luzerner kantonsspital
LUZERN SURSEE WOLHUSEN

Project Title: A pilot study of cervical stiffness assessment with an aspiration-based device in high-risk pregnancies for preterm birth

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Research legislation: Ordinance on human research with the exception of Clinical trials (HRO) [1].

Type of Research Project: Research project involving human subjects

Risk Categorisation: Risk category A

Sponsor

Principal investigator

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PROTOCOL SIGNATURE FORM

Study Title	A pilot study of cervical stiffness assessment with an aspiration-based device in high-risk pregnancies for preterm birth

The project leader has approved the protocol version 5, 7th October 2024 *and* confirms hereby to conduct the project according to the protocol, the Swiss legal requirements [1, 2], current version of the World Medical Association Declaration of Helsinki [3] and the principles and procedures for integrity in scientific research involving human beings.

Sponsor:

Principal investigator:

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GLOSSARY OF ABBREVATIONS

BASEC	*Business Administration System for Ethical Committees*
CCI	*cervical consistency index*
CI	*cervical insufficiency*
CRF	*Case report form*
CI	*cervical insufficiency*
CSI	*cervical stiffness index*
EKZ	*Ethikkommission Zentralsschweiz*
FMF	*Fetal Medicine Foundation*
FOPH	*Federal Office of Public Health*
HRA	*Human Research Act*
HRO	*Ordinance on Human*
ICF	*Informed Consent Form*
PI	*Principal investigator*
PIS	*Patient Information Sheet*
PPROM	*preterm premature rupture of membranes*
PPS	*preterm parturition syndrom*
PTB	*preterm birth*
PTL	*preterm labour*
ROI	*region of interest*
Wp	*weeks of pregnancy*

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1 BACKGROUND AND PROJECT RATIONALE

Preterm birth (PTB), defined by birth before 37th weeks of pregnancy (wp), is a public health concern and the most relevant risk factor for neonatal morbidity and mortality (4). The prevalence of PTB is between 5 to 9% in Europe. 40% occurs before 33 wp, whereas neonatal morbidity and mortality are related inversely to the gestational age (5). Despite advances in antenatal pregnancy care, the spontaneous preterm birth trend could not be reduced significantly in most countries except for black women (6, 7, 8).
A combination of symptoms leading to PTB, summarized as the preterm parturition syndrome (PPS), involves multiple etiologies and pathological processes (6, 9, 10). Among those cervical insufficiency (CI) is a syndrome with a prevalence of around 1%, which is preterm cervical ripening without uterine contractility (9). Usually, recurrent pregnancy loss in the mid-trimester, bulging membranes without contractions, prior cervical surgery (conization, repeated cervical dilation associated with termination of pregnancy or missed abortions), or congenital cervical disorders (i.e., hypoplastic cervix, DES exposure in utero, congenital connective tissue disease) are related to cervical insufficiency (9, 11).
Different interventions exist to reduce the preterm birth risk significantly. Vaginal progesterone use reduced the risk of recurrent preterm birth by up to 55% (12-18), even though the benefit was not equal for all women for reasons not well understood (12, 16, 17). Cerclage has been shown beneficial in pregnancies with a short cervix of less than 25 mm and a history of preterm birth in single pregnancies (12, 15) but stayed without benefit in low- or medium-risk pregnancies (19, 20). Neither cerclage nor progesterone was efficient in multiple pregnancies (21, 22). Nevertheless, the outcome was comparable for both interventions (15). Cervical pessary, introduced in the 1950s, showed some conflicting results in pregnancies with a cervical length less than 25 mm, while Goya et al. stated the benefit in reducing the preterm birth rate before 34 wp (23, 24, 25).

