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BEWISE Protocol

Bed rest with a short cervix on preterm birth

BEWISE

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Content BEWISE Protocol

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1. Title

Bed rest with a short cervix on preterm birth (BEWISE).

2. Trial sponsor and principal investigator

Trial sponsor: Consultant, PhD, Associate Professor, lector Julie Glavind
Aarhus University Hospital, Denmark

Principal investigator: Consultant, PhD, Associate Professor, lector Julie Glavind
Medical doctor, PhD student, Kirsten Bünemann Jacobsen
kirsten.bunemann@clin.au.dk
Department of Obstetrics and Gynaecology
Aarhus University Hospital
Palle Juul-Jensens Boulevard 99
8200 Aarhus N
Denmark

A list of participating sites and the responsible site investigators is included in appendix 1 at the end of the protocol.

3. Purpose

a. The study's problem statement, hypothesis, endpoints, and rationale

The overall aim of this study is to compare gestational age at birth in women with a short cervix who are prescribed activity restriction versus those who are not.

We hypothesize that no activity restriction (NAR) is non-inferior to activity restriction (AR) in preventing preterm birth in pregnant women with a short cervix, and that NAR may lower risk of maternal depression.

With this study, we want to answer the following questions

Is NAR non-inferior to AR in prolonging pregnancy?

Does NAR compared to AR decrease the risk of maternal depression?

b. Brief literature review and reference list

Preterm birth (PTB) is birth < 37 weeks of gestation. PTB accounts for ~10% of all deliveries internationally (15 million babies per year) and is the main cause of neonatal death and serious lifelong disabilities [1]. Known risk factors of PTB include prior cervical surgery, prior midtrimester loss or PTB, previous emergency caesarean section during labour [2, 3].

The aetiology of PTB is complex and multifactorial as it may involve several pathological processes such as cervical disease, uterine overdistension, infection, hormonal, vascular or stress issues, whereas some may yet be unknown [4]. Moreover, it is suggested that spontaneous PTB has a long preclinical stage, frequent foetal involvement in the process, predisposing gene-environment interactions and with clinical manifestations often adaptive in nature[5].

Irrespective of the multiple aetiological causes PTB will be preceded by an activation of the common pathway of parturition (uterine contractility, membrane activation, cervical dilatation) which will be manifested by clinical signs of preterm uterine contractions, preterm prelabour rupture of membranes and/or cervical insufficiency[5, 6]; the latter can be detected by a shortening of the cervix using transvaginal ultrasound (TVU) [4, 6, 7]. Cervical length screening is performed in women at increased risk of PTB or used as a diagnostic examination in women with symptoms of a short cervix or preterm labour.

There are few preventive strategies for PTB. These include cervical cerclage, progesterone and physical activity restriction (AR).[8].

Maternal AR has long been used to prevent PTB [9, 10]. The definition of AR varies widely, spanning complete bed rest to limiting physical activity for one or more hours daily [11-13]. In research the definition of AR has been inconsistently reported [14] and often used without specific definition [15]. To enhance transparent and generalizable research results a standardised and stratified definition of AR in pregnancy was suggested (light, moderate and strict activity restriction) [10].

The theoretical reasoning behind recommending antenatal AR in impending PTB is to ease the mechanical power and force of the presenting part of the foetus on the internal cervical ostium. These theoretical presumptions that AR eases the intrauterine fetal pressure on the lower uterine segment and the internal cervical ostium has never been confirmed [6].

The existing, small body of evidence on the effects of maternal AR to prevent PTB has not revealed any positive effects on either preventing or postponing PTB. Instead, emerging evidence has shown an increase in PTB following AR [11, 16, 17] and significant adverse maternal and fetal effects [10].

Thus, in women at risk of PTB, a meta-analysis from 2019 found a higher PTB rate with AR (12.8%) versus no activity restriction (NAR), (6.2%) (RR 2.07, 95% CI 1.15–3.73) [18]. The interventions (activity levels) in these studies were unmeasured [11, 17] and heterogenous [13, 19], and women in mid-trimester pregnancies (gestational week 20 to 28) were poorly represented [18]. Additionally, confounding by indication is a concern, as women at higher risk of PTB would be more likely to be prescribed AR [11, 17].

