INFORMATION ABOUT THE STUDY

Laparoscopic vs. vaginally placed cervical stitch (cerclage) to prevent very preterm birth – a pilot study of a randomized Nordic multicenter study (NORACT)

(Pilot study of the Nordic randomized trial on laparoscopic versus vaginal cerclage (NORACT))

Request to participate in the study

You are invited to participate in a study comparing the effectiveness of laparoscopic and vaginal cerclage to prevent very preterm birth (before week 32 of pregnancy). This information describes the study and your possible role in it.

Please read this information carefully. If you have any questions, please contact the research physician or other research staff (contact details can be found at the end of the document).

If you decide to participate in the study, you will be asked to sign a separate consent. The regional medical research ethics committee at HUS has approved the study.

Voluntary, suspension and withdrawal of consent

Participation in this study is voluntary. You may refuse to participate, cancel your participation or withdraw your consent at any time during the study without prejudice to your right to receive necessary care.

If you want to withdraw your consent, please contact the principal investigator of the study, Professor Oskari Heikinheimo(tel: 050-4271533).

If you withdraw your consent, the data and/or samples collected up to that point will be used as part of the research material.

What is being investigated and why

Preterm birth (before 37+0 weeks of pregnancy) and its prevention remain major challenges in obstetrics. It often necessitates neonatal intensive care and may lead to developmental delays and long-term health complications, impacting both the child's future and the well-being of the entire family. The incidence of preterm birth varies by country, ranging from 5% to 16%. In Finland, the rate was 5% in 2022, one of the lowest globally.

Several factors contribute to preterm birth, including infections of the reproductive organs, bleeding, uterine overdistension (e.g., in twin pregnancies), and cervical insufficiency. Cervical insufficiency occurs when the cervix shortens and dilates prematurely in the second or third trimester, increasing the risk of preterm birth. This condition can also result from previous surgical procedures, such as conization for cervical cell changes.

One treatment for cervical insufficiency is cerclage, a supportive stitch placed around the cervix before or during pregnancy to help prevent premature birth. The traditional vaginal cerclage has been used to varying degrees worldwide, but research on its effectiveness remains inconclusive. As a result, cerclage is rarely performed in Finland, with only 30–50 procedures annually.

In addition to vaginal cerclage, the procedure can also be performed abdominally via laparoscopic or open surgery, allowing placement higher up on the cervix. A randomized UK study (2020) found that among women at risk of preterm birth, only 8% (3/39) of those who received an abdominal cerclage (open surgery) gave birth before 32 weeks, compared to 33% (11/33) of those who received a vaginal cerclage**.**

This Nordic researcher-initiated multicenter study aims to compare the effectiveness of laparoscopic and vaginal cerclage in preventing very preterm birth. The study recruits women with a significantly increased risk of preterm birth and is coordinated by Aarhus University, Denmark**.** It is conducted across all Nordic countries (Denmark, Norway, Sweden, Iceland, and Finland) as well as the United Kingdom**.** In Finland, Helsinki, Oulu, and Turku University Hospitals are participating.

The study begins with an 18-month pilot study according to the study plan.

Background and purpose of the study

The aim of the NORACT study is to investigate the rate of very preterm births (before 32 weeks of pregnancy) differs between women who have received transvaginal cerclage or transabdominal. In addition, this pilot study will examine practical aspects of conducting the study as well as the criteria for patient inclusion.

We will also investigate any side effects of the procedure, the course of pregnancy after cerclage, as well as the health of the babies born.

We invite adults who are planning pregnancy or are early pregnant (maximum 10+0 weeks of pregnancy) and have an increased risk of premature birth and are considered to benefit from cerclage treatment to participate in the study.

This could, among others, be persons with a history of:

• Previous emergency caesarean section followed by a late miscarriage or very premature birth in pregnancy weeks 14+0 - 28+0 in the subsequent pregnancy.

• Previously planned or acute vaginal cerclage and yet late miscarriage or very premature birth in pregnancy weeks 14+0 - 28+0.

• Previous conization of the cervix and shortened cervix (15-20 mm measured by ultrasound) before pregnancy.

• One or more late miscarriages or very premature births at pregnancy weeks 16+0 - 28+0.

• Three or more late miscarriages or premature births at weeks 16+0 - 36+6.

A representative of the research group will assess whether you are suitable to participate in the study.

The study is being conducted in Finland at the university hospitals of Helsinki, Oulu and Turku.

How is the study conducted?

