EVA

Episiotomy in Vacuum Assisted delivery

A randomized controlled trial of lateral episiotomy vs. no episiotomy in vacuum assisted delivery in non-parous women

Sponsor: Sophia Brismar Wendel

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1 Protocol Summary

PROTOCOL IDENTITY AND OBJECTIVES	
Protocol Title:	EVA – Episiotomy in Vacuum Assisted delivery. A randomized controlled trial of lateral episiotomy vs. no episiotomy in vacuum assisted delivery in non-parous women.
Study Objectives:	The aims are to investigate if lateral episiotomy can reduce the prevalence of obstetrical anal sphincter injury (OASIS) in operative vaginal delivery, notably vacuum extraction, in non-parous women, and to investigate secondary outcomes such as immediate maternal complications like post-partum haemorrhage and hospital stay, medium term effects like prolapse symptoms, incontinence, sexual dysfunction, birthing experience, and aspects of neonatal care. In a long-term follow-up, we will investigate if episiotomy/spontaneous tear is associated with caesarean section, episiotomy or OASIS in a subsequent pregnancy/childbirth. We will also re-evaluate symptoms of incontinence, prolapse and sexual function after 5 years.

METHODOLOGY	
Study Design:	The study is a randomized controlled trial with parallel groups.
Intervention:	The effect of lateral episiotomy vs. no episiotomy in vacuum assisted delivery in non-parous women in Sweden will be studied. Women with a singleton, live fetus in cephalic presentation, after week 34+0 requiring vacuum assisted vaginal delivery will be randomized to lateral episiotomy or no episiotomy. At least three sites are planned to participate.
Primary Endpoint:	The primary endpoint is third or fourth degree perineal tear (OASIS, ICD-10 code O70.2 or O70.3).

POPULATION OF STUDY SUBJECTS

Description of Study Subjects: Inclusion Criteria:

- Non-parous woman
- Singleton, live fetus in cephalic presentation
- Gestational week 34+0 or more
- Requiring vacuum assisted vaginal delivery
- Signed informed consent

Exclusion Criteria:

- Previous surgery for incontinence or prolapse

Number of Subjects: 1400 subjects

STUDY TIMETABLE

First Subject In:	June 2017
Last Subject In:	June 2021
Last Subject Out:	Sept 2031

2 Abbreviations

Abbreviation	Explanation
AE	Adverse Event
BMI	Body Mass Index
BSS-R	Birth Satisfaction Scale-Revised
CEQ	Child Experience Questionnaire
CRF	Case Report Form
FSDS	Female Sexual Distress Scale
FSFI	Female Sexual Function Index
GCP	Good Clinical Practice
ICD-10	International Statistical Classification of Diseases and Related Health Problems - Tenth Revision
ICH	International Conference of Harmonization
IEC	Independent Ethics Committee
NICU	Neonatal Intensive Care Unit
OASIS	Obstetric Anal Sphincter Injury
PDB	Pudendal Block
POP-Q	Pelvic Organ Prolapse Quantification
SAE	Serious Adverse Event
SBU	Statens Beredning för Medicinsk och Social Utvärdering
SNQ	Swedish Neonatal Quality Register
SOP	Standard Operating Procedure
VAS	Visual Analogue Scale
WMA	World Medical Association

3 Administrative Information

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4 Background

4.1 Purpose and aims

The purpose is to improve obstetrical care in Sweden by making the second stage safer, specifically to reduce obstetric anal sphincter injury (OASIS) in operative vaginal delivery. OASIS prevalence in all vaginal deliveries is 5-7% in Sweden. The prevalence of perineal tears increases with operative vaginal delivery, and the frequency of OASIS is 12-14% in vacuum extractions in Sweden.

The aims are to investigate if lateral episiotomy can reduce the rate of OASIS in operative vaginal delivery, notably vacuum extraction, in non-parous women, and to investigate secondary outcomes such as immediate maternal complications like postpartum hemorrhage and hospital stay, medium term effects like prolapse symptoms, incontinence, sexual dysfunction, birthing experience, and aspects of neonatal care (cord pH, Apgar score, subcutaneous hemorrhage, birth trauma). In a long-term follow-up, we will investigate if episiotomy/spontaneous tear is associated with cesarean section, episiotomy or OASIS in a subsequent pregnancy/childbirth. We will also re-evaluate symptoms of incontinence, prolapse and sexual function after 5 years.