In a prospective pilot study [20] women (n=49) at high risk of preterm birth between 24 and 32 weeks of gestation, with a sonographic short cervix < 20 mm were assessed. The women were asked to wear smart band activity trackers continuously for at least one week and were given no specific recommendations on the level of physical activity. PTB occurred in 75% of participants, with a significantly lower median step count in those who delivered preterm, suggesting an inverse association between PTB risk and daily activity levels. Although limited by its small sample size, this is the only study to date that

quantitatively assesses the association between physical activity and PTB using quantitative data. Its findings support the hypothesis that AR does not prevent PTB in high-risk patients.

AR in the Danish context

While several international medical societies no longer recommend AR [21], in Denmark the regimen is still being recommended without evidence to support its effectiveness [16, 22, 23]. A descriptive multi-centre study has demonstrated that Danish pregnant women (n=72), monitored with activity sensors, highly adhered to AR recommendations [24]. Further, the study demonstrated that discriminating between strict and moderate AR did not alter how physical resting positions and activities were carried out, neither did the admission status influence how participants adhered to strict AR[24].

Strict AR is defined as continuous rest in the supine or sitting position the entire day except for meals and bathroom use and without doing household chores or lifting. Moderate AR is defined as continuous rest in the supine or sitting position 2-8 hours daily and without doing household chores or lifting [24, 25].

In the present clinical Danish context AR is recommended before gestational age 28 to pregnant women with a cervix≤25 mm [25]. Thus, strict AR is recommended in singleton pregnancies with a cervix <10mm, twin pregnancies with a cervix <15mm and preterm prelabour rupture of membranes (PPROM) pregnancies with a cervix <10mm. Moderate AR is recommended in singleton pregnancies with a cervix 10-15mm, twin pregnancies with a cervix 15-20mm and PPROM pregnancies with a cervix <25mm [25].

AR and Maternal Mental Health

The Edinburgh Postnatal Depression Scale (EPDS) is a widely used and validated screening tool for identifying depressive symptoms during pregnancy and after childbirth. Developed to capture emotional and cognitive symptoms rather than somatic complaints common in the perinatal period, the EPDS consists of ten items scored 0–3, yielding a total score of 0–30[26].

The EPDS is translated into Danish and routinely used in municipal health services. A Danish validation study found that a cut-off of ≥11 provides the best balance of sensitivity and specificity for detecting probable depressive disorders according to ICD-10 and DSM-5 criteria[27]. International evidence further supports the scale's reliability across diverse perinatal populations[28].

Women with high-risk pregnancies on AR experience higher anxiety and depression than those with uncomplicated pregnancies [29]. While the EPDS is an effective screening instrument, it is not diagnostic. Elevated scores should always be interpreted in clinical context, and any indication of suicidal ideation (item 10) requires immediate follow-up. Early identification of depressive symptoms is essential, as untreated perinatal depression may adversely affect maternal well-being, parent–infant interaction, and child development.

c. Objectives

Primary endpoint

The primary endpoint is gestational age at birth.

d. Expected scientific contribution and clinical relevance

With this study, the current treatment regime for women with a shortened cervix will be changed from routine use of AR to discontinuation of AR, while simultaneously generating evidence on the clinical consequences of this change compared with previous practice.

The study will generate new national data from Danish obstetric care, with particular focus on women between gestational weeks 20 and 28, where available evidence is limited. Specifically, the study will evaluate whether discontinuation of AR is non-inferior with respect to gestational age at birth and assess potential effects on neonatal outcomes and maternal psychological well-being.

The project is clinically relevant and justified, as AR remains part of Danish practice despite limited evidence of its effectiveness. A structured evaluation of the change in recommendation using a stepped wedge cluster design may contribute to ensure evidence-based management and the results may directly inform national clinical guidelines. If discontinuation of AR is shown to be non-inferior, the findings may support the revision of current recommendations. Conversely, if inferior outcomes are observed, the study will provide a robust basis for adjusting future guideline recommendations.

