suture is also better than a lock suture (3,4). Regarding surgical time, it single-layer continuous sutures shorten the surgical duration compared with single-layer interrupted suture (5). In addition, one retrospective report revealed that interrupted suture had a lower risk of developing placenta accreta in a subsequent pregnancy (3). However, it remains unclear whether two-layer interrupted or two-layer continuous sutures are better regarding the prevention of a CSD.

[Purpose] To clarify which of the two is better for suturing the uterine wound during cesarean section to avoid CSD development: two-layer interrupted or two-layer continuous sutures.

[Significance] The next pregnancy rate after cesarean section is approximately 9% lower than that after vaginal delivery (6). We consider that the background of the result is associated with CSS. The frequency of CSD occurrence is estimated to be 56% to 84%, and the frequency of symptoms is considered to be at least 20% (7). Because the current annual number of births in Japan is 920,000, Fermi estimate indicated that approximately 37,000 cases of CSS might occur annually. This number cannot be ignored. Further, the importance of this study is expected to increase as the rate of cesarean section administration is growing.

④ Research method and period

Research period: Approval date to December 31, 2024

Registration period: Approval date to January 30, 2024

Follow-up/observation period: Approval date to July 31, 2024

Research design (select from below)

■Intervention research

Study participants will be randomly assigned to either an interrupted suture group (Group I) or a continuous suture group (Group C). We will perform myometrial suture using the method of the assigned group. At 6 to 8 months postpartum, a blinded examiner will perform sonohysterography and measure the depth of CSD and residual myometrial thickness. After the examination of all participants, we will evaluate the participants' background, information related to cesarean section, and matters related to CSD at 6-8 months after delivery in both groups.

□Observational research

□Others

(Specific) research method

During the above research period, written consent will be obtained from pregnant women who are scheduled to give birth at the Shiga University of Medical Science Hospital. If a subject whose consent has been obtained undergoes a cesarean section, a registration number will be given to indicate a study participant. Study participants will be assigned to either Group I or Group C; assignment will be randomized. The person in charge of assignment provides the registration number in Excel to randomly assign the participants to Group I and Group C in advance. The allocation will be made with 20 cases in each block, resulting in a total of 11 blocks. A code sheet will be created for 220 cases, and the allocation code table will be stored appropriately by the person in charge of allocation. The created allocation code table No. 1 to No. 220 will be kept in the Maternal and Fetal Medicine department, and the cesarean section operator will suture the uterine myometrium following the allocation table. The examiner will perform sonohysterography at 6-8 months and save the images in the medical record. Later, an examiner blinded to the allocation will perform measurements of the CSD. The item of measurement is the depth of the CSD and residual myometrial thickness. Analysis of the obtained data will be performed after all results are available. The obtained data will be compared between groups as shown below. The group allocation will be disclosed to the subjects 6 to 8 months after delivery.

⑤ Research subject selection policy

[Overview of research subjects]

Among the patients who visited the Maternal and Fetal Medicine department of our hospital during the registration period from the date of approval to January 2024, pregnant women who are planning to give birth at our hospital will have a cesarean section after providing written informed consent.

[Eligibility criteria]

Age: 20 years or older (at the time of registration)

[Exclusion criteria]

Those who have uterine fibroids around the incision line of the uterus

Those with uterine malformations that affect the uterine isthmus

[Dropout/discontinuation criteria]

・Those who have a cesarean section wound in a direction other than the lateral direction

・If there is a request to cancel study participation

・Those who underwent another laparotomy between the time of cesarean section and the evaluation
・If the entire exam is canceled
・Other cases where the doctor determines that the patient is not suitable for the study

Planned number of cases and rationale for setting

Using Easy R, we examined the sample size using past reports with a power (1-β) of 0.90 and an α-value of 0.058. Assuming that the difference in the mean value between the two groups for the primary outcome, residual myometrial thickness (0.85 (cm) and the standard deviation is 1.73), the required sample size per group will be 88. A total of 176 cases will be required. Assuming a dropout rate of 20% for visits 6 to 8 months after the delivery, 220 cases would be required. If we estimate the cesarean section rate at our hospital to be 40% and we predict that approximately 60 patients will participate in the study each year, it will take approximately 3.7 years to accumulate 220 cases. Considering that the final enrollees will be observed for 6-8 months, the study period will be approximately 4.5 years from the date of approval.