However, prediction of CI in an ongoing pregnancy remains difficult unless there is a previous history of recurrent pregnancy loss in the mid-trimester or a history of extremely premature birth (10, 12). So far, cervical length measurement by ultrasound, which is inversely related to the risk of preterm birth, digital cervical assessment, and fibronectin testing are used to predict the preterm risk, but low sensitivities (sn < 40%) make them unsuitable as a screening test (12, 26, 27). Concluding we need more accurate methods to estimate preterm birth risk. Therefore, recent research of the mechanical tissue property of the cervix may be promising, as cervical shortening is an equation between different forces and its mechanical property (28). Internal uterine pressure represents opening force pressure, whereas the lower abdomen or the pelvic floor represent external closing forces. The longitudinal deformation in the length of any material after applying a predefined pressure can be described by a percentage change in longitude or called a strain, which can be a positive or negative (tensile or compressive strain). The mechanical property of any material depends on the strain, the applied force, and the stressed area. This behavior can be visualized by stress-strain curves. So, either the mechanical pressure on a stiff cervix is significantly high, or the stiffness of the cervix is relevantly low to result in a cervical shortening. The cervical changes before, during, and after labor reflect its dynamic character. Collagen fibers degradation, distribution, cross-link density, organization, and composition of glycosaminoglycans explain this dynamic histologically (29, 30). So far, mechanical cervical behavior is analyzed by ultrasound, elastography, and an aspiration-based device.

Cervical tissue deformability or cervical consistency index (CCI) was calculated using the percentage change of cervical length before and after applying manual pressure by a hand-held transvaginal ultrasound (31). This ratio showed a detection rate of spontaneous PTB of 100% before 32 wp decreasing to 79% before 37 wp, respectively, for a 10% screen-positive rate. The detection rate by only measuring the cervical length was less accurate, such as 33% and 26%, respectively, for a 10% screen-positive rate.

Elastography analyzes quantitative tissue deformability. Image analysis algorithms track many points at any time during the pushing and retracting of the hand-held ultrasound probe. Whereas a perfectly rigid organ would show a stable position of these points during motion, a soft organ would display broad changes in distance between the points, also called strain (28). Elastography assessments showed significant differences between cervical strains of women with PTB versus women with term birth (32-34). A reduced cervical length or advanced gestational age was associated with higher strain (32-34). The lack of standardization of applied pressure or strain depending on different ROI stays a limitation of this methodology. Others used shear wave elastography which calculates strain using a high-frequency ultrasound pulse at a steady-state to avoid these limitations (35, 36). Significant differences in cervical elasticity in patients with high-risk factors for preterm birth and women who delivered preterm are found (35, 36).
Another recent technique to reduce the mentioned constraints is an aspiration-based device, the Pregnolia System, which creates negative pressure to deform a tissue until a prespecified distance. The closing negative pressure (closing pressure or p_{cl}) or the cervical stiffness index (CSI), is measured perpendicular at a specified region of the ectocervix, for instance at 12 o'clock, at a tissue deformation of up to 4 mm. A lower CSI is associated with reduced stiffness (28). The intra-observer and inter-observer variability compared between CSI measurements of 5 silicone cervix models were as high as 3.4 % (37). Digital palpation was unreliable (37). Different ROI of the cervix showed different standard deviations, whereas the smallest standard deviation was at 12 o'clock (38). CSI between non-pregnant and pregnant women or between the 1st and 2nd trimesters showed significant differences, but not between the 2nd and 3rd trimesters (38, 39). So far, 100 pregnant patients have not shown any adverse effects (pain, discomfort, bleeding) (38, 39) proving a low risk for use in clinical practice. Other ongoing studies including more than 1000 executed measurements have neither reported any serious adverse events related to the device according to the Pregnolia System provider (clinicaltrials.gov: NCT02037334; NCT05477381; NCT05267717; NCT05200117). One pilot study carried out on high-risk pregnant women showed significantly lower cervical stiffness in the history-indicated cerclage group compared with a low-risk control group (40). But so far, sparse data on high-risk patients is available.
The current pilot investigation aims to assess cervical stiffness in women at high risk of premature birth who will be offered treatment with progesterone. According to international guidelines, a cervical length less or equal to 25 mm until the 24th wp is considered a high risk for preterm birth, and therefore progesterone treatment and close follow-up are initiated after ruling out other aetiologies for a short cervix such as contractions (41-44). In clinical practice, a cervical length inferior or equal to 25 mm is generally used until 34 wp as a cut-off for a more frequent follow-up to assess preterm birth risk. Nevertheless, the 5th centile is gestational age-dependent and corresponds to a cervical length of 24,7 mm at 25 wp (45). Primarily we want to assess the cervical stiffness of pregnant women with a short cervix inferior to or equal to 25 mm before 32 wp and before the start of progesterone treatment. Secondarily we want to measure the effect of progesterone treatment on cervical stiffness during follow-up visits. For the assessment of the cervical stiffness, we will use the Pregnolia System (CE-marked device).