4. Methods

The recommendation to restrict physical activity for pregnant women with a short cervix is about to be phased out of the Danish national guidelines, meaning that the current recommendation to restrict physical activity will be replaced with new recommendations, where activity restriction is not recommended any longer. In this study, we will collect data from women before and after this change in clinical practice[25]. The recommendation will be changed one region at a time following a stepped wedge design and according to Figure 1. Due to the planned administrative merge of Capital Region of Denmark and Region Zealand in year 2027, these two regions will, for the purpose of this study, be handled as a single cluster in the stepped-wedge design, referred to as Eastern Denmark Region. This approach ensures administrative feasibility, consistency in clinical organisation, and alignment with anticipated structural changes within the Danish healthcare system during the study period.

After one year, all regions will have changed their practice from AR to NAR.

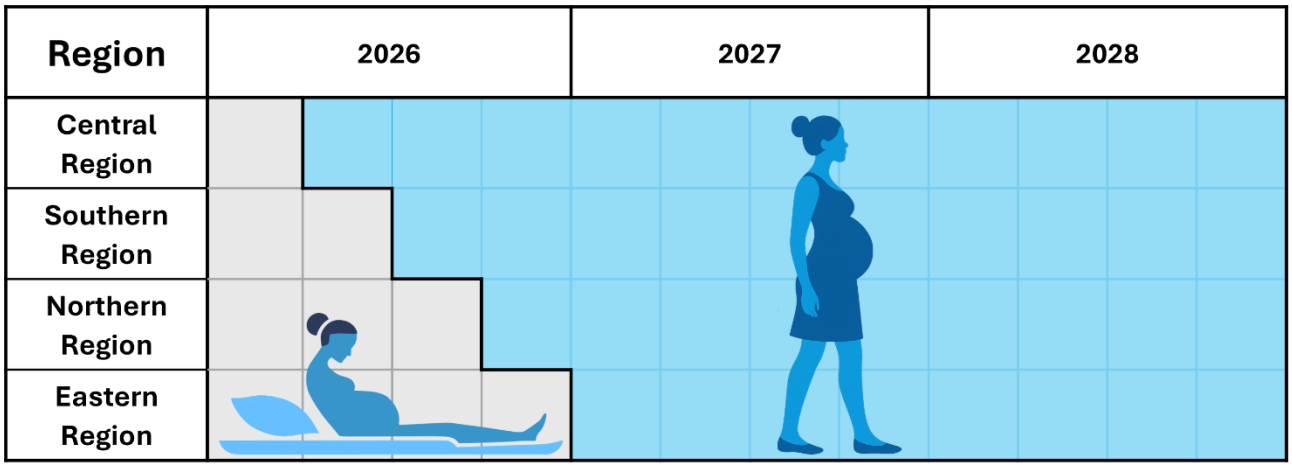

Figure 1 Grey fields: AR, blue fields: NAR

As part of the routine postnatal care programme in Denmark, all women are screened for postpartum depression by the municipal health nurse approximately eight weeks after delivery, typically using the Edinburgh Postnatal Depression Scale (EPDS). This has been used for depression screening post-partum for nearly 20 years. In the present study, we make use of this existing procedure by sending the EPDS questionnaire to participants in accordance with the established timeline for routine screening. Thus, participation in the study does not introduce any additional assessments or interventions beyond what women would undergo as part of standard care.

Study design

The study is designed as a non-inferiority stepped-wedge cluster randomized controlled trial. The transition from activity restriction (AR) to no activity restriction (NAR) in each region is determined as part of the study's stepped-wedge cluster randomized design. The sequence and timing of each region's transition are randomized at cluster level by the study statistician prior to study initiation. The transition schedule therefore does not follow an independently pre-determined national implementation plan but is defined by the research protocol.

The recommendation provided to each woman depends solely on the implementation phase of her region and is not influenced by individual study participation or consent.

The management teams of all obstetric departments in Denmark have reviewed and approved participation in the study and have committed to its implementation.