Observation/Inspection items

The size of the CSD will be measured by sonohysterography.
Measurer: Obstetrics and gynecology specialist certified by the Japan Society of Obstetrics and Gynecology
Measurement items: Depth of the CSD, measurement of residual myometrial thickness
Measuring institution: Shiga Medical University Hospital
Measurement schedule: 6-8 months after cesarean section

Evaluation item

Primary endpoint: residual myometrial thickness 6-8 months after cesarean section
Secondary evaluation items:
1. The characteristics of the participants (Age, BMI, the number of gravidities, the number of parities, the number of cesarean sections, indication for cesarean section, the diameter of external OS at cesarean section)
2. Total operation time for cesarean section
3. Total blood loss in cesarean section
4. The number of sutures to close the cesarean scar in cesarean section
5. Fever or not after cesarean section
6. The value of CRP one day post cesarean section
7. The period of admission for cesarean section
8. Healing ratio in cesarean scar defect

Analysis overview

The residual myometrial thickness and healing ratio (=residual myometrial thickness/residual myometrial thickness + depth of CSD) will be calculated and examined between the two groups. After confirming whether each is normally distributed, we will use a parametric test if it is normally distributed or a nonparametric test if it is non-normally distributed, and consider whether there is a significant difference. The significance level is set

at 5% on both sides.

⑥ Basis of the scientific rationality

The sample size of this study was calculated through the statistical analysis described above. In addition, this study will be conducted as a randomized controlled trial. It means that the bias of the operator who will perform the cesarean section and the examiner who will measure the postpartum myometrium would not affect the results. Therefore, the scientific rationality of the research is guaranteed.

⑦ Procedures for obtaining informed consent, etc.

Please check additional obligations (select from below)

□Invasive research

■It is an interventional study that does not involve invasiveness.

□Observational research that does not involve invasive research but uses human samples

□Observational research that does not use human samples

As a result of the above, please select one of the methods below, write the details of the IC procedure in the relevant section, and please submit the attached documents at the time of application.

■Written explanation and consent

□Oral explanation and record creation

□Perform consent IC

Policy for selecting a representative, etc.:

Explanation to the representative

The reason it is necessary to include the person as research subject:

□Perform ascent

□Other than the above

Please be sure to provide detailed information regarding the consent acquisition procedure mentioned above.

During the above-mentioned research period, written explanations will be given to pregnant women before delivery at the Shiga University of Medical Science Hospital. Afterwards, the subject's intention to participate in this study will be confirmed by obtaining a consent form. The consent form will be scanned and saved in an electronic medical record.

⑧ Handling of personal information

Personal information handled (select from below)

□Use personal information that can uniquely identify a specific individual

□Using personal identification codes such as DNA base sequences and digitized biometric data

■Using personal information that requires consideration, such as medical history and medical examination results
□Create anonymously processed information/de-identified processed information (creation method is attached)
□Others ( )

Anonymization procedure (select from below)
□Do not handle information that requires anonymization.
□Anonymize without creating a correspondence table so that individuals cannot be identified (unlinkable anonymization).
■Create a correspondence table and anonymize it so that individuals cannot be immediately identified (linkable anonymization).
We will register with the clinical research support system provided by the Shiga University Hospital Electronic Medical Record and assign a registration number.
We will link the correspondence table with the electronic medical record and use the list of registered patients in the clinical research support system as data on the correspondence table. The correspondence table will be managed by Takashi Murakami, who is the research director.
□If anonymization is not implemented (below, be sure to state)
State the reasons for not anonymizing:

Regarding safety management for personal information (select from below)
□We do not handle personal information.
■We handle personal information
How to safely manage personal information: Information such as medical history with a registration number is password-protected in an Excel file, and a secure security system is set up in the Department of Obstetrics and Gynecology under the control of Daisuke Katsura who is a co-researcher.
How to manage the allocation code table: Research collaborators will keep it in a locked place in the department of obstetrics and gynecology.