The proposed study is a randomized controlled trial of lateral episiotomy vs. no episiotomy in vacuum assisted delivery in non-parous women in Sweden. Women with a singleton, live fetus in cephalic presentation, after week 34+0 requiring vacuum assisted vaginal delivery will be randomized to lateral episiotomy or no episiotomy.

4.2 Survey of the field

A third or fourth degree tear (OASIS) is considered to be the most important cause of anal incontinence in women, and therefore important to avoid. In Finland, the prevalence has been very low since several decades, probably due to a different technique (no pushing) at delivery of the fetal head and an effective perineal support, as well as a longstanding tradition of lateral episiotomy (1-3). A lateral episiotomy involves an incision at least 1 cm from the midline and at least at 30 degrees angle from the midline, as measured after healing (4). In Norway, a national prospective multi-center study during 2000-2010, with

implementation of a “Finnish” perineal support and lateral episiotomy, decreased anal sphincter injury from 4.0% to 1.2% in the total population and from 16.3% to 4.9% in vacuum extractions (5). In an American study, a change to mediolateral episiotomies in instrumental deliveries (commonly forceps) decreased the prevalence of sphincter tears from 41 to 26% (6). Similarly, a Dutch prospective study, showed a risk reduction at instrumental deliveries by 90% using mediolateral episiotomy (7). On the contrary, medial (midline) or too small episiotomies are associated with an increased risk of sphincter injury (8). In a British study comparing routine (93%) vs. restrictive (52%) use of episiotomy, there was a small non-significant difference in the rate of anal sphincter tears (8.1% routine versus 10.9% restrictive, OR 0.72, 95% CI 0.28-1.87) but the trial was underpowered (9). There is a recent randomized study comparing mediolateral and lateral episiotomy, finding equal although very low prevalence of sphincter injury (1.5 vs. 1.3%) (10). The objection that lateral incisions bleed more or causes more pain is contradicted by studies comparing incision techniques (11, 12). Little is known about chronic pain after episiotomy or spontaneous perineal injury, although there seem to be a correlation between the extent of tissue damage and degree of pain (13-15). An SBU report (Statens beredning för medicinsk och social utvärdering, www.sbu.se) published in April 2016 concludes that mediolateral episiotomy can protect against OASIS in operative vaginal deliveries in non-parous women based on two retrospective cohort studies (7, 8) although in Sweden, there is no correlation between a hospital’s rate of episiotomy and OASIS. The SBU report states that there is a knowledge gap regarding function and symptoms after episiotomy compared to moderate spontaneous tears/OASIS. Several others, including Cochrane and DUETS/NICE Evidence Search, state that the protective effect of lateral episiotomy at operative vaginal delivery should be investigated in an adequately sized randomized study (8, 16-18).

5 Objectives

5.1 Primary Objective

The primary objective is to investigate if lateral episiotomy protects against obstetrical anal sphincter injury (OASIS) compared to no episiotomy in operative vaginal delivery by vacuum extraction, in term and late pre-term (gestational week 34+0 or more), non-parous women with one live fetus in cephalic presentation.

5.2 Secondary Objectives

The secondary objectives are to investigate if lateral episiotomy compared to no episiotomy in the above specified group of patients can reduce:

- Prevalence of other degree of perineal injury, prevalence of postpartum hemorrhage, duration of hospital stay, pain, and duration of pain medication, compared to spontaneous perineal injury of different degrees (1st, 2nd, 3rd and 4th degree)
- Neonatal morbidity measured as prevalence of low Apgar score, metabolic acidosis, prevalence of admission to the Neonatal ward, and prevalence of scalp trauma/other birth trauma
- Prevalence of urinary, anal and fecal incontinence, prolapse symptoms, sexual dysfunction, or discontent with birthing experience after 2 months
- Prevalence of ultrasound evidence of extended pelvic floor injury at 6-12 months after delivery
- Prevalence of urinary, anal and fecal incontinence, prolapse symptoms, or sexual dysfunction after 1 and 5 years
- Prevalence of elective cesarean in a subsequent pregnancy/delivery, the prevalence of OASIS in a subsequent pregnancy/delivery, or of episiotomy in a subsequent pregnancy/delivery within 5 and 10 years

6 Endpoints

6.1 Primary Endpoint

The primary endpoint is third or fourth degree perineal tear (OASIS, ICD-10 code O70.2 or O70.3). The diagnosis is made clinically. Clinical diagnosis is quality controlled in a sub-study in one site by ultrasound of the pelvic floor muscles at 6-12 months after delivery.

