Cover page - protocol

Title

Obstetric outcome in pregnancies treated with laparoscopic cerclage: an observational study in a Danish cohort

Roles and Responsibility

Study group

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Conflicts of interest

The members of the study group have no conflicts of interest to declare. The study sponsor has no ultimate authority over any aspects of the study design, conduct, or reporting.

Trial registration

The study is registered at clinicaltrials.gov using the administrative authorities of Aarhus University (UAarhus). NCT not yet assigned.

Funding

Funding for the study is provided as a part of a larger grant by the Novo Nordic Foundation.

Introduction

Annually, approximately 15 million babies worldwide are born preterm [1, 2]. Preterm birth is a leading cause of neonatal mortality and morbidity [3]. Cervical insufficiency is one factor implicated in the complex mechanisms involved in spontaneous preterm birth [4]. Cervical insufficiency is characterized by acute and painless dilatation of cervix in absence of uterine contractions resulting in the inability of cervix to retain a pregnancy to term. Insertion of a cervical cerclage suture can be used to treat cervical insufficiency. A cervical cerclage is a mechanical support to the cervix, where a surgical band or string is applied around the cervix to prevent preterm opening of the cervix, and thereby preventing preterm birth. It can be applied either vaginally or trans-abdominally. The latter can be applied either by laparoscopic or open access surgery. Growing evidence support that both open access and laparoscopic cerclage procedures are safe and effective [5]. Still, many aspects of the abdominal cerclage remains uncertain. Recently, a study by Ades et al. was published on the obstetric outcome of subsequent pregnancies in women from an Australian single-center cohort who had a laparoscopic cerclage left in situ [6]. They reported on 22 women who became pregnant a second or third time after a laparoscopic cerclage. The authors encouraged other groups to report their obestric outcomes on subsequent pregnancies after laparoscopic cerclage in order to gather a lager data material to describe this gap in evidence. Therefore, we plan to study the obstetric outcome from the first and subsequent pregnancies after laparoscopic cerclage in a Danish cohort from Aarhus University Hospital in a 10 years' period.

Objective

In a Danish cohort, to investigate the obstetric outcome after laparoscopic cerclage placement in the first and subsequent pregnancies.

Material and Methods

Study type

Observational study based on medical chart review.

Eligibility criteria

Women who underwent laparoscopic cerclage at Aarhus University Hospital, Denmark between May 2011 and May 2021. In this group no further exclusion criteria are defined.

The laparoscopic cerclage procedure

The surgical method of the laparoscopic cerclage procedure at Aarhus University Hospital is previous described in a paper by Riiskjaer et al [7]. The primary surgeon has been one of three laparoscopic surgeons with a long experience in performance of the procedure.

Variables and outcomes

Below is provided an overview of the included variables collected from the in-hospital electronical medical chart.

Demographics and obstetric history

Maternal characteristics at time of laparoscopic cerclage:

- Maternal age (years)
- Parity (reflect the number of births ≥22 gestational weeks)
- Body mass index (BMI) (kg/m2)
- Smoking (yes/no)
- Previous caesarean delivery (yes/no)
    - If yes; emergency/laboring caesarean delivery (yes/no)
    - If emergency/labouring; cervical dilatation prior to the caesarean section (cm)
    - If emergency/labouring; indication (labour dystocia/fetal distress/maternal request/non-cephalic presentation/extensive vaginal bleeding/maternal medical complication/other)
- Previous cervical conisation (0/1/2 or 3)
- Previous surgery of the uterine wall (yes/no)
    - If yes; myomectomy/septum resection/other
- Timing of laparoscopic cerclage (before conception/in early pregnancy)
    - If in early pregnancy; gestational age at cerclage placement
- Indication for the laparoscopic cerclage placement as stated by the clinician;
    - History of emergency/laboring cesarean delivery followed by a spontaneous singleton late miscarriage and/or preterm birth from 16+0 to 28+0 weeks
    - History with a prior elective vaginal cerclage placement but nonetheless a spontaneous late miscarriage and/or preterm birth between 14+0 and 28+0 weeks
    - History of a previous ultrasound-indicated emergency cerclage with preterm birth between 14+0 and 28+0 weeks
    - Any conization and a short pre-pregnancy cervix
    - History of two or more deliveries GA 16+0 to 28+0 weeks and a clinical diagnosis of cervical insufficiency
    - History of three or more deliveries GA 16+0 to 36+6 weeks
    - Others (free text)

Characteristics of the surgical procedure

- Additional procedures performed during surgery (e.g. hysteroscopy, removal of endometriosis)
- Performed in Day Surgery (yes/no)
- Date of surgery (dd-mm-yyyy)
- Early complications from the laparoscopic cerclage (follow-up time is 30 days from the procedure):
    - Conversion to laparotomy during surgery (yes/no)
    - Haemorrhage > 500 ml (yes/no)
    - Postoperative infection treated at hospital (yes/no)

    - Damage to internal organs (yes/no)
    - Need for re-operation (yes/no)
    - Admission to Intensive Care Unit (yes/no)
    - Thromboembolic events (defined as deep vein thrombosis, pulmonary embolism or stroke) (yes/no)
    - Maternal cardiopulmonary arrest (yes/no)
    - Maternal death (yes/no)
- Late complications from the laparoscopic cerclage (follow-up in the entire period of data collection subsequent to the laparoscopic cerclage):
    - Erosion into the vagina treated in hospital (yes/no)
    - Pain complaints from the stiches leading to intervention in pregnancy (yes/no)
    - Other complications from the cerclage leading to intervention in hospital (free text)