⑨ Comprehensive evaluation of the burden on the research subjects, expected risks and benefits, and measures to minimize the burden and risk

Both two-layer continuous and two-layer interrupted sutures are methods currently used in clinical practice; therefore, there is no additional risk no matter which suturing method is selected.

In addition, sonohysterography, which evaluates the size of the CSD, is a non-invasive test that uses transvaginal ultrasound; thus, there is no additional risk. However, examinations are usually not performed at 6-8 months after childbirth. Therefore, we will pay 2,000 yen to those who come to the hospital as compensation. On the other hand, we believe that it is a benefit for the research subjects who participate in this study that they can receive a free gynecological examination from 6 to 8 months after delivery.

⑩ Methods for storing and disposing of samples and information (including materials related to information used in research)

Regarding handling of materials (information) (select from below)

■As a general rule, materials (documents, numerical data, images, etc.) will be retained for 10 years after the end of the research.

How to dispose the information after the storage period: The research director will ensure that the data stored at the Shiga University of Medical Science Hospital and the Department of Obstetrics and Gynecology will be deleted 10 years after the completion of the research.

□Other than the above (must be listed below)

Valid reason for not storing for 10 years:

Regarding sample handling (select from below)

■This research does not handle samples.

□Collect samples and use them for research (please select below and make sure to include specific methods of storage and disposal)

□Saving samples even after the research period ends

The reason:

Storage method:

□Do not store samples after the research period ends

The reason:

Sample disposal method (select from below)

□Dispose in a sealed container in an anonymous state

□Incineration in an anonymous state

□Others

⑪ Contents and methods of reporting to the head of the research institution (select from below)

■Regular reports should be made at least once a year in the prescribed format.

□Periodically report using a method other than the above (must be described below)

Specific method:

■When canceled or terminated, promptly report the cancellation or termination using the scheduled format.

□Completion report must be made using a method other than the above (must be described below)

Specific method:

⑫ Research funding source, etc./conflict of interest (select from the following and describe the specific funding source)

□Internal budget ( )
□Joint research expenses ( )
□Commissioned research expenses ( )
□Donation
■Public research funds from ministries, etc. (Grants-in-Aid for Scientific Research (KAKENHI, 20K09616)
□Research grants from companies, organizations, etc.
□Other (specifically:)

Conflict of interest (select from below)
■No conflict of interest
□Conflict of interest
(Conflict of interest management plan:)

⑬ Method of disclosing information regarding research (select from the following and list the specific publication destination)
□Do not publish
■Publish
■University Hospital Medical Information Network Research (UMIN) Center Clinical Trial Registration System
□Japan Pharmaceutical Information Center iyaku Search (drug database)
□Japan Medical Association Clinical Trial Promotion Center Clinical Trial Registration System (JMA CCT)
□National Institute of Health and Medical Sciences homepage
■Academic conference presentation
■Submit to paper
□Other ( )

⑭ Response to consultation (required below)
■Inquiries regarding general research (person in charge, affiliation, contact information, contact method)
Shunichiro Tsuji, Department of Maternal and Child Medicine, Shiga University of Medical Science Hospital / [Daytime] Phone: 077-548-xxxx (internal) Line xxxx); [Holidays/Nighttime] FAX" 077-548-xxxx; Email: xxxx@belle.shiga-med.ac.jp
■Inquiries regarding privacy policy (person in charge, affiliation, contact information, contact method)
Shunichiro Tsuji, Department of Maternal and Child Medicine, Shiga University of Medical Science Hospital / [Daytime] Phone: 077-548-xxxx (internal, Line 2267);
[Holidays/Nighttime] FAX" 077-548-xxxx; Email: xxxx@belle.shiga-med.ac.jp

⑮ Existence and content of compensation (select from below)
□No reward

■Remuneration available (must be listed below)

Content: Participants who come to the hospital 6 to 8 months after delivery will be given a Quo Card worth 2,000 yen as a reward. Regarding the handling of Quo Cards, a co-researcher will use their own funds to purchase one block of Quo Cards (for 20 individuals). Receive acceptance inspection will occur at the acceptance inspection center. When a Quo Card is given to a subject, the subject will be asked to sign the receipt. Yamamoto, a research collaborator and medical office secretary, will manage the receipts and management forms in a locked place (secretary's office) along with the Quo Card. When one block is finished, we will submit a request for advance payment to the contract section of our hospital's accounting department. We will repeat this action for all 11 blocks.