6.2 Secondary Endpoints

The secondary endpoints are:

- other degree of perineal injury (O70.0, O70.1, O71.4 or O71.7)
- blood loss postpartum (ml)
- neonatal outcome (prevalence of Apgar score <7 at 1 min, 5 min and 10 min, umbilical artery pH <7.05)
- admission to the Neonatal ward (hours of stay and prevalence)
- fetal trauma (clinical diagnosis of hematoma/fracture/obstetric brachial plexus palsy/hypoxic ischemic encephalopathy by neonatologist)
- duration of hospital stay after delivery (days)
- pain and birth experience after delivery (Visual Analog Scale (VAS))
- duration of pain medication after delivery (days)
- symptoms regarding anal incontinence (Wexner score) (19) at 2 months, 12 months and 5 years after delivery
- symptoms regarding urinary incontinence at 2 months, 12 months and 5 years after delivery
- sexual function, prolapse and bowel symptoms at 2 months, 12 months and 5 years after delivery
- birthing experience and satisfaction 2 months after delivery
- ultrasound evidence of OASIS or levator ani muscle injury at 6-12 months after delivery
- mode of delivery, episiotomy, and OASIS in a subsequent pregnancy at 5 years and 10 years after index delivery
- quality of life at 12 months and 5 years after delivery

7 Design and Procedures

7.1 Outline

The study is a randomized controlled trial with parallel groups. The effect of lateral episiotomy vs. no episiotomy in vacuum assisted delivery in non-parous women in Sweden will be studied. Women with a singleton, live fetus in cephalic presentation, after week 34+0 requiring vacuum assisted vaginal delivery will be randomized to lateral episiotomy or no episiotomy. Lateral episiotomy will be performed after local anesthesia at crowning. After delivery routine care is given.

Primary outcome is obstetrical anal sphincter injury (OASIS) diagnosed clinically. In at least one center, transperineal, endovaginal and transrectal ultrasound validation of the clinical diagnosis and effects on pelvic floor will be made at 6-12 months after delivery.

Follow-up will be performed at 2 months, 12 months and 5 years using web-based questionnaires and at 5 years and 10 years through the Pregnancy Register.

7.2 Procedures

The procedures at each time point are described below and can also be found in Appendix 21.1 Schedule of Investigational Events.

7.2.1 At the maternity clinic

7.2.1.1 Before delivery

After admission to the clinic the women will be given information about the study and asked to participate. Before any screening and study related activities take place, written informed consent must be obtained from the subject. The Investigator will review the inclusion and exclusion criteria for eligibility. If all the inclusion criteria and none of the exclusion criteria are met the subject will be included in the study.

Included subjects are randomized to lateral episiotomy at crowning or no episiotomy. Randomization and lateral episiotomy is performed as described in 9.1 and 9.2. Lateral episiotomy is also described in the study specific Standard Operating Procedure (SOP), see Appendix 21.2 Standard Operating Procedures.

Background and explanatory variables to be recorded are maternal age, country of birth, weight at registration in the antenatal clinic and height.

7.2.1.2 Shortly after delivery

Perineal incisions and tears are sutured according to the clinical routine or as suggested by the study specific SOP, see Appendix 21.2 Standard Operating Procedures.

Perineal injury, blood loss, and neonatal outcomes (Apgar score, umbilical artery pH and birth related diagnosis) are recorded.

Background and explanatory variables to be recorded are use of Oxytocin, use of regional or local anesthesia, birthweight, head circumference, neonatal length, second stage duration, indication for vacuum extraction, fetal position and station, operator skills, number of pulls, and use of sequential instruments.

7.2.1.3 On the maternity ward

Pain after delivery (VAS, included in the questionnaires), birth experience (VAS), duration of hospital stay, and admission to the Neonatal ward will be recorded.

Assessment of baseline data on pelvic floor function will be performed using the questionnaire “Uppgifter om hälsa före graviditeten”. The questionnaires “Female Sexual Function Index” (FSFI) and “Female Sexual Distress Scale” (FSDS) will be used for in depth assessment of sexual function. Quality of life will be measured using the questionnaire Euro-QoL-5D.