This study examines the effectiveness of laparoscopic and vaginal cerclage in preventing very preterm birth. If your physician assesses that you may benefit from cerclage and you have the risk factors described, you can choose to participate in the study.

You cannot participate in the study if you are a minor, have significant medical contraindications for laparoscopy, if you are more than 10+0 weeks pregnant, if you and the research staff do not have a common language, or if you do not sign the informed consent.

You will receive both written and oral information about the study. The study also has its own website (www.noract.dk). If the inclusion criteria are met, there are no contraindications and you want to participate in the study, you will be asked to sign the consent. Your treatment group (laparoscopic or vaginal cerclage) is determined by random allocation using a computer program. Both laparoscopic and vaginal cerclage are possible at all participating university hospitals in Finland. In this study the cerclage is only set by research physicians who have received special training in uniform technology for cerclage placement.

Participation in the study begins with the signing of the consent. Next, you will randomly be assigned either a vaginally or a laparoscopic abdominal inserted cervical cerclage. The time from the cerclage procedure to childbirth can vary significantly between the groups. The abdominal insertion is mainly done before pregnancy, while vaginal insertion is done during early pregnancy. Recruitment period for this pilot study is 18 months, but the total study time for patient follow-up is five years.

The study includes at least two visits to the research physician at the beginning of the study and after the insertion of the cerclage. Research staff can also contact you by phone. In addition, data on your health is monitored 28 days after any termination of pregnancy/delivery.

An abdominally inserted cerclage is a day surgery procedure performed under general anesthesia. A non-absorbable suture is placed around the upper part of the cervix and tied securely, while the cervix itself remains open to allow menstrual blood to leave the uterus normally.

If you are not pregnant at the time of cerclage insertion, you can try to conceive as usual once you have recovered from the procedure. However, the non-absorbable suture will remain permanently around the cervix, meaning that any future births must be delivered by caesarean section.

A vaginal cervical cerclage can be inserted as a day surgery procedure under either spinal or local anesthesia during early pregnancy, up to a maximum of 16+0 weeks. The suture is removed when labor begins or, at the latest, by 36 weeks of pregnancy. A vaginally inserted cerclage does not affect the mode of delivery.

All participants in the study are recommended to use vaginally administered progesterone (200 mg) from 16–18 weeks of pregnancy until 34+0 weeks to help prevent preterm birth. The suture or its placement does not increase the risk of other pregnancy complications or affect routine pregnancy monitoring. However, individual pregnancy history will be considered when planning antenatal care.

The primary aim of the study is to assess the incidence of very preterm birth (before 32+0 weeks). Additionally, the study will evaluate the general well-being of the pregnant women, any complications related to the cerclage procedure, pregnancy, and childbirth. Factors associated with miscarriage and newborn health will also be examined.

We collect your data from the hospital’s patient record files when the cerclage procedure is performed. Pregnancy-related data is collected from the hospital's electronic systems. The information is stored in the RedCap system, which is widely used in medical research, and is administered centrally by Aarhus university in Denmark.

Completion of the study

The first pilot phase of this study lasts for 18 months. After the pilot phase, some changes may be made to The NORACT study, for example change of the inclusion criteria. If the pilot study shows that the study is not feasible to continue, the study may be discontinued after the pilot phase. A decision on this will be made by the international stury steering group if necessary.

Despite the randomization, this study is open-label, which means you will know which study group you belong to. All participants in the study will be informed of the results of the study when it is finished.

From the start of the study to the publication of the results, it is estimated to take a total of ten years.

The research team and its funding

This international researcher-initiated multicentre study is coordinated by Aarhus University in Denmark. The study is funded by the Danish Novo Nordic Foundation.

The local principal investigator of this study at the HUS Women's Hospital is Professor Oskari Heikinheimo, who is responsible for the safety of study participants. The leader of the study is

Professor Niels Uldbjerg from Aarhus University, and international partners include hospitals in the Nordic region and the UK.

Study costs and financial reports

The study is funded by the Novo Nordic Foundation. Novo Nordic Foundation pays the research centre a reimbursement for the conduct of the study and the costs involved. Researchers and other staff do not receive any separate compensation for conducting the study.

Potential benefits of the study

In this study, patients with cervical insufficiency who are at increased risk of preterm birth are recruited. Insertion of a cervical cerclage is expected to reduce the risk of preterm delivery in the patients participating in the study.