⑯ Measures to be taken when serious adverse events occur

■Not applicable

□Applicable

⑰ Existence and content of compensation for health damage caused by the research concerned

■None

□Yes

In case of change in research plan (select from below)

■ Obtain approval from the head of the research institution after review by the ethics review committee.

□Other than the above (must be listed below)

Describe specifically the reason and alternative method:

⑱Issues related to the provision of medical care to research subjects after conducting research

■Not applicable

□Applicable

⑲ Presence or absence of incidental findings and response (select from the following, and if applicable, describe the disclosure policy in detail)

□Not applicable

■Applicable (select from below)

■It is our policy to disclose incidental findings (must be described below)

The reason: There is a possibility that an ovarian tumor or uterine fibroid may be discovered by chance during an ultrasound examination 6 to 8 months after delivery.

Method of disclosure: Oral explanation during medical examination

□It is our policy not to disclose incidental findings (must be described below)

The reason:

□Others

⑳ Part of the research will be outsourced (select from the options below, and if outsourced, enter details of the outsourcing company and method of supervision)

■Do not outsource

□Entrust (below, be sure to write)

Name of the outsourcing organization, name of outsourcing representative, and location:

Method of anonymization when transferring samples and information:

Supervision methods including safety management measures for outsourced companies:

㉑ Possibility of being used for future research or providing to other research institutions (select from below)

■There are no plans to use it for future research.

□Used for future research (including incidental research) (must be listed below)

General purpose and content of the research:

Provision of specimens and information to other organizations (including banks, etc.) (select from below)

■Do not provide

□Provide (must be described below)

Name of the provider institution/obtainer name:

Items of samples and information to be provided:

Time of provision:

Anonymization method:

Storage period for records related to provision: *Storage (3 years) is mandatory; however, if the records are to be stored with the recipient, this will be stated.

㉒Monitoring/audit

■Not applicable

□Applicable

Handling of intellectual property (select from below)

■The results, data, and intellectual property rights obtained from this research belong to our university.

□Other than the above (must be listed below)

Specifically:

References

1. Tsuji S, et al. Management of secondary infertility following cesarean section: Report from the Subcommittee of the Reproductive Endocrinology Committee of the Japan Society of Obstetrics and Gynecology. J Obstet Gynaecol Res. 2015 41(9):1305-12.
2. Tsuji S, et al. Impact of hysteroscopic surgery for isthmocele associated with cesarean scar syndrome. J Obstet Gynaecol Res. 2018 44(1):43-48.
3. Sumigama S, et al. Myometrial suturing method Perinatal Medicine (in Japanese) 2016 46. 9.
4. Miki Goto et al. Evaluation of uterine wound thinning due to different myometrial suturing methods during caesarean section. (in Japanese) Journal of the Japanese Society of Perinatal and Neonatal Medicine 2018 54(3):789-792

5. Hohlagschwandtner M, et al. Continuous vs interrupted sutures for single-layer closure of uterine incision at cesarean section. Arch Gynecol Obstet. 2003 268(1):26-8
6. Gurol-Urganci I, et al. Impact of Caesarean section on subsequent fertility: a systematic review and meta-analysis. Hum Reprod. 2013 29:1320-6.
7. Kremer TG, Ghiorzi IB, Dibi RP. Isthmocele: an overview of diagnosis and treatment. Rev Assoc Med Bras (1992). 2019 65(5):714-721.
8. Tekelioğlu M, et al. Incomplete healing of the uterine incision after elective second cesarean section. J Matern Fetal Neonatal Med. 2019 (30): 1-5.