7.2.2 Follow up 2 months (up to 6 months after delivery)

Assessment of duration of pain medication, pelvic floor and sexual function will be performed using the questionnaire “Din värdering av behandlingen av förlossningsbristningen (ca 8 veckor)”. Assessment of birth satisfaction will be performed using the Birth Satisfaction Scale (BSS-R) and the Child Experience Questionnaire (CEQ 2.0).

7.2.3 Follow up 6 months (up to 12 months after delivery)

(In at least one site) The scar after tears/episiotomy will be measured using a ruler and a protractor, pelvic organ prolapse will be quantified using a specific score (POP-Q), and transperineal, endovaginal and transrectal 2D/3D ultrasound will be used to evaluate occult OASIS and other injuries to the muscles of the pelvic floor. In the other sites, an individual clinical follow-up will be offered at six months after delivery, without any planned data entry points.

7.2.4 Follow up 12 months (up to 18 months after delivery)

Assessment of pelvic floor and sexual function will be performed using the questionnaire "Din värdering av behandlingen av förlossningsbristningen (ca 1 år)". The questionnaires "Female Sexual Function Index" (FSFI) and "Female Sexual Distress Scale" (FSDS) will be used for in depth assessment of sexual function. Quality of life will be measured using the questionnaire Euro-QoL-5D.

7.2.5 Follow up 5 years (up to 5 years and 6 months after delivery)

Assessment of pelvic floor and sexual function will be performed using the questionnaire "Din värdering av behandlingen av förlossningsbristningen (ca 1 år)". *The questionnaires "Female Sexual Function Index" (FSFI) and "Female Sexual Distress Scale" (FSDS) will be used for in depth assessment of sexual function. Quality of life will be measured using the questionnaire Euro-QoL-5D.*

Data on mode of delivery, episiotomy, and OASIS in a subsequent pregnancy will be collected from the Pregnancy Register.

7.2.6 Follow up 10 years

Data on mode of delivery, episiotomy, and OASIS in a subsequent pregnancy will be collected from the Pregnancy Register.

7.3 End of Study

The end of study is defined as the last follow up for the last subject.

8 Selection and Withdrawal of Subjects

8.1 Inclusion Criteria

- Non-parous woman
- Singleton, live fetus in cephalic presentation
- Gestational week 34+0 or more
- Requiring vacuum assisted vaginal delivery
- Signed informed consent

8.2 Exclusion Criteria

- Previous surgery for incontinence or prolapse

8.3 Subject Log

Investigators must keep a record, a screening log, of all patients that were considered for enrolment even if they were not subsequently enrolled. In this study, this applies to all women who have given consent to participation. This information is necessary to verify that the patient population was selected

without bias. The reasons for non-eligibility are to be defined in terms of one or more of the eligibility criteria.

Investigators must also keep a Subject identification log of all patients enrolled (equals to randomized) which includes sufficient information to link records, i.e. the Case Report Form (CRF) and clinical records.

9 Intervention

9.1 Description of the intervention

Intervention: Lateral episiotomy
Comparison: No episiotomy

In all women, the urinary bladder should be emptied by catheterization before application of the vacuum cup. For pain relief, a pudendal block (PDB) can be administered using for example Mepivakain (Carbocain) 10 mg/ml 5-10 ml. The anesthetic substance is injected using a Kobak needle on each side localizing the ischiadic spines bilaterally.

For women randomized to the intervention group, lateral episiotomy is performed as follows.
Local anesthesia is administered using for example Mepivacaine (Carbocain) or Lidocaine (Xylocain) in the hymeneal plane, 1 ml subcutaneously at the incision point and 9 ml in a fan-like fashion from the incision point. The vacuum cup is then applied and the extraction is performed until the fetal head is crowning, i.e. the cup is visible in the vaginal opening.

Lateral episiotomy is then performed using specific episiotomy scissors, Mayo scissors, or similar.

- Distance from incision point to the posterior fourchette: at least 1 cm, up to 3 cm.
- Angle from the sagittal or parasagittal plane: 60° (45-80°, aim at the ischiadic tuberosity)
- Length of the incision: 4 cm (3-5 cm)

All women will receive perineal support using verbal guiding and manual support of the perineum during the delivery of the head and body. The third stage, examination and diagnosis of perineal tears is managed according to clinical routine. Suturing is managed according to clinical routine or as suggested in the study specific SOP, see appendix 21.2 Standard Operating Procedures.

9.2 Randomization

The physician in charge of the operative delivery is responsible for randomization. Women included in the study will be randomized to lateral episiotomy or no episiotomy using opaque envelopes on the vacuum extractor equipment wagon.