2 PROJECT OBJECTIVES AND DESIGN

2.1 Hypothesis, primary and secondary objectives

To date, no accurate prediction of preterm birth risk is possible. An aspiration-based device is a promising tool for measuring cervical stiffness index and possibly predicting outcomes. So far, sparse data on cervical stiffness in high-risk patients is available. Additionally, the effect of progesterone treatment on the mechanical cervical property is not well understood. We want to analyze cervical stiffness in patients with a short cervix ≤ 25 mm between 16weeks 0 days and 32weeks 0 days of pregnancy before the initiation of progesterone treatment.

This study is an exploratory pilot study without any formal hypotheses. The aim is to obtain some data for an initial characterization of the distribution of the Cervical Stiffness Index (CSI) in the defined population of pregnant women with short cervix before initiation of progesterone treatment and within a month after start of progesterone treatment.
This may serve as a basis for planning of larger studies in order to investigate the relationship between occurrence of cervical stiffness, course of cervical stiffness under progesterone treatment and the impact on birth and neonatal outcomes.

Primary objective

The primary objective is an initial characterization of the distribution of the median Cervical Stiffness Index (CSI, in mbar), corresponding to the median of three consecutive measurements at each presentation, at pregnant women of gestational age between 16weeks 0 days and 32weeks 0 days with a cervical length ≤ 25 mm before the initiation of progesterone treatment.

Secondary objectives

- At each presentation three consecutive CSI measurements will be carried out and as a secondary objective the first, the highest, lowest and mean measurement will be analyzed for each secondary outcome.
- Evaluate Cervical Stiffness Index 1, 2, 3 (CSI, in mbar) at follow-up visits on day 10-14 and on day 24-28 after initiation of progesterone treatment, which is defined as day 1; further follow-up is not mandatory, but possible
- Determine a first estimate of the correlation of the initial CSI and CSI changes with birth outcome (gestational age at birth)
- Determine a first estimate of the correlation of CSI with cervical length (longer cervical length stiffer?)
- Determine first signals for potential associations of CSI with additional treatments for preterm birth (tocolysis, cerclage, pessary)
- Determine first signals for potential associations of CSI with neonatal outcome (birth weight, APGAR, arterial pH, admission to neonatal intensive care)
- Safety objective: safety of the device, by assessing incidence, severity, and seriousness of device-related adverse events (discomfort, bleeding, lesion, irritation).

2.2 Variables for primary and secondary endpoints

Primary endpoint: Median Cervical stiffness Index (CSI, in mbar) measured before progesterone treatment start

Secondary endpoints:

- Cervical Stiffness Index 1, 2, 3 (first, max, min, mean) (CSI, in mbar) at follow-up visits
- Cervical length at study entrance and during follow-up
- Additional treatments during pregnancy (tocolysis, cerclage, pessary)
- Birth outcome (gestational age at birth)
- Neonatal outcome (birth weight, APGAR, arterial pH, admission to neonatal intensive care)
- Safety outcome: Device-related adverse events, such as discomfort, bleeding, lesion, irritation or serious adverse events (incidence, severity, and seriousness).

2.3 Project design

A prospective, observational, non-interventional, post-market, single-center pilot study at the cantonal hospital of Lucerne will be carried out to answer the primary and secondary objectives. Patients presenting at or referred to our prenatal care will be included into this study.
CSI measurements, general, clinical, laboratory, history and pregnancy data relevant for the study objectives will be collected and recorded under a unique study ID under which all data will be held in-line with the Data Protection Act in REDCap. Patient data corresponding to the study ID will be only known to the principal investigator and protected with a password on the hospital server.

