CONFIDENTIAL

Study plan (2nd version from 26.03.2019)

Register study for the recording of deliveries in patients with deep endometriosis

Short name:
Birth register for deep endometriosis

Study management
(in alphabetical order)**:**
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* For further study centers see subchapter "Study centers".

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INTRODUCTION / BACKGROUND:

Endometriosis is a benign disease defined by the presence of endometrial tissue outside the uterine cavity [1]. Although the exact prevalence is unknown due to the lack of large cohort studies [2], it is estimated that about 10 percent of all women suffer from this disease [3]. The endometriosis lesions mainly lead to dysmenorrhea, chronic pain, dyspareunia and infertility [3]. The exact pathogenesis of the disease is still unknown [4], but most theories assume retrograde menstruation and changes in immunological processes that lead to the displacement of endometrial tissue and growth of these lesions [1].

It is known that fertility is impaired in women suffering from endometriosis [5]. However, endometriosis is also associated with an increased rate of pregnancy complications [2]. These include a higher risk of ectopic pregnancy, pre-eclampsia, premature birth, or peripartum haemorrhage [2]. For example, there have also been reports of severe intraperitoneal bleeding in endometriosis patients in whom pregnancy has led to a decidualisation of endometriosis lesions [2,6].

So far, only a few studies have dealt with the influence of deep endometriosis on delivery. For this reason, the initiative to create a birth register for deep endometriosis has emerged. The main focus is to gather information about birth injuries, delivery mode and fetal outcome in patients with deep endometriosis. The results of this survey should help to better advise affected women during pregnancy on the mode of delivery and individual risks.

STUDY OBJECTIVE:

The general aim is the documentation of peripartal parameters by women with deep endometriosis over a longer period of time (not limited to date). The main focus is on obtaining information on birth injuries, the delivery mode and the fetal outcome.

The status of the study is purely descriptive / exploratory.

STUDY DESIGN:

It is a prospective, non-interventional multi-centre database project (register, register study) with 1 cohort:

Women with deep endometriosis (operated or non-operated) and childbirth

The nature of a register study allows that the number of inclusions, the number of participating centres and the study duration are not defined a priori.

SELECTION OF PARTICIPANTS:

Inclusion criteria:

- Deep endometriosis (operated or non-operated)
- Delivery
- Written consent to participate in the study after sufficient prior written and oral information (Informed Consent Form = accompanying document)
- Age ≥ 18 years

Exclusion criteria:

- Multiple pregnancy
- Position anomalies (e.g. breech position)

METHODS:

Study centers:

In addition to Study Centre 1 (Department of Gynecology, Obstetrics and Gyn. Endocrinology, Kepler University Hospital, Linz, Austria), further study centres are planned in an a priori not limited number.

Gynecological clinics and departments are invited to participate via an information page on the Internet (register homepage). If you are interested in participating in the study, you can contact the study team via an online form on the register homepage. The register homepage also contains the study plan and the Informed Consent Form approved by the local ethics committee for study centre 1.

If a clinic or department is interested in participating, it must ensure that all national and local formal and legal requirements are met. This may include, for example, a requirement by the local hospital's governing body to obtain a local ethics vote and/or the modification of the information and consent procedure in accordance with local practice. The responsibility for meeting all local and national requirements (including compliance with applicable data protection and data ownership regulations) lies solely with the interested clinic or department.

If all requirements are met, the participating clinic or department will receive a specific access link and a password to a protected area on the register homepage (with access-secure data transfer) in order to be able to enter the study data in electronic case report forms. The study management reserves the right in exceptional cases to reject requests for participation with appropriate justification.

Data entry and administration:

The data of the participants is entered into a secure, web-based data entry system. The data entry mask is accessible on the register homepage via the centre-specific access link, which is additionally secured by a password. Each study centre can only view its own data.

The requested data is structured in such a way that it is not possible for third parties (outside the study centre) to identify study participants. The study participants are pseudonymised (allocation of a personal code).

Each woman can also participate in the study several times (in the case of multiple births), but the same personal code is always applied.

The administration and maintenance of the register homepage (including the provision of amendments) is carried out by the Study Management. They are also responsible for data security and compliance with local data protection regulations in relation to the received data. The data entered in the online register is hosted in a computer centre in Linz (Austria, European Union). The contact details of the study team are available on the register homepage.