10 Assessments

10.1 Perineal injury

A physician specialist or a senior registrar physician will make the diagnosis clinically. In a subgroup, diagnosis will be confirmed by transperineal and transrectal ultrasound at six to 12 months after delivery. This will be performed in a participating site where the method is established for the diagnosis

of OASIS. Any degree of perineal injury will be recorded. Data will be entered manually and collected from the Pregnancy register.

10.2 Blood loss

Postpartum hemorrhage is measured in milliliters. Data will be collected from the Pregnancy register.

10.3 Neonatal outcome

Assessment of Apgar score is performed according to clinical routine. The score at 1, 5, and 10 min is recorded for the study. Umbilical cord blood is sampled routinely in all operative deliveries. Arterial and venous blood gases are analyzed using regular equipment in the ward. Data will be collected from the Pregnancy register.

10.4 Admission to the Neonatal ward

Admission to the Neonatal ward (duration of stay and prevalence) will be collected from the Swedish Neonatal Quality Register (SNQ).

10.5 Scalp trauma and other neonatal trauma

Clinical diagnosis of cephalic hematoma/subgaleal hematoma/intracranial hemorrhage as well as diagnosis of fractures, obstetric brachial plexus palsy and hypoxic ischemic encephalopathy by neonatologist. These variables will be collected from the Pregnancy register and the SNQ.

10.6 Duration of hospital stay

Duration of hospital stay (days) after delivery will be collected from the Pregnancy register.

10.7 Pain and birth experience after delivery

Pain after delivery will be assessed using a simplified VAS (0-10) and this assessment will be included in the questionnaires.

Birth experience after delivery will be assessed using a simplified VAS (1-10). This variable will be collected from the Pregnancy register.

10.8 Questionnaires

The questionnaires ”Uppgifter om hälsa före graviditeten” and “Din värdering av behandlingen av förlossningsbristningen” will be used for assessment of pelvic floor and sexual function. The questionnaire is identical to the baseline questionnaire used in ”Bristningsregistret”, a national register of perineal injuries in obstetric care. The questionnaire consists of a set of questions regarding pelvic floor function, i.e. urinary and anal continence, symptoms of vaginal prolapse, sexual function, and bowel function.

The questionnaires “Female Sexual Function Index” (FSFI) and “Female Sexual Distress Scale” (FSDS) will be used for in depth assessment of sexual function. Both contain questions on sexual arousal, lubrication, pain, and orgasm.

The Birth Satisfaction Scale (BSS-R) (20, 21) and The Childbirth Experience Questionnaire (CEQ 2.0)(22) will be used for assessment of the birthing experience and satisfaction. The questionnaires contain questions regarding self-empowerment, fear, and overall satisfaction with care.

Euro-QoL-5D will be used for assessment of quality of life. The questionnaire contains 5 questions on mobility, personal hygiene, anxiety, and an over-all health evaluation using a VAS scale (23).

All the questionnaires will be managed by the patient survey company ImproveIT AB, with extensive experience in web-based questionnaires. Data will be encrypted and kept confidential and forwarded to the research team for clinical follow-up.

10.9 Perineal evaluation with ultrasound and clinical pelvic exam

In a subgroup of patients at specific sites, a structured clinical pelvic exam at 6-12 months after delivery will be done. The scar after tears/episiotomy will be measured, a pelvic organ prolapse quantification (POP-Q) score will be applied, and transperineal, endovaginal and transrectal 2D/3D ultrasound will be used to evaluate different parts of the pelvic floor. This exam will be accompanied by a questionnaire under development called (Q-SOPhIE, Questionnaire on Symptoms of Obstetric Perineal tears).

10.10 Pregnancy register and patient register

Data on several background variables, a number of outcome variables, and mode of delivery, episiotomy, and OASIS in a subsequent pregnancy will be collected from the Pregnancy Register. Data on outcomes regarding pelvic floor function may be collected from the Patient register in a later sub-study.

11 Proceedings for Adverse Events

11.1 Definition of Adverse Events

11.1.1 Definition of Adverse Events

An Adverse Event (AE) is any untoward medical occurrence in a subject and which does not necessarily have a causal relationship with the allocated treatment. An AE can be any unfavourable and unintended sign, abnormal laboratory finding, symptom or disease temporally associated with the subject participating in the clinical study, whether or not related to the allocated treatment.