To evaluate the clinical consequences of the change in recommendation, outcomes will be monitored before and after introduction of NAR. Eligible participants will receive study information with an opt-out possibility during the clinical encounter in which eligibility is identified. The same information will subsequently be provided via the secure national digital mailbox system (e-Boks) within 7-10 days.

Participation will include the following:

1. Collection of data from electronic patient records.
2. Receiving the Edinburgh Postnatal Depression Scale (EPDS) questionnaire [26, 27] in the secure digital mailbox system 6-8 weeks after the due date.

Setting

All Danish birth centres.

Inclusion and exclusion criteria

Inclusion criteria

Pregnant women in gestational age 20+0 to 33+6 days with a short cervix, defined as less than 25 mm in singleton pregnancies and less than 30 mm in multiple pregnancies. Participants must be above 18 years of age and be able to read and understand Danish or English.

Exclusion Criteria

None.

Outcomes

Obstetric outcomes

- Gestational age at birth
- Number of days from inclusion to birth
- Onset of birth (spontaneous, induction or CS)
- Mode of birth
- Non-occipital presentation
- Interventions during birth
- Duration of birth
- Complications during birth
- Birth tear
- Maternal serious morbidity
- Umbilical cord pH
- EPDS depression score

Neonatal outcomes

- Neonatal mortality
- Late miscarriage
- Fetal loss
- Birth weight
- Neonatal admission
- CNS morbidity
- Retinopathy of prematurity
- Gastrointestinal morbidity
- Respiratory support
- Respiratory distress syndrome
- Early onset infection
- Apgar score at 5 minutes
- Hypoglycaemia

Data Collection

Clinical data will be collected and managed using REDCap electronic data capture tools hosted at Aarhus University, Denmark [30]. 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.

A data dictionary is developed prior to patient enrolment to ensure clear and consistent definitions of all included variables. It specifies each variable's name (including its corresponding database code), a

detailed description, category options for categorical variables, and units and expected ranges for continuous variables. The data dictionary will be made publicly available.

1. **Prospective data**
   Prospective data on clinical variables will be collected by a research assistant in each region from the electronic patient record and registered in electronic standardized forms (eCFR) using REDCap. See section 8 for a full list of variables that will be collected.

2. **Mental health**
   Maternal depression will be evaluated using the Edinburgh Postnatal Depression Scale (EPDS) [26, 27] through electronic questionnaires 6-8 weeks post-partum. The questionnaires will be sent to the participants e-boks.

Deviations from standard treatment

All women in the study will receive standard antenatal care. This means that any prophylactic or therapeutic interventions during pregnancy are based on national or local clinical practice.

After answering the EPDS questionnaire the participants will be contacted if the EPDS score is ≥ 11. If the score is ≥ 11 [27] she will be advised to contact her general practitioner for follow up as would she be if the same score was registered form the health nurse post-partum.

5. Statistical considerations

This study is designed as a stepped-wedge cluster randomized trial evaluating the change in recommendations from using activity restriction to not using activity restriction to prevent preterm birth in women with a short cervix.

Since the study is designed around a practice change at cluster level, the sample size is not based on a conventional power calculation for a single primary outcome. Instead, the projected number of participants is determined pragmatically, based on feasibility and expected case numbers. We estimate the expected number of cases to be approximately 3000 women over the full study period. This number is considered sufficient to provide meaningful evidence on maternal and neonatal outcomes within the stepped-wedge design. To verify the estimated number of cases, we wish to extract data from Astraia on pregnant women with a cervical length below 25 mm (below 30 mm in twin pregnancies) between gestational weeks 20+0 and 33+6 during the period from 1 October 2024 to 1 October 2025. In 2024, the Central Denmark Region accounted for approximately 24% of all births in Denmark. Based on this information, the Astraia data will be used to extrapolate the estimated total number of eligible women nationwide.

This large-scale data collection allows for the evaluation of multiple clinical outcomes with high generalizability. Statistical analyses will include appropriate adjustments for potential confounding factors such as gestational age at diagnosis, parity, prior preterm birth, and cervical length. A full statistical

analysis plan (SAP), including definition of the non-inferiority margin and sensitivity analyses will be available.