For every known/confirmed pregnancy subsequent to the laparoscopic cerclage* (follow-up in the entire period of data collection subsequent to the laparoscopic cerclage)*:*
**defined as a pregnancy confirmed by urine and/or serum hcg and/or ultrasound AND described in the medical record*

- Pregnancy;
    - Maternal age (years)
    - Parity (numerical)
    - Conceivement (Spontaneous/Assisted Reproductive Technologies)
    - Certain gestational age, defined as gestational age determined by Crown-Rump-Length (yes/no)
    - Gestation (singleton/multiple)
    - Treatment with vaginal progesterone (Vaginal/rectal/intramuscular)
- At miscarriage or delivery;
        - Gestational age (weeks and days)
        - If gestational age < 22 weeks and 0 days of gestation;
            - Need for operative surgery in connection with miscarriage (yes/no)
        - If gestational age < 34 weeks and 0 days;
            - Administration of lung maturation(yes/no)
            - Administration of tocolytics <34 weeks of gestation (yes/no)
        - If gestational age ≥ 22 weeks and 0 days;
            - Chorioamnoinitis (defined as antibiotic treatment or intervention leading to delivery)
            - Indication for delivery (spontaneous labor contractions/PPROM/PROM/obstetric indication)

Outcomes

The outcomes of this study apply to a set of core outcomes for evaluation of interventions to prevent preterm birth leaving out the late neurodevelopmental morbidity [8].

Maternal:

- Pregnancy and delivery (follow-up in the entire period of data collection subsequent to the laparoscopic cerclage):
    - Time from the laparoscopic cerclage to first known/confirmed pregnancy (counting from the first day in pregnancy based on results from ultrasonography if available, otherwise on the date of her last menstrual period)
    - Pregnancies subsequent to the laparoscopic cerclage (numerical)
    - Miscarriages
        - Early miscarriages (<16 weeks and 0 days)
        - Late miscarriages (<22 weeks and 0 days)
    - Deliveries <28 weeks and 0 days of an infant living at time of discharge from hospital
    - Deliveries <32 weeks and 0 days of an infant living at time of discharge from hospital
    - Deliveries <34 weeks and 0 days of an infant living at time of discharge from hospital
    - Deliveries <37 weeks and 0 days of an infant living at time of discharge from hospital
    - Uterine rupture (yes/no)

Neonatal:

The following neonatal outcomes are reported for neonates delivered with a gestational age ≥ 20 weeks and 0 days.

- Gestational age (weeks and days)
- Birthweight (g) (follow-up at delivery)
- Neonatal survival (defined as survival at time of discharge from hospital)
- Survival without major neonatal morbidity (time point: at discharge from hospital)
    - Necrotising enterocolitis (NEC)
    - Bronchopulmonary Dysplasia (BPD) (defined as respiratory/oxygen support at postmenstrual age (PMA) 36 weeks)
    - Intraventricular haemorrhage (IVH) Grade III and IV
    - Hydrocephalus with ventriculoperitoneal (VP) shunt
    - Periventricular leukomalacia
    - Retinopathy of prematurity (ROP)

Statistical analysis plan

Statistics will be descriptive and data will be presented with counts and percentages for categorical variables, mean and standard deviation for continuous Gaussian distributed variables, and median and interquartile range for continuous non-Gaussian variables. Proportions will be presented with a 95% confidence interval for the dichotomous outcomes *'neonatal survival'* and *'neonatal survival without major neonatal morbidity'*.

Subgroup analyses of the primary outcome will be undertaken for the following subgroups:

- Prior versus no prior cesarean delivery at time of laparoscopic abdominal cerclage

- Prior versus no prior conisation at time of laparoscopic abdominal cerclage
- Placement of laparoscopic abdominal cerclage before or during early pregnancy

STATA will be used for data management and analyses.

Data collection

Prior to data collection the relevant authority (Central Denmark Region) will be applied for permission to access the relevant data source. All data is already available and will be extracted from the patients' electronic data records. Women will be identified on the ICD-10 Procedure Code KLDD10B. The follow-up period extends to May 2022 to allow at least one year of follow-up for all procedures.
The primary investigator performs a pilot collection of data from the electronic data records of ten random women in the data set giving birth at Aarhus University Hospital. The pilot collection aims to test the accessibility of the variables, the use of the eCRFs, and the time spent. Following the pilot of data collection, the study group meet to adjust the variables if needed.

Data management

All data will be entered in to an eCRF designed for this study using the REDCap database Study. Data will be collected and managed using REDCap electronic data capture tools hosted at Aarhus University [9]. REDCap is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.
Data will be handled according to all relevant Danish laws including the General Data Protection Regulation ("Databeskyttelsesforordningen") and the Data Protection Act ("Databeskyttelsesloven"). The project is registered with the Central Denmark Region's internal list of research projects.

Publication plan

Results from this study will be published in a peer-reviewed journal.
The principal investigator will draft the paper as first author, and the daily supervisor will be last corresponding author. Additional authorship will follow standard authorship guidelines and will include all members of study group. Authorships of additional publications will depend on the nature of involvement.

Confidentiality

The investigators will preserve the confidentiality of the participants in the study according to the Danish national legislation (The General Data Protection Regulation (GDPR) and the Data Protection Act).

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