11.1.2 Definition of Serious Adverse Events

Each AE is to be classified by the investigator as serious or non-serious. Seriousness is not defined by a medical term; it is a result or an outcome. An AE is defined as a Serious Adverse Event (SAE) if it:

- results in death
- is life-threatening
- requires admission to an intensive care unit
- results in persistent or significant disability/incapacity
- other medically important event

11.2 Assessment of Adverse Events

11.2.1 Assessment of Intensity

Each AE is to be classified by the investigator as mild, moderate or severe.
Mild: Acceptable. The subject is aware of symptoms or signs, but these are easily tolerated.
Moderate: Disturbing. The AE is discomforting enough to interfere with usual daily activities.
Severe: Unacceptable. The subject is incapable of working or performing usual daily activities.

11.2.2 Assessment of Causality

Unlikely: The event is most likely related to an aetiology other than the allocated treatment.
Possible: A causal relationship is conceivable and cannot be dismissed.
Probably: Good reason and sufficient documentation to assume a causal relationship.

11.3 Methods for Eliciting Adverse Events

AEs are spontaneously reported by subject, or reported by subject to study personnel during study visit or other visits at the participating the clinic, or by laboratory test results. Events will be registered when reported in the CRF AE form by date, time, symptoms and course of events.

11.4 Reporting of Adverse Events

All AEs will be rated as serious or non-serious and the causality will be assessed. Only AEs classified as serious (SAEs) will be recorded in the CRF. AEs reported in the questionnaire at 2 months' follow-up do not need separate recording in the CRF. SAEs will be reported by the investigator to the sponsor within 72 hours after the SAE has been communicated to the investigator. Follow-up information describing the outcome of the SAE and actions taken will be reported as soon as available.

11.5 Follow-up of Adverse Events

For all AEs, the subject will be followed until either the AE has ceased or until the subject is under professional medical care and a potential causality between the study treatment and the AE has been assessed.

12 Statistics and Data Management

12.1 Data Management

Data will be entered electronically from the Pregnancy register and from the questionnaires into the database. Data from the CRF will be entered manually into the database, until an eCRF has been developed.

12.2 Statistical Analysis

Descriptive statistics will be used to characterize the groups of individuals recruited to the study to investigate comparability of the two groups at baseline. T-tests and Chi-square tests will be used depending on variable characteristics.

Data will be analysed both by intention to treat and per protocol. The primary analysis will comprise intention-to-treat comparisons between the intervention group and the control group for both primary and secondary maternal and fetal outcomes. Results will be presented as absolute prevalence (rate of OASIS) or measurement (post-partum haemorrhage in millilitres), and after univariable and multivariable logistic regression analysis as odds ratios with 95% confidence intervals. The multivariable logistic regression models will adjust for possible confounders/effect modifiers such as maternal Body Mass Index (BMI) (>30), operator skills (specialist or not), long duration of labour >12 hours, epidural and use of oxytocin expressed as binary variables.

Secondary analyses will compare secondary outcomes using comparison of test of proportions, t-test and logistic regression depending on variable characteristics in the research questions. Outcomes based on evaluation scores (Wexner score and Birth Satisfaction Scale) will be analysed by non-parametric

tests (Mann-Whitney, Rank sum or Wilcoxon two unpaired samples) but also paired analyses for change over time (up to 5 years after delivery) in the subgroups using Sign test.

12.3 Determination of Sample Size

Primary outcome variable is prevalence of OASIS in the intervention group (lateral episiotomy) compared to the control group (no episiotomy). The average prevalence of OASIS in operative vaginal delivery in all women (not only non-parous women) was 12.4% in Sweden according to the Medical Birth Register in 2015. At Danderyd Hospital, the prevalence of OASIS has varied between 14 and 18% in primiparous women. In normal vaginal delivery, the prevalence of OASIS is 6-7% in primiparous women in Sweden. A reduction of OASIS from 12.4% to 6.2% ("normal delivery rate") can be detected with 80% power and 5% risk of alpha-error (p-value <0.05) with 350 women in each group using Chi-square test comparing two independent proportions in a two-sided test (1.5% loss of follow-up). A reduction to 7.8% is clinically valuable, thus a sample size of 694 women in each allocation group is needed. Total number of patients are 1400 women. We will perform a first interim analysis after 350 randomized women, to detect a possible reduction from 12.4% to 2.5% with 80% power and p-value <0.01, and a second interim analysis after 700 randomized women, to detect a possible reduction from 12.4% to 6.2% with 80% power and p-value <0.05. We are planning at least three sites. Depending on the size of the delivery ward, each site will contribute with approximately 5% of non-parous women giving birth vaginally (70-200 patients annually). Inclusion rate is expected to be 3 patients/week at a site with 300 annual vacuum extractions in non-parous women, if 50% of women accept participation.