3 PROJECT POPULATION AND STUDY PROCEDURES

3.1 Project population, inclusion, and exclusion criteria

Project population
We are studying pregnant patients older then 18 years of age and pregnant between 16w0d and 37w0d. We estimate the number of patients with a short cervix inferior or equal to 25 mm (<5th centile at 25 wp) opting for a progesterone treatment around 10-20 at our center per year. For our pilot study we want to include 10 patients. After inclusion of the first 10 patients we want to continue our pilot study until latest June 2025.

Inclusion criteria at study entry

1. Informed consent signed by the participant
2. Pregnant women ≥ 18 years of age.
3. Singleton gestation
4. Weeks of pregnancy between 16 weeks 0 days and 32 weeks and 0 days
5. Cervix ≤25 mm (inferior to the 5th centile at 25 wp according to Salomon et al. (45))
6. No regular contractions
7. Planned progesterone treatment

Exclusion criteria at study entry

Any of the following criteria will lead to the exclusion of the subject:

Cognitively impaired adults
Cerclage or pessary on place
Ongoing progesterone (if continued or started after 13+0 wp) treatment
Multiple pregnancies
Placenta praevia totalis with hemorrhage (irrespective of severity)
Vasa praevia
Light bleeding (if the bleeding can be stopped it is no longer an exclusion criterion)
Heavy vaginal bleeding, hematoma or chorioamniotic membrane separation
Rupture of membranes (exclusion with ROM+ test if PPROM is suspected)
History of cervical surgery only if visible scaring at 12 o'clock
Cervical dilation ≥ 3 cm
Signs of chorioamnionitis
Symptomatic genital infection
Known carrier of HIV or Hepatitis B/C
Fetal malformations

3.2 Recruitment, screening, and informed consent procedure

Patients presenting with or referred to our unit for any reason with a finding of a cervix of ≤25 mm meeting the inclusion and excluding the exclusion criteria will be recruited to the study after

informed consent is given. The same procedure can be also applied to patients presenting emergently and fulfilling the study criteria without delay if informed consent can be obtained. Patient recruitment is planned over a period of two years after study start.

Study recruitment will only take place at our fetomaternal center. But referral doctors will be informed about the study purpose and procedure in case one of their patients meet the study criteria and has interest to participate. Written and oral informed consent will be taken from all patients agreeing with the study protocol by the principal investigator (PI) or an appropriate delegate. If time to consider study participation is needed, it will be respected. In that case medical treatment can be delayed upon the patient's agreement by a few days usually without negative consequence, as treatment effect is based on its continuos use. No obligation for study participation and the possibility of later withdrawal without giving any reason will be explained to all participants. A copy of the signed Informed Consent Form (ICF) and the approved Patient Information Sheet (PIS) will be given to the study participant. The original signed and dated consent form will be retained in a study file after having been scanned into the electronic patient file. Study participation is voluntary, and no payment is planned for participation. Secondarily the Pregnolia probe and System will be offered for free to the study participants.

3.3 Study procedures

A short cervix ≤25 mm can occur any time in pregnancy. It can be a coincidental finding during routine check-ups, or a woman may be presenting with symptoms like for instance lower back or abdominal pain or vaginal pressure. A short cervix of ≤25 mm is a risk factor for preterm birth if diagnosed before 34 weeks of pregnancy. Therefore, in such situations we routinely assess the fetus and the placenta, and we carry out bacterial genital swabs, urinary and laboratory tests. Additionally in the study, we will measure the cervical stiffness index (CSI). The patient will be in lithotomy position; a typical gynecological examination position and a vaginal speculum will be inserted. After visualization of the anterior cervical lip the Pregnolia probe will be placed at 12 o'clock and a weak vacuum will be applied deforming the cervical tissue into the probe tip by a fixed distance of 4 mm. The vacuum needed to deform the cervical tissue inside the probe is a proxy value for the cervical stiffness, is expressed in mbar and is called Cervical Stiffness Index (CSI). The stiffer the cervical tissue, the higher the vacuum needed to deform it. The vacuum will be created three times at the same place giving three values before removing the probe and completing the examination. The three values will be noted into the patients' file. An additional 5-10 minutes is calculated for this measurement during routine obstetric care. Details about the Pregnolia System can be also found under the following link: https://en.pregnolia.com/gebrauchsanweisung.