6. Identification and recruitment

Identification: The participants can be identified through the following pathways:

- 1. During hospital admission
- 2. During visits to the outpatient clinic
- 3. During scheduled ultrasound visits

Potential participants will be identified from antenatal visits based on the inclusion criteria.

When a woman meets the inclusion criteria, the healthcare professional involved in her care will provide written study information directly to the patient during the clinical encounter and add her to a dedicated list in the electronic patient record (BEWISE list). Following this, the same study information will be sent via the secure national digital mailbox system (e-Boks) within 7-10 days after registration on the BEWISE list, again allowing the participant to consider the opt-out possibility. In the written information, she will be informed that the department is currently conducting a low-risk clinical study investigating the effect of activity restriction on pregnancy outcomes. t

The written study information includes clear instructions on how to decline participation (opt-out), including a QR-code with direct access to Redcap, where she can mark the opt-out wish. Participants who choose to opt out will not receive further study-related communication, and no data will be collected for research purposes. Participants who have already opted out prior to the e-Boks follow-up will not receive additional communication. The principal investigator together with the regional project koordinators will ensure that all opt-out answers are documented.

To ensure consistent implementation across all participating sites, each department will appoint a local responsible clinician, who will ensure that all relevant healthcare professionals are instructed in the identification procedure and the distribution of study information.

No public advertisement or social media recruitment will be used.

7. Risks, side effects, and disadvantages

Activity restriction is currently implemented without strong supporting evidence and may be associated with physical and psychological harm. The ethical justification for this study lies in evaluating whether discontinuation of an unproven intervention improves or maintains outcomes.

There are currently no known or anticipated risks, side effects associated or disadvantages with changing the recommendation from AR to NAR; however, participants will be monitored in accordance with standard clinical practice, and any unexpected concerns will be addressed promptly.

8. Variables

Collected variables will be used for baseline descriptive statistics and for outcome analysis.

Data variables

Maternal characteristics at time of inclusion

Collected data from the in-hospital electronic medical records:

- Maternal age
- Body mass index (BMI)
- Parity
- Congenital uterine malformation
- Previous conization
- Date at recruitment
- Previous pregnancies and outcomes of the pregnancies
- Ultrasound determined due date
- Cerclage treatment
- Danish region

Obstetric data during pregnancy

Collected data from the in-hospital electronic medical records from time of inclusion until birth.

- Treatment with: vaginal progesterone, tocolysis, magnesium sulphate and/or lung maturation
- Preterm prelabour rupture of membranes
- Shortest sonographic cervical length
- Number of contacts to obstetric department
- Total number of admission days in the obstetric department before onset of labour/caesarean section
- Level of recommended activity restriction at time of inclusion
- Pessary
- Cerclage
- Gestational diabetes mellitus
- Preeclampsia
- Gestational hypertension
- Eclampsia

Obstetric data during birth

Collected data from the in-hospital electronic medical records after birth

- Date and time at onset of birth (active labour)
- Date and time at birth or loss
- Onset of birth (spontaneous, induction, CS)
- Mode of birth
- Fetal presentation

- Oxytocin-infusion during birth
- Epidural anaesthesia during birth
- Placental abruption
- Post partum haemorrhage
- Administration of iv antibiotics
- Retained placenta (transferred to operating theatre)
- Fetal asphyxia
- Degree of birth tear
- Smoking status

Neonatal data

Collected data from the mother's electronic record until discharge or 44 postmenstrual weeks

- Birth weight
- Apgar score at 5 minutes
- Umbilical arterial cord pH
- Stillbirth

Collected data from the newborn's electronic record until discharge or 44 postmenstrual weeks

- Neonatal death (within the first 28 days of life), date and time
- Date of discharge from the hospital
- Serious adverse prematurity outcomes (Intraventricular haemorrhage, Periventricular leukomalacia, Retinopathy of prematurity, Surgery due to necrotizing enterocolitis or spontaneous intestinal perforation, Mechanical ventilation or non-invasive ventilation (NIV)
- Administration of iv antibiotics (start and end date)

The data are used to identify differences in demographic and pregnancy-related factors between the groups that may explain any differences in pregnancy outcomes. In addition, data on pregnancy outcomes are collected for the main purpose of the project, namely to compare the two treatments in terms of pregnancy prognosis and the participant's health.