Potential risks, drawbacks, and discomfort of the study

The most common/expected drawbacks of this study are related to the insertion of the cervical cerclage. Abdominal insertion of the cerclage is performed as a day surgery procedure under general anaesthesia, and the risks to healthy individuals are small. The incisions in the abdominal wall required for the use of laparoscopic instruments may be bruised and sore a few days after the laparoscopy. Usually, sick leave of 2-3 days is recommended after laparoscopic surgery.

If you are randomised to a laparoscopic cerclage but do not become pregnant after procedure, the procedure has been in vain. As the cerclage is made of non-absorbable material and cannot be removed during pregnancy, any deliveries must be done by caesarean section. Caesarean section is a common method of delivery; In 2022, 19.6% of all babies in Finland were born by caesarean section.

Like the abdominal insertion, the insertion of a vaginal cerclage involves day surgery, discomfort and a slight risk of bleeding from the procedure area.

Other potential drawbacks will be explained by the research physician, whose names are listed below.

There may also be unexpected disadvantages to participating in the study. These may be related to the procedure performed during the study. If unknown side effects are discovered by chance in the study results, the doctor conducting the study will assess their significance and refer you to appropriate follow-up care.

During the study, you should consider the following aspects that affect your daily life: the study recruits patients with an increased risk of premature birth. Therefore, follow the general pregnancy-related advice and instructions given to you by the healthcare professional. All patients in the study are recommended to use vaginal progesterone (200 mg daily). This medicine is commonly used to prevent preterm birth, also in Finland.

Insurance and compensation to participants

HUS has insured the participants in the study in accordance with the Patient Insurance Act. If you suffer a personal injury as a result of the procedure performed due to the study, you may apply for compensation. Compensation for personal injury can be applied for from HUS patient insurance. More information about the insurance and how to apply for reimbursement is provided by the local principal investigator at HUS Women's Hospital, Professor Oskari Heikinheimo.

Compensation for inconvenience and costs to participants

There is no financial compensation for participating in this study. The visits included in the study are free of charge for you. Travel expenses related to participation in the study will be reimbursed according to actual costs based on receipts.

Handling of personal data and confidentiality

This study complies with Finnish legislation on research and data protection. Researchers and other research staff is committed to follow the responsible conduct of research and ethical guidelines. A more detailed description of the legal basis for the study can be found at the end of this information.

Your personal data is processed for scientific research purposes. The information and results collected about you will be treated as confidential in accordance with legal requirements. All parties and persons who handle your data are bound by a duty of confidentiality. More information about the treatment of your personal data and your rights can be found at the end of this information.

Further information and contact persons

If you have any questions about the study, you can contact the research physician or other staff at the department. You can discuss any side effects, suspected symptoms and other issues that concern you during the course of the study.

The local principal investigator is:

Professor Oskari Heikinheimo
Women's Hospital (Haartmaninkatu 2) P.O. Box 140, 00029-HUS
Phone: 050-4271533

PROCESSING OF PERSONAL DATA AND STUDY PARTICIPATION RIGHTS

Controllers
The data controller of the study is HUS, which is responsible for the processing of personal data that takes place in connection with the study.

The research database only stores the personal data that is necessary for the purpose of the study. Collection of data are based on a research plan.

Processing criteria for personal data
In a medical study, your personal data may be processed on the basis of Article 6.1 e and Article 9.2 I in GDPR, when the processing is necessary to protect public health:
1) for the purpose of investigating or assessing the purpose of use, performance, properties, consequences and efficacy or to ensure its quality, efficacy or safety;
or
2) to ensure the safety of the study participants or other people.

In a medical study, your personal data may be processed on the basis of Article 6.1 e and Article 9.2 I in GDPR, when the processing is necessary to protect public health:
1) to fulfil the obligation related to the notification of complications or adverse reactions or the obligation to report other things related to security;
2) to fulfil other reporting or investigation obligations in connection with the study or to fulfil the obligation to store information or documents; or
3) to fulfil the obligation to provide information to the authorities.
The processing of your personal data is subject to section 6, subsection 2. of the Data Protection Act.

Handling of personal data

Those who handle your personal data

Your personal data will only be processed by persons who have been appointed to the study group and in whose data processing is included.

The identity of the participants is only known to the study staff, who are bound by a duty of confidentiality. All data that we collect about you is processed in coded form after collection and therefore your data cannot be identified from the study's results, investigations or publications. Encoding data means that your name and personal identity code will be removed and replaced with an individual code. From now on, the data can no longer be identified without a code key and its storage is the responsibility of the person who is responsible for the study. The study's client, the study group member or an external party don't have access to the code key. We analyze the study results in coded form.