The cervical length measurement will be carried out according to the criteria of the fetal medicine foundation (FMF London). All designees, the PI and the Sponsor will have been taught to use the Pregnolia System by the time of study start.

If during follow-up there will be a need to apply a cervical cerclage or pessary, it will be discussed with the patient and applied without delay. A cerclage or pessary placement is a reason for exclusion from further follow-ups, as both may influence the cervical CSI. No disadvantage will arise for any patients by study participation or later withdrawal. The study will be carried out over a period of two years.

Assessment schedule

Enrolment

Routine:

Inform patient about study, purpose, risks, voluntary participation, the device, the right of withdrawal at any time and no disadvantages in case of study participation or disapproval

Gather informed consent signature, thereafter, enroll subject into the study

Demographic data (age, race)
Chronic medical disease and obstetrical risk factors for preterm birth (gravidity, parity, D&C, cesarean, history of preterm birth or pregnancy loss > 12 wp, history of cervical conization)
Reason for check-up (routine, symptoms at presentation)
Gestational age at study enrolment
Bacterial samples (yes/no, if yes which bacteria)
Bacterial vaginosis (yes/no)
Preexisting prematurity treatments (yes/no, if yes which treatment)
Ultrasound-based measurement of cervical length

Additional assessment for the study objectives:
Acquire 3 consecutive CSI measurements with the Pregnolia System at 12 o'clock position on the squamous epithelium of the cervix, taking care to keep the probe tip in exactly the same position (study objective: first measurement; second and third measurement for documentation)
Record day, hour, minute of the CSI measurement session
Discomfort and side-effect assessment of the CSI measurement (taking care of distinguish between discomfort of the speculum insertion and of the measurement)
Record adverse events (discomfort, bleeding, lesion, irritation) or if measurement is not possible and the reason for it
Record remarks.

Follow-up

Routine
At least two follow-up visits every 10-14 days, further follow-ups are optional
Record obstetrical data if anything new arrives (hospitalization, tocolytics, lung maturation, cerclage, pessary)
Speculum examination and CSI measurement
Ultrasound measurement of cervical length

Additional assessment for the study objectives:
Acquire 3 consecutive CSI measurements with the Pregnolia System at 12 o'clock position on the squamous epithelium of the cervix, taking care to keep the probe tip in exactly the same position
Record day, hour, minute of the CSI measurement session
Discomfort and side-effect assessment of the CSI measurement (taking care of distinguish between discomfort of the speculum insertion and of the measurement)
Record adverse events (discomfort, bleeding, lesion, irritation) or if measurement is not possible and the reason for it
Record remarks.

Postpartum (data collection in absence of the participant)

Check and record other interventions and/or treatments if occurred during pregnancy and at birth (hospitalization, tocolytics, lung maturation, cerclage, pessary)
Delivery information (GA at delivery)
Newborn data and morbidities (APGAR, pH, weight, admission to NICU during the first 7 days)
Record adverse events *(discomfort, bleeding, lesion, irritation)*
Record remarks.

Graphical assessment schedule

Time (days)	0	+10-14	+24-28	(+38-42)	(+xx-xx)	postpartum
Visit	Study inclusion	1st follow-up	2nd follow-up	Optional 3rd follow-up	Optional further follow-up	In absence of the patient
oral and written Information	+					
Written consent	+					
inclusion-/ exclusion criteria	+					
Demograophic data	+					
Medical data	+					
Obstetric data	+					
Study withdrawal or discontinuation	(+)	(+)	(+)	(+)	(+)	(+)
Clinical exam and CSI measurement	+	+	+	(+)	(+)	
Safety outcome	+	+	+	+	+	
Laboratory results	+	+	+	+	+	
Treatments	+	+	+	(+)	(+)	
Birth data						+
Neonatal data						+
Remarks	+	+	+	+	+	+

3.4 Withdrawal and discontinuation

If a patient withdraws informed consent she will be excluded from the further study, which will be indicated in the CRF. Data which has been collected until that moment will be utilized.