9. Processing of personal data in the project

Data will be handled according to national laws on data protection (in Denmark including the General Data Protection Regulation and the Data Protection Act) and will be registered at www.ClinicalTrials.gov. In Denmark, the project will also be registered with the Central Denmark Region's internal list of research projects. Data will be used for the purpose outlined in this trial protocol.

10. Economy

The trial is investigator-initiated. The Independent Research Fund Denmark has funded the trial with approximately 4,2 million DKK.

The funding is administered at the Department of Gynaecology & Obstetrics, Aarhus University Hospital, Denmark and can be used for salary for named collaborators, data handling, and additional operational expenses according to the funding terms. Private and public funds will be sought for additional costs. The funding agencies will have no role in any aspects of conducting and reporting of the trial.

The Health Research Foundation of Central Denmark Region has funded 100.000 DKK for salary for a research assistant during the preparation of the trial. This funding was administered by the Department of Gynaecology & Obstetrics, Viborg Regional Hospital, Denmark.

If additional funding is obtained during the study period, this information will be submitted to the Danish National Committee on Health Research Ethics as a protocol amendment in accordance with committee requirements.

11. Dissemination policy

The study will be registered at www.clinicaltrials.gov.

Positive, inconclusive as well as negative results from the trial will be published in peer reviewed international scientific journals. Results will furthermore be presented at national and international conferences and shared via public and social media platforms.

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13. Appendix 1: Participating Sites and Site Investigators

Capital Region Denmark

1: Bornholms Hospital

Department: Graviditet, Jordemor og Fødsler

Adress: Ullas vej 8, 3700 Rønne

Site investigator: Karen R. Wøjdemann, Consultant, PhD, Department of Obstetrics & Gynaecology, Bornholm Hospital

2: Herlev Hospital

Department: Afdeling for Graviditet og Fødsel

Adress: Borgmester Ib Juuls vej 1, 2930 Herlev

Site investigator: Signe Fogsgaard, Obstetrician, PhD, Department of Obstetrics & Gynaecology, Herlev Hospital

3: Hvidovre Hospital

Department: Gynækologisk-Obstetrisk afdeling

Adress: Kettegård Alle 36

Site investigator: Helene Hvidman, Chief Physician, PhD, Department of Obstetrics & Gynaecology, Hvidovre Hospital

4: Nordsjællands Hospital

Department: Graviditet, Fødsel og Barsel

Adress: Dyrehavevej 29, 3400 Hillerød

Site investigator: Ellen Løkkegaard, Consultant, Professor, PhD, Department of Obstetrics & Gynaecology, North Zealand Hospital

5: Rigshospitalet

Department: Afdeling for Gynækologi, Fertilitet og Fødsler

Adress: Juliane Maries Vej 8, 2100 København Ø

Site investigator: Lone Storgaard, Consultant Obstetrician, PhD, Department of Obstetrics & Gynaecology, Rigshospitalet, Copenhagen University Hospital

Northern Region Denmark

6: Regionshospital Nordjylland, Hjørring

Department: Afdeling for Kvindesygdomme, Graviditet og Fødsel

Adress: Bispensgade 37

Site investigator: Ulla B Christensen Consultant Obstetrician, Department of Obstetrics and Gynaecology, Hjørring Hospital

7: Aalborg Universitetshospital

Department: Gynækologisk-Obstetrisk Afdeling

Adress: Reberbansgade 15, 9100 Aalborg

Site investigator: Aiste Kloster, Consultant Obstetrician, Department of Obstetrics and Gynaecology, Aalborg University Hospital

8: Aalborg Universitetshospital, Thisted

Department: Afdeling for Gynækologi, Graviditet og Fødsel

Adress: Højtoftevej 27700 Thisted

Site investigator: Kristine Nielsen, Chief Physician, Department of Obstetrics and Gynaecology, Thisted Hospital

Region Zealand

9: Holbæk Sygehus

Department: Afdeling for Graviditet, Fødsel og Barsel

Adress: Smedelundsgade 60, 4300 Holbæk

Site investigator: Anders Atke, Chief Obstetrician, Department of Obstetrics and Gynaecology, Holbæk Hospital

10: Sjællands Universitetshospital, Nykøbing Falster

Department: Gynækologisk og Obstetrisk Afdeling

Adress: Fjordvej 15, 4800 Nykøbing F.