13 Quality Control and Quality Assurance

13.1 Source Data

The requirements regarding information in the medical records follows the “Patientdatalagen” (SFS 2008:355) and the coming General Data Protection Regulation (from May 2018). Information that is of importance for the wellbeing and care of the patient, must be recorded in the medical records. The following study specific information should also be recorded:

- Study title and a brief description of the study in terms of intervention and assessments
- Date when patient information was given and when signed Informed Consent was obtained
- Subject randomization number
- Medically responsible study doctor, with contact details

Details and information that is study specific and of no interest for the medical care of the subject can be recorded in the CRF and other documents and may be considered as source data. Prior to study start the expected location of source data (e.g. medical record notes, CRF, work sheets), must be identified and documented. This will be done by completing a site-specific Source Data List.

13.2 Monitoring

The Sponsor will appoint an independent monitor for quality control of the study. Monitoring will be performed before, during and after study completion in accordance with the International Conference of Harmonization Good Clinical Practice (ICH GCP) guidelines. The extent of monitoring will be described in a monitoring plan, which will be approved by the Sponsor. Study conductance, source data, adherence to the study protocol and ICH GCP will be monitored.

14 Direct Access to Source Documents

The Investigator(s) will permit study-related monitoring, providing direct access to source data/hospital records. The Investigator verifies that each patient has consented in writing to direct access to the original source data/hospital records using written patient information and signed Informed Consent. During the monitoring, the data recorded in the CRFs by the Investigator will be controlled for consistency with the source data/hospital records by the study monitor (source data verification). The monitor will sign a secrecy agreement.

15 Ethics

15.1 Independent Ethics Committee

It is the responsibility of the Investigator to obtain approval of the study protocol/protocol amendments, the subject information and the Informed Consent from the Independent Ethics Committee (IEC) before enrolment of any subject into the study.

15.2 Ethical Conduct of the Study

The study will be performed in accordance with the protocol, ICH GCP, and the ethical principles of the World Medical Association (WMA) Declaration of Helsinki (as amended by the 64th WMA General Assembly, Fortaleza, Brazil, October 2013).

15.3 Risk - benefit assessment

Childbirth is associated with pain and discomfort, which may increase with an episiotomy as well as with a perineal injury. An estimated 80% of women sustain at least a 2nd degree perineal injury in operative vaginal delivery, which is similar in size to a lateral episiotomy. Thus, the risk of pain and discomfort is similar in both allocation groups. Negative sensations are reduced by routine local anesthesia. The risk of long term pain is not known, and will be assessed.

The questions in the questionnaires in follow-up are private in nature and can be perceived as psychologically disturbing or intrusive. Information about the importance of the answers before distribution may reduce discomfort.

Benefits of study participation could be a standardized anesthetic routine before the vacuum extraction, a standardized perineal support, and a standardized follow-up including a contact person at the research clinic, and an optional follow-up visit at 6 months after delivery. In clinical routine, there is only follow-up of third-fourth degree tears.

15.4 Subject Information and Informed Consent

It is the responsibility of the Investigator, or a person designated by the Investigator, to provide each subject with full and adequate verbal and written information about the objectives, procedures and possible risks and benefits of the study. All subjects should be given the opportunity to ask questions about the study and should be given sufficient time to decide whether to participate in the study or not.

The subjects will be notified of their voluntary participation and of their freedom to withdraw from the study at any time and without giving any reason. Subjects must also be informed that withdrawing from the study will not affect their future medical care, treatment or benefits to which the subject is otherwise entitled.

The Investigator, or a person designated by the Investigator, is responsible for obtaining written Informed Consent from all subjects prior to enrolment in the study. The Informed Consent Form must be signed and dated before any study-specific procedures are performed. The Investigator should file the signed Informed Consent Forms in the Investigator's File for possible future audits and inspections. A copy of the subject information and the Informed Consent Form should be given to the subject.

16 Data Handling and Record Keeping

16.1 Case Report Forms

Case Report Forms (CRF) will be provided for the recording of all data. The Investigator is responsible for ensuring the accuracy, completeness, legibility and timeliness of the data recorded in the CRFs.