Another reason for discontinuation from further measurement follow-ups is an increasing shortening of the cervical length requiring additional treatments with a pessary or a cerclage due to treatment change, which makes CSI comparison no longer possible. Discontinuation applies also in case of a PPROM or in case of repetitive, strong bleedings of the utero-placental interface. Furthermore, a very short or soft cervix might make the CSI measurement impossible, or the specular examination might be undesirably uncomfortable which are other reasons of discontinuation. In these cases, all data will be used. The latter reasons or if examination is impossible will be noted as a remark and will be mentioned in the final analysis.

3.5 Identification and description of the medical device for cervical stiffness measurement

Pregnolia System, composed of the Pregnolia Control Unit (REF 100058) and Pregnolia Probe (REF 100026).
Manufacturer: Pregnolia AG[redacted]
The device is composed of a single-use sterile probe and a reusable control unit. The Pregnolia System is designed for use in a gynaecological examination room

equipped for speculum-based vaginal examinations.
Description of use see paragraph 3.3.
See instructions for use:
https://en.pregnolia.com/gebrauchsanweisung

Labelling, supply (re-SUPPLY) and storage conditions

Pregnolia is a CE certified device, which has been manufactured and labelled in accordance with the applicable Swiss and European requirements, including but not limited to the MDR or MDD (which ever applies), ISO 13485:2016 and Good Manufacturing Practice Guidelines (GMP) in their current version.
Upon delivery of the the reusable control unit and the single-use sterile probes they will be identified and stored in a board in our outpatient prenatal clinic disposable only for the purpose of this study. If stored in a board then there is no special requirement for the storage. The device remains in the sole property of Pregnolia. The Device will only be used in the manner intended and only as described in written directions provided by the manufacturer Pregnolia AG.

Accountability of the Pregnolia device

The key for the locker, where the Pregnolia is stored will be available for the team of the prenatal outpatient clinic. All designees will get appropriately instructed about the protocol and how to use the Pregnolia unit only defined for use in this study. Every use will be recorded on a documentation sheet next to the Pregnolia device storage. Additionally, the LOT number of the Pregnolia probe will be documented for each patient in their file.

We will promptly notify Pregnolia upon becoming aware of the need for Device maintenance or repair with appropriate care within the littlest delay. The serial number, any date of reception, use, return or repair of the device will be documented on a documentation sheet located in the storage next to the Pregnolia device, which will be checked by the PI regularly.

Return of the device

At the completion of the Investigation the Institution will return to Pregnolia, the Device and all related materials. In case of any deficiency including malfunction, usability issues, or inadequacy in the information supplied by the manufacturer Pregnolia AG will be notified in the shortest delay.

4 STATISTICS AND METHODOLOGY

4.1. Statistical analysis plan

In this pilot study, 10 (an estimated 20 subjects after continuation of the study) subjects will be included for the analysis of the pilot study. We chose 10 (to around 20) subjects because it is a feasible number to recruit and is supposed to sufficiently support to exploratory aim to obtain some data for an initial characterization of the distribution of the Cervical Stiffness Index (CSI) and to receive feedback on how the investigation is perceived in the defined population of pregnant women. As recruitment has progressed, we would like to continue to recruit more subjects to broaden the initial data base meanwhile we will evaluate the so far collected data.

The Cervical Stiffness Index (CSI) is a continuous variable. Quantitative parameters will be described in terms of absolute values and changes from baseline by time point. Descriptive statistics will comprise median, interquartile range, minimum and maximum, mean and standard deviation and, where appropriate (especially for changes from baseline), 95% confidence intervals for the mean or median.

Qualitative parameters will be analysed utilizing frequency tables by time point and treatment.

Scatterplots or Box Plots may be used to visualize associations of CSI with some of the secondary endpoints. Evaluation of potential associations by measures of association or correlation coefficients will be purely exploratory.

4.2. Handling of missing data

The number of subjects who completed the study and discontinued from the study will be provided. A participant who will withdraw from the study will be asked for her reason and questions will be answered if desired. She has the right to withdraw without giving any reasons. As far as the reasons for study withdrawal are known they will be presented.