Site investigator: Hanne Trap Wolf, MD, PhD, Department of Obstetrics and Gynaecology, Zealand University Hospital (Roskilde and Nykøbing Flaster)

11: Sjællands Universitetshospital, Roskilde

Department: Afdeling for Kvindesygdomme og Fødsler

Adress: Sygehusvej 10, 4000 Roskilde

Site investigator: Hanne Trap Wolf, MD, PhD, Department of Obstetrics and Gynaecology, Zealand University Hospital (Roskilde and Nykøbing Flaster)

12: Slagelse Sygehus

Department: Gynækologisk-Obstetrisk Afdeling

Adress: Fælledvej 11, 4200 Slagelse

Site investigator: Louise Vibede, Chief Physician, PhD, Department of Obstetrics and Gynaecology, Slagelse Hospital

Southern Region Denmark

13: Esbjerg Sygehus

Department: Afdeling for Kvindesygdomme og Fødsler

Adress: Finsensgade 35, 6700 Esbjerg

Site investigator: Mette Holm Ibsen, Chief Obstetrician, University Hospital of Southern Denmark, Esbjerg

14: Kolding Sygehus

Department: Afdeling for Kvindesygdomme og Fødsler

Adress: Sygehusvej 24, 6000 Kolding

Site investigator: Anne Cathrine Hoffgaard Munk, Chief Physician, Department of Obstetrics & Gynaecology, Lillebaelt Hospital

15: Odense Universitetshospital

Department: Gynækologisk Obstetrisk Afdeling

Adress: J. B. Winsløws Vej 4, 5000 Odense

Site investigator: Kamilla Karlsen, Consultant Obstetrician, Department of Obstetrics & Gynaecology, Odense University Hospital / Research Unit of Gynaecology & Obstetrics, University of Southern Denmark

16: Sygehus Sønderjylland, Aabenraa

Department: Kvindesygdomme og Fødsler

Adress: Kresten Philipsens Vej 15, 6200 Aabenraa

Site investigator: Katrin Löser, Chief Physician, Department of Obstetrics & Gynaecology, Sønderjylland Hospital

Central Region Denmark

17: Aarhus University Hospital

Department: Kvindesygdomme og Fødsler

Adress: Palle Juul-Jensens Boulevard 141

Site investigator: Julie Glavind, Senior Consultant, PhD, Associate Professor, Dep. of Obstetrics and Gynecology, Aarhus University Hospital

18: Gødstrup Hospital

Department: Kvindesygdomme og Fødsler

Adress: Hospitalsparken 15, 7400 Herning

Site investigator: Iben Sundtoft, Consultant, PhD, Associate Professor, Dep. of Obstetrics and Gynecology, Gødstrup Hospital

19: Hospitalsenhed Midt, Viborg

Department: Kvindesygdomme og Fødsler

Adress: Heibergs Alle 4, 8800 Viborg

Site investigator: Richard Farlie, Chief Obstetrician PhD, Associate Professor, Dep. of Obstetrics and Gynecology, Viborg Hospital

20: Regional Hospital Randers

Department: Afdeling for Kvindesygdomme og Fødsler

Adress: Skovlyvej 1, 8930 Randers NØ

Site investigator: Isa Niemann, Chief Physician, Department of Obstetrics & Gynaecology, Randers Hospital

21: Horsens Hospital

Department: Kvindesygdomme og Fødsler

Adress: Strandpromenaden 35, Indgang B, 8700 Horsens

Site investigator: Birgitte Freilev Lindved, Chief Obstetrician, Department of Obstetrics & Gynaecology, Horsens Hospital