16.2 Record Keeping

To enable audits and evaluations by the Sponsor, the Investigator shall keep records (essential documents) of the study for at least 10 years after end of the study. This includes any original source data related to the study, the subject Identification log (with subject numbers, full names and addresses) and the original signed Informed Consent Forms.

The Sponsor is also, as per ICH GCP-requirements, responsible for archiving their part of the study documentation.

17 Financing and Insurance

This is a non-commercial study financed by research grants. Subjects in the study are covered by the Patient Insurance (LÖF).

18 Publication Policy

The results from the study will be published in peer reviewed medical journals. Furthermore, information about the study will be publicly accessible in a clinical trial registry (www.clinicaltrials.gov).

19 Supplements

19.1 Amendments

No change in the study procedures shall be effected without the mutual agreement of the Investigator and the Sponsor (except where necessary to eliminate an immediate hazard to subjects). All changes of the final study protocol must be documented by signed protocol amendments. Any substantial changes to the design or procedures of the study should be reviewed and approved by the IEC before implementation.

19.2 Personnel Information

It is the responsibility of the Investigator to ensure that all personnel involved in the study are fully informed of all relevant aspects of the study, including detailed knowledge of and training in all procedures to be followed.

20 References

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21 Signed Agreement of the Study Protocol

"I agree to the terms of this trial protocol. I will conduct the study in accordance with the procedures specified in the protocol, the ethical principles in the latest version of the Declaration of Helsinki and ICH GCP."

Principal Investigator

Name

Signature

Date

Coordinating Investigator
Sophia Brismar Wendel, MD PhD
Department of Women's Health, Danderyd Hospital

Signature

Date

Sponsor
Sophia Brismar Wendel, MD PhD
Department of Women's Health, Danderyd Hospital

Signature

Date

22 Appendices

22.1 Schedule of Investigational Events

	Before delivery	Shortly after delivery	At the maternity ward	Follow up 2 months	Follow up 6 months	Follow up 12 months	Follow up 5 years	Follow up 10 years
Information	x							
Informed consent	x							
Inclusion/exclusion criteria	x							
Randomization	x							
Episiotomy/no episiotomy	x							
Background variables	x[1]	x[2]						
Data from Pregnancy register (primary and secondary endpoints)		x[3]	x[4]				x[5]	x[6]
Data from SNQ on neonatal outcome (secondary endpoints)			x					
Questionnaire BR 1[7]			x					
Questionnaire FSFI+FSDS			x			x	x	
Questionnaire Euro-Qol-5D			x			x	x	
Questionnaire BSS-R				x				
Questionnaire CEQ 2.0				x				
Questionnaire BR 2[8] (8 w)				x				
Questionnaire BR 3[9] (1 y)						x	x	
Ultrasound evaluation					x			
POP-Q score					x			
Measurements of scar					x			
Questionnaire Q-SOPhIE					x			
Serious adverse events		x	x	x	x	x		

[1] maternal age, country of birth, weight at registration in the antenatal clinic and height
[2] use of Oxytocin, use of regional or local anesthesia, birth weight, head circumference, birth length, second stage duration, indication for vacuum extraction, fetal position and station, operator skills, number of pulls, use of sequential instruments
[3] perineal injury, blood loss, and neonatal outcomes (Apgar score, umbilical artery pH and birth related diagnosis)
[4] birth experience, duration of hospital stay
[5] mode of delivery, episiotomy, and OASIS in a subsequent pregnancy
[6] mode of delivery, episiotomy, and OASIS in a subsequent pregnancy
[7] ”Uppgifter om hälsa före graviditeten”
[8] ”Din värdering av behandlingen av förlossningsbristningen (ca 8 veckor)”
[9] ”Din värdering av behandlingen av förlossningsbristningen (ca 1 år)”

22.2 Standard Operating Procedures

Lateral episiotomi vid sugklocka
Primär suturering av bristningar och klipp

22.3 Questionnaires

Uppgifter om hälsa före graviditeten
Din värdering av behandlingen av förlossningsbristningen
Female Sexual Function Index (FSFI)
Female Sexual Distress Scale (FSDS)
Birth Satisfaction Scale (BSS-R)
Childbirth Experience Questionnaire (CEQ 2.0)
Euro-QoL-5D
Questionnaire Q-SOPhIE