Recruitment of study participants:

How potential study participants are contacted and the process of Informed Consent (written consent to participate in the study after sufficient prior written and oral information) depends on the practices, possibilities and regulations in the area of the respective study centre.

In study centre 1, a candidate for the study is identified in the run-up to an upcoming delivery. The woman is asked for her consent to participate in the study before the delivery (unless there are particularly stressful circumstances, then a certain period after delivery).

Definition of deep endometriosis:

Deep endometriosis (DE) has a special place in the clinical picture of endometriosis. It is defined as solid endometriosis lesions with an infiltration depth of ≥ 5mm and is associated with a significantly higher morbidity than the more frequent superficial endometriosis of the peritoneum [7].

COLLECTED DATA:

See data entry matrix in the appendix of the study plan

STUDY PARAMETERS:

Intervals are calculated from provided time parameters (e.g. maternal age at delivery time). Apart from that, the study parameters are identical to the collected data (see data entry matrix in the appendix of the study plan).

BIOSTATISTICAL PLANNING AND ANALYSIS:

General:

As permitted for a register study, the timing and details of various (interim) evaluations are determined as required. This need is assessed and decided by the study management.

The nature of a register study also allows the number of inclusions to be a priori undefined. Estimates for Study Centre 1 assume 5-10 inclusions per year.

Implausible Values and Missing Values:

Implausible values (classification by the study management) are converted into missing values. Missing values are not replaced.

Presentation of results:

Categorical variables will be presented using counts and percentages.

Variables measured on ordinal scales will be presented using counts and percentages (where appropriate) or minimum, 25%-percentile, median, 75%-percentile and maximum and number of patients (where appropriate).

Continuous variables will be presented using minimum, 25%-percentile, arithmetic mean, median, 75%-percentile, maximum, standard deviation and number of patients.

If necessary, graps (box plots and bar charts) can be created.

Statistical analysis:

Estimate the true effect size:
Two-sided 95% confidence intervals (95%CI) are calculated.

Post-hoc analysis:
If, after completion of the planned (interim) evaluations, constellations arise which make one or more post-hoc analyses (subgroup comparisons, correlation or regression analyses, etc.) appear to be useful, such analyses are possible. Among other things, correlations between specific variables and the existence of factors with an impact on outcome variables can be investigated with correlation and regression analyses, and subgroups (e.g. formed according to outcome, or according to regions or centres to check regional/centre effects) can be compared by common tests for independent samples. Intra-individual comparisons (between first and second births, etc.) are also an option if sufficient case numbers are available.

Type I error adjustment:
No adjustment for the type I error will be made. Therefore the results of inferential statistics will be descriptive only.

QUALITY MANAGEMENT:

Continuous plausibility and completeness checks are performed as part of data management.

FORMAL STATUS AND LEGAL ASPECTS:

The study will be conducted in accordance with the Helsinki Declaration (Fortaleza 2013). The nationally applicable data protection regulations as well as all nationally and/or locally applicable legal regulations are observed.

From a formal point of view, this register is an academic prospective non-interventional study.

Only women who have documented their written consent to participate after written and oral information are included in the study.

The study will only be started in the respective study centre after a positive vote of the competent ethics committee (or, if applicable, after clarification that no local vote is required or that one or more existing votes of other ethics committees are sufficient). The vote of the ethics committee responsible for the study centre of the study lead (study centre 1) is always obtained.

The data of the study participants are processed and evaluated exclusively in pseudonymised form (keeping and storing a study participant identification list in

each study centre). The data from the individual study centres are pseudonymised when the data are entered on the register homepage.

Before the documentation phase begins (before the first woman is included in the study), the study is reported in a publicly accessible study register (study registration).

PUBLICATION OF THE RESULTS:

The study design and the results of each (interim) evaluation of the database associated with relevant findings are published under the responsibility of the study team and the biometrician (with the involvement of all other parties involved in the conduct of the study as co-authors or in an addendum).

STUDY PLAN CHANGES:

All changes to the study plan are only valid if all signatories of the study plan agree to them. The changes are then to be documented by amendments (signed analogously to the primary study plan). These are published on the register homepage. The responsibility for referrals to local ethics committees or other local studyplan owners lies with the respective center responsible person.