Where is the information collected from

We collect your personal data for the study from the patient data of the HUS Women's Hospital. The data we collect during the study is not stored in your patient record.

Disclosure of personal data

In this study, your personal data or samples are not disclosed to other parties and they are used for a scientific research purpose.

Storage of personal data

The storage period of your personal data is regulated by legislation and good clinical research practice. Oskari Heikinheimo is responsible for your personal data at the HUS Women's Hospital. Your details are stored in a secure environment for x years and after that they are destroyed in an authorized manner.

Rights of study participation

You have the right to receive information about the processing of your personal data. You also have the right to request to review your data and ask for them to be corrected or supplemented, for example if you discover errors or omissions in them or if they are inaccurate. You also have the right to object to the use of your personal data. However, in the context of a scientific study, these rights may be restricted. The law may require controller to store your study data for a certain period of time, regardless of the data subject's rights. The law allows derogations from the rights of the data subject when it is necessary to ensure the scientific study results and the safety of the participants.
You can ask us at any time if we are processing your personal data and request a justification for management. You can also ask where we get your data from and where your samples and data has been submitted. You have the right to receive the information free of charge and within a reasonable period of time (within one month upon request). If your data request is very extensive or the reason is very complicated, the time allowed can be extended by a maximum of two (2) months. You will receive information about the extended time and the reason.
For questions about data protection, we recommend that you contact the person responsible for the study.

Contact details of the person responsible for the study

Oskari Heikinheimo, professor
Women's Hospital/University of Helsinki and HUS
tel 050 4271533

HUS's Data Protection Officer is
Petri Hämäläinen, Development Manager, Data Protection Officer
HUS Helsinki University Hospital, Administration and Law
eutietosuoja@hus.fi
Postal address: P.O. Box 440, 00029 HUS

You have the right to lodge an appeal separately with the control authority in accordance with the place where you live or work, if you believe that there has been a violation of the EU General Data Protection Regulation in the processing of their personal data (EU) 2016/679. In Finland, the supervisory authority is the Data Protection Ombudsman.

Office of the Data Protection Ombudsman
Lintulahdenkuja 4, 00530 Helsinki
PB 800, 00531 Helsingfors
Switchboard: 029 566 6700
Email (Registry): tietosuoja@om.fi

CONSENT OF THE RESEARCH SUBJECT TO PARTICIPATE IN THE RESEARCH

Laparoscopic vs. vaginally placed cervical stitch (cerclage) to prevent preterm birth – a pilot study of a randomized Nordic multicentre study (NORACT)

I, _____, have been asked to participate in the above-mentioned scientific study, which aims to investigate the effect of laparoscopic and vaginally placed cervical stitch to prevent preterm birth (before week 32 of pregnancy).

I have read and understood the information that I have received about the study and give my consent to participate according to this information. I have received sufficient information about the study and the data collection, processing and disclosure that takes place in connection with it. The content of the information has also been explained for me verbally and I have received satisfactory answers to all my questions about the study. Information was given by:

_____ [name of person or organisation]

_____ [date].

I have had enough time to consider my participation in the study. I have received sufficient information about purpose and implementation of the study, its benefits and risks, and my rights. I haven't been pressured or enticed to participate in the study.

I know that my data is treated confidentially and will not be disclosed to third parties. Research data collected and analysed centrally at Aarhus University in Denmark.

I am aware that my personal data may be processed in connection with inspections of national and international authorities, regular quality control of a person who does not belong to the research team (research monitor) and/or quality assurance activities carried out by a representative of the client.

I understand that participation in this study is voluntary. I am aware that I have the right to refuse participate in the study. I can also, later, if I wish, discontinue the study or withdraw my consent at any time without giving any reason, and this does not affect my treatment or the care I receive.

I can cancel my participation at any stage of the study without giving any reason.
I also have the right to withdraw my consent at any time before the end of the study. I am aware that if I discontinue the study or withdraw my consent, the data and samples collected up until my withdrawing will be used as part of the study. I know that no compensation is paid for participation in the study. However, hospital visits related to the study are free of charge for me. Also travel in public transport related to these visits will be reimbursed.

With my signature, I confirm my participation in this study and voluntarily agree to be research subject.

_____ _____
Signature of the participant Date

_____ _____
Name in capital letters Date of birth / personal identification number

_____
Address of the participant

_____ _____
Signature of the research physician Date

_____
Name in capital letters

The original signed document remains in the records of the research physician and a copy of the signed consent is given to the research subject.