All available data will be included in the analysis and will be used to the largest possible extent. Missing data will not be imputed for the descriptive and exploratory evaluations. However, the potential impact of missing values will be discussed when the study is reported. If deemed necessary, sensitivity analyses will be performed.

5 REGULATORY ASPECTS AND SAFETY

5.1 Local regulations / Declaration of Helsinki

This research project will be conducted in accordance with the protocol, the Declaration of Helsinki [3], the principles of Good Clinical Practice, the Human Research Act (HRA) and the Human Research Ordinance (HRO) [1] as well as other locally relevant regulations. The Project Leader and the Sponsor acknowledge their due responsibilities.

5.2 Notification of safety and protective measures (HRA Art. 15, HRO Art. 20)

If, during the research project, circumstances arise which could jeopardise the safety or health of the participants or lead to a disproportionate relationship between the risks and burdens and the benefits, all the measures required to ensure protection are to be taken without delay.
The project leader and the sponsor are promptly notified (within 24 hours) if immediate safety and protective measures have to be taken during the conduct of the research project. The Ethics Committee will be notified via BASEC of these measures and of the circumstances necessitating them within 7 days.

5.3 Serious events (HRO Art. 21)

If a serious event occurs, the research project will be interrupted, and the Ethics Committee will be notified on the circumstances via BASEC within 7 days according to HRO Art. 21[1]. Therefore, the template to report safety events to the Ethics Committee on the swissethics webpage will be used (www.swissethics.ch).

5.4 Procedure for investigations involving radiation sources

Not applicable.

5.5 Amendments

As recruitment progresses, it will be evaluated whether an amendment to the clinical investigation plan is feasible and appropriate. Substantial changes to the project set-up, the protocol and relevant project documents will be submitted to the Ethics Committee for approval according to HRO Art. 18 before implementation. Exceptions are measures that have to be taken immediately in order to protect the participants.

[1] A serious event is defined as any adverse event where it cannot be excluded, that the event is attributable to the sampling of biological material or the collection of health-related personal data, and which:
a. requires inpatient treatment not envisaged in the protocol or extends a current hospital stay;
b. results in permanent or significant incapacity or disability; or
c. is life-threatening or results in death.

5.6 End of project

Upon project completion or discontinuation, the Ethics Committee will be notified within 90 days. Details about the storage of the study data are in paragraph 7.4.

5.7 Insurance

In the event of project-related damage or injuries, the Sponsor will be liable, except for damages that are only slight and temporary; and for which the extent of the damage is no greater than would be expected in the current state of scientific knowledge (Art. 12 HRO). As there is no specific need of a liability guarantee in this HRO study category A and the sponsor is working at the hospital, the hospital liability insurance is covering any damage or injuries if needed.

6 FURTHER ASPECTS

6.1 Overall ethical considerations

Measuring cervical stiffness is a promising recent method with a potential of closing the gap of predicting premature risk. Exploring data in low-risk populations exist and cervical stiffness measurement with the Pregnolia System is already offered at certain obstetrical offices and will be also offered in little time in our hospital on demand and self-cost of the patient (outside of the study protocol; some complementary insurances pay the costs), but data for best use in clinical practice is still missing. We need to have a deeper understanding to establish it in routine clinical care. We chose an observational study design to further increase knowledge in high-risk populations and finally open the floor for randomized clinical trials. The Pregnolia System has already been used in over 1000 pregnancies without considerable adverse events. Participation is voluntarily and examination is done during routine clinical care in patients already at risk for preterm birth with a possible desire to use this device and to improve clinical care for future pregnancies.