SIGNATURES:

We have read this study plan for the “Birth Register for Deep Endometriosis” dated 26.03.2020 and confirm that it contains all the information necessary to conduct this register study. We intend to conduct the register study according to this concept.

Study management:
- Dr. Christina Allerstorfer
- Dr. Simon-Hermann Enzelsberger
- Prof. Dr. Peter Oppelt, MBA

Biometrician:
Dr. Wolfgang Schimetta

Regarding signatures → see German Study Plan.

ANNEX:

Literature

Data entry matrix

ACCOMPANYING DOCUMENT:

Informed Consent Form (Study center 1)

LITERATURE:

1. Kortelahti M, Anttila MA, Hippelainen MI, Heinonen ST. Obstetric outcome in women with endometriosis--a matched case-control study. *Gynecologic and obstetric investigation* 2003;56(4):207-12.
2. Brosens I, Brosens JJ, Fusi L, Al-Sabbagh M, Kuroda K, Benagiano G. Risks of adverse pregnancy outcome in endometriosis. *Fertility and sterility* 2012;98(1):30-5.
3. Bulun SE. Endometriosis. *The New England journal of medicine* 2009;360(3):268-79.
4. Haas D, Wurm P, Schimetta W, Schabetsberger K, Shamiyeh A, Oppelt P, et al. Endometriosis patients in the postmenopausal period: pre- and postmenopausal factors influencing postmenopausal health. *Biomed Res Int* 2014;2014:746705.
5. Fadhlaoui A, Bouquet de la Joliniere J, Feki A. Endometriosis and infertility: how and when to treat? *Frontiers in surgery* 2014;1:24.
6. O'Leary SM. Ectopic decidualization causing massive postpartum intraperitoneal hemorrhage. *Obstetrics and gynecology* 2006;108(3 Pt 2):776-9.
7. Koninckx PR. Deep endometriosis: definition, diagnosis, and treatment. *Fertil Steril* 2012;98(3):564-71.

DATA ENTRY MATRIX:

REGISTRATION OF PATIENT:

- **Pseudonym - Working Title**
- **Date of birth of patient/mother (month/year)**
- **Delivery date (month/year)**
- **Hospital of delivery**

BASIC DATA / DEMOGRAPHY:

- **Gravidity (*number*)**
- **Parity (*number*)**
- **Miscarriages/Abortions *(number)***
- **Ectopic pregnancies *(number)***
- **Assisted reproductive technology (ART) – IVF/ICSI? (*yes/no*)**
    - If yes:
        - **Indication?**
            - *Male factor*
            - *Tubal factor*
            - *Endometriosis*
            - *Other*
        - Fresh or frozen embryo transfer? (Fresh / Frozen / Not known.)
- Ethnicity:
  Caucasian / Asian / African American / Hispanic / Other / Not known
- Body height (in cm): (number without decimal places)
- Body weight before pregnancy (in kg): (number without decimal places)
- Smoking status (*Smoker / Non-smoker*)

HISTORY OF ENDOMETRIOSIS:

- **Patient with history of deep endometriosis? *(yes/no)***
    - If yes: **Previous surgery for deep endometriosis? (*yes/no*)**
        - If yes: **Number of previous surgeries for deep endometriosis?**
            - **Month/Year of surgery: (*mm/yyyy*)**
            - **Route of access: (Laparoscopy/Laparotomy)**
                - *In the case of conversion from laparoscopy to laparotomy, "Laparotomy" has to be selected.*
            - **rASRM stage: *(stage I / stage II / stage III / stage IV / unknown)***
            - **ENZIAN A: (*number 0-3*)**
            - **ENZIAN B: (*number 0-3*)**
            - **ENZIAN C: (*number 0-3*)**
            - **ENZIAN F: (*free field)*)**
                - 'FA' – adenomyosis, 'FB' – deep endometriosis of urinary bladder, 'FI' – intestinal endometriosis (other than rectum), 'FU' – ureteral endometriosis, 'F()' – other deep endometriosis with location information in brackets
                - If compartment F not affected: F-
                - If F not known: Fx
            - **Endometrioma of the ovary: *right / left / bilateral / no endometrioma***
            - Description of the surgery:
                - **Opening of vagina (*yes/no*)**

        - **Opening of bowel (*yes/no*)**
        - **Opening of urinary bladder (*yes/no*)**
    - **Final result of the surgery:**
        - **Compartment A:** ***Complete Surgery / Partial surgery / no surgery / Not affected***
        - **Compartment B:** ***Complete Surgery / Partial surgery / no surgery / Not affected***
        - **Compartment C:** ***Complete Surgery / Partial surgery / no surgery / Not affected***
        - **Compartment F:** ***Complete Surgery / Partial surgery / no surgery / Not affected***
- If no (no surgery):
    - **Method of endometriosis diagnosis?**
      Clinical examination (palpation/specula) / Ultrasound / MRI / CT / biopsy / other type of diagnostic procedure
        - If other type of diagnostic procedure: Which other typ of diagnostic procedure?
    - **Localization of deep endometriosis?**
        - **Rectal endometriosis? *(yes/no)***
            - if yes: Largest diameter? [mm]
        - **Urinary bladder? *(yes/no)***
            - if yes: Largest diameter? [mm]
        - **Vagina? *(yes/no)***
            - if yes: Largest diameter? [mm]
        - **Rectovaginal fascia? *(yes/no)***
            - if yes: Largest diameter? [mm]
        - **Uterosacral ligaments? *(yes/no)***
            - if yes: Largest diameter? [mm]
        - **Other localization of deep endometriosis?**
- **Suspected adenomyosis? *(yes/no)***

PREGNANCY:

- **Diseases/complications during pregnancy? *(yes/no)***
    - If yes: **Type of disease/complication?**
        - Preeclampsia *(yes/no)*
        - Gestational diabetes *(yes/no)*
        - Preterm labor/cervical insufficiency *(yes/no)*
        - Placenta praevia *(yes/no)*
        - Premature rupture of membranes (PPROM < 37+0) *(yes/no)*
        - SGA/IUGR *(yes/no)*
        - Other diseases/complications

DELIVERY:

- **Gestational age at delivery:** *Week of pregnancy [number+number]*
- **Delivery mode: Vaginal spontaneous delivery / Vacuum extraction / Forceps / Primary cesarean section / Secondary cesarean section**
    - If Operative vaginal delivery (vacuum/forceps): Reason for operative vaginal delivery?
        - Pathological CTG pattern? (yes/no)
        - Prolonged second stage of labor? *(yes/no)*

        - Other
    - If primary cesarean section: Reason for primary c-section?
        - Repeat ceasarean delivery *(yes/no)*
        - Fetal malpresentation *(yes/no)*
        - Known endometriosis (yes/no)
        - Other
    - If secondary cesarean section: Reason for secondary c-section?
        - Pathological CTG pattern? (yes/no)
        - Labor dystocia (yes/no)
        - Other
- **Medical induction of labour? (yes/no)**
    - If yes (optional): Type of labour induction? [ocytocin, prostaglandin, other medication, not known]
- **Fetal Outcome:**
    - **Birth weight: *(number in grams)***
    - **Umbilical artery pH:**
        - „x“ if not known
    - **Apgar: Apgar 1 min / 5 min / 10 min**
        - „x“ if not known
- **Birth injury: *(yes/no)***
    - If yes: **Type of birth injury?**
        - **Perineal tear I°/II° *(yes/no)***
        - **Perineal tear III° *(yes/no)***
        - **Perineal tear IV° *(yes/no)***
        - **High vaginal laceration *(yes/no)***
        - **Cervical laceration *(yes/no)***
        - **Bowel injury (without perineal tear IV°) (yes/no)**
        - **Other birth injuries or place for additional information**
- **Further information on the delivery:**
    - **Retained placenta *(yes/no)***
    - **Uterine atony *(yes/no)***
    - **Occiput posterior position *(yes/no)***
    - **Episiotomy *(yes/no)***
    - **Other additional information on the delivery**
- PDA *(yes/no)*
- Postpartum discharge day
- Severy anaemia (Hb < 8g/dl) (yes/no)
- Need for blood transfusion *(yes/no)*

For the study plan a template of the Working Group for System Optimization of Clinical Research Projects (ASOKLIF) was used with their kind permission.