6.2 Risk-Benefit Assessment

Considering the exclusion criteria for study inclusion potential risks are minimized and will not differ substantially from routine clinical practice. High-risk patients for preterm birth may benefit from additional assessment of cervical stiffness, but main benefit will be reserved for future pregnancies such as the accuracy of the prediction of risk for prematurity and therefor decisions about the frequency of follow-up or therapy.
The cervical stiffness measurement is done with the Pregnolia System. It has been CE-marked by TÜV Süd. Part of the registration process included a risk-benefit analysis according to ISO 14971 of the Pregnolia System.
Careful application of the Pregnolia System according to the instructions for use should result in minimal risks for the patients. The instructions for Use can be found under the following link: https://en.pregnolia.com/gebrauchsanweisung.
Potentially, an irritation and sensitization of the mucosal tissue may happen. This may result in a spotting or a light bleeding, which can be easily treated by applying a light pressure with a soft swab. Light, self-limiting bleedings can be also caused by specula insertion or by manual palpation exams during usual obstetric or gynecological care. Besides, we will assess the discomfort and the side-effects after each measurement check-up. All possible complications and side-effects can be also found in the Instructions for Use.
The use of the Pregnolia System as specified in the Instructions for Use reduces the risk of potential complications. All doctors and designees will have received appropriate instructions for use before study start.

6.3 Rationale for the inclusion of vulnerable participants

Indeed, pregnant patients at risk for preterm birth have generally a certain vulnerability due to their clinical findings but our staff is trained to answer the demands of our patients. Additionally, the study aims to offer specifically patients at risk for preterm birth an improved prediction in the future.
Patient recruitment will only start after EKNZ has given study approval. The study protocol and the pseudonymous data storage will be explained to all eligible pregnant patients, who wish to enter the study. The study recruitment, screening and informed consent procedure is explained in chapter 3.2.

7 QUALITY CONTROL AND DATA PROTECTION

7.1 Quality measures

All designees and the principal investigator will be trained to do cervical stiffness measurements if no previous traning has been conducted. CSI measurements will be noted on a CSI documentation form, which is an additional template to the ICF, and will be scanned into the patient's file after every visit.

Additionally, the electronic data capture (EDC) system REDCap will be used in this study, a secure web application for building and managing online surveys and databases. The EDC system REDCap is accessible via Webbrowser over the internet. [redacted] Furthermore, specific training for the use of REDCap will be provided. Plausibility rules and range-checks will be established to promote data quality. Furthermore, data will be reviewed and verified on a risk-based approach prior to data entry completion.

For quality assurance the Ethics Committee may visit the research sites. Direct access to the source data and all project related files and documents must be granted on such occasions.

7.2 Data recording and source data

Data recording is already described above. Basically, all data recordings will exist on the patient file which will be transferred to REDCap by the PI. Only the following persons will get access to the EDC system REDCap: the PI (writing and reading permission) and the Sponsor (writing permission on demand, reading permission). The database set up will be prepared by the PI and tested by the sponsor and or other medical leading staff of the women's department. The data entry, monitoring and data release will be done by the PI. Nevertheless, the sponsor may be involved any time.
Data will first be collected using electronic patient chart. All data is then transferred into the EDC system REDCap by the PI. CRFs and data entries will be kept current to reflect subject status at each phase during the course of study.

7.3 Confidentiality and coding

Project data will be handled with uttermost discretion and is only accessible to authorized personnel who require the data to fulfil their duties within the scope of the research project.
Study participants will not be identified in the CRF by name or initials or birth date. Instead, an encrypted identification number (code) will be used. Encrypted data will be exported from the EDC system by the study personal for analysis in statistic software.
For each enrolled study participant, an eCRF is maintained.
The patient identification list, which contains the person-identifying data (e.g., name) of each patient along with the assigned unique identifying number is stored on the hospital server under the password only known to the PI. This folder Data is only accessible to the study personnel according to their level of authorization. The PI, the sponsor, the medical chiefs of the women's department will have access to all data on demand whereas the statistician or research staff will only have access to encrypted data.

7.4 Retention and destruction of study data

The data will not be anonymized after statistical analysis. Electronic study data are archived in an encrypted form for a minimum of 10 years after study termination or premature termination of the clinical trial in an electronic archive maintained and controlled by the IT department of LUKS.
Source data and identification list will be stored in a locked archive room with limited access for a minimum of 10 years.

8 FUNDING / PUBLICATION / DECLARATION OF INTEREST

All study materials and procedures are part of routine clinical care in patients with a risk of preterm birth except the Pregnolia System, which will be provided by the Pregnolia company. The written contract with the Pregnolia company can be found attached to this protocol.

All contributors to the study have no conflict of interest to declare and there is no financial interest to report.

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