Effect of
history-indicated early treatment with Arabin cervical pessary
versus
expectant management treatment with rescue cerclage placement in cases with cervical shortening
in singleton pregnancies at high-risk for preterm birth on childern's long-term survival
without neurodevelopmental disability
THE PROSPECTIVE RANDOMIZED PROMETHEUS-TRIAL

Code: PROMETHEUS-Trial

Version 1.3 (January 2018)

Summary

Description: Clinical Trial with a sanitary device in its authorized using conditions.

Title: **Effect of history-indicated early treatment with Arabin cervical pessary versus *expectant management treatment with rescue cerclage placement in cases with cervical shortening* in singleton pregnancies at high-risk for preterm birth on childern's long-term survival without neurodevelopmental disability**

The Prometheus-Trial

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Sanitary device: The Arabin cervical pessary, which is CE-certified for preventing SPB (CE 0482 / EN ISO 13485: 2012 + AC:2012 annex III of the council directive 93/42 EEC).

Main objective: To assess the impact of a prophylactic treatment with a cervical pessary in women at high risk of spontaneous Preterm Birth (PTB) due to a history of previous preterm deliveries and/or a history of previous cervical surgery (conisation) on the children´s survival without neurodevelopmental disability at the age of 3. Recruitment will be offered to all women at 12+0 -16+0 weeks of gestation with status after PTB in previous pregnancies and/or conisation.

Study design: Prospective Open-label Multicentre International Collaborative Randomized Controlled Trial, in parallel groups, based on intention to treat comparing the early placement of a cervical pessary with standard care management in cases of a singleton pregnancies at high-risk for PTB. The standard care arm (control group) shall receive a rescue cerclage in cases with cervical shortening. Therefore, serial cervical length measurements should be conducted onward the 12+0 week every 4 weeks.

Main outcome: Children´s survival without neurodevelopmental disability at 3 years of age.

Study population: The study will be proposed to women with a singleton pregnancy at 12+0 – 16+0 weeks of gestation and a history of at least one previous preterm delivery and/or a history of previous cervical surgery attending the reference hospital and who do not fulfil the exclusion criteria. In this context, cases with previous preterm birth should only be considered, when birth occurred before the 34+0 week of pregnancy.
The patients will be informed of the intended therapeutic effect and possible side effects. If they agree and after obtaining their informed consent, they will be randomised according to either cervical pessary placement up to 37+0 weeks (= pessary group) or expectant management according to standard care and a

McDonald cerclage placement as soon as a cervical shortening below 25 mm is diagnosed (=control arm).
Hereby, patients of the control arm shall receive serial cervical length measurements by transvaginal ultrasound (TVS) every 4 weeks started at 12+0 weeks.
A cerclage may be indicated when the cervical length is below 25 mm.[1] (s. consort-diagram).

Sample size:
For sample size calculation, we assume a combined event rate for the primary outcome (long-term survival without neurodevelopmental disability at 3 years of follow up) of 8% for the pessary group and an event rate of 20% for the control group van't Hooft 2016. Group sample size of 121 in both groups achieve 80% power to detect this difference using a two-sided chi-square test with significance level alpha=5%. To account for a dropp out rate around 25%, sample size of 155 in each group, overall n=310 women will be recruited.

Study calendar:
Starting recruitment: June, 1st, 2018
Finishing recruitment and follow-up: est. June 1st, 2023.
Final report: Sept. 1st, 2023.

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1. General information

1.1. Title, protocol identifying number and date.

Effect of history-indicated early treatment with Arabin cervical pessary versus *expectant management standard care treatment with cerclage placement only in cases with cervical shortening* in singleton pregnancies at high-risk for preterm birth on childern's long-term survival without neurodevelopmental disability

The Prometheus-Trial

Code: The Prometeus-Trial
Version and date: version 1.3 (Jan. 19, 2018)

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2. Rationale

2.1. Justification of the relevance of the trial.

Preterm birth complicates 13% of all pregnancies worldwide and is the most important cause of neonatal morbidity and mortality.[2] Although disability-free survival rates have increased over the years as a result of improved facilities and treatments, preterm birth is still accountable for 75% of all perinatal deaths and >50% of morbidities.[3,4]
Women with a history of a preterm delivery have a distinctly increased risk to deliver preterm in a subsequent pregnancy. This risk ranges from 17,2% with one previous preterm delivery up to 28% for two previous preterm deliveries.[5] This also applies to women with a history of a second trimester fetal-loss after 20 weeks of gestation who show an increased risk of 12% for preterm birth in a subsequent pregnancy.[6] Yet another independent risk factor for PTB is a previous cervical surgery; after a single surgical conisation the risk of PTB increases almost 5 fold and after two even10-fold.[7]

Evidence based treatment guidelines for these high-risk pregnancies are not available in Germany, expectant management is the usual care for these patients. The European Association of Perinatal Medicine[8] and the Society for Maternal-Fetal Medicine Publications Committee (SMFM) [9] recommends for the US 17-alpha hydroxyprogesterone caproate (17-OHPC) therapy for women with a history of PTB in a subsequent singleton pregnancy. But this is not a treatment option for the majority of European countries as the drug is only available in some EC-countries on basis of old regime accreditations. The SMFM-statement details that vaginal progesterone should not be considered a substitute for 17-OHPC, whereas the European guideline does not differentiate between 17-OHPC and vaginal progesterone.
Up to now the risk factor previous PTB has only been investigated in RCTs for 17-OHCP [10, 11, 12, 13] or in RCTs where the risk factor previous PTB was combined with the risk factor cervical shortening (vaginal progesterone [14, 15]; cerclage [16], 17-OHP [1]). Looking at the evidence of therapeutic effectiveness of vaginal progesterone these risk factors should be addressed separately. Vaginal progesterone proved to be ineffective in the prevention of recurrent PTB [14, 15] but effectively reduced PTB in women with a short cervix [17, 18] .
For cervical pessary therapy there is up to now only one cohort analysis [19] for the combined risk factors available proving the placement of a cervical pessary to be as effective as cerclage or treatment with 200 mg vaginal progesterone in reducing preterm birth rate.
The risk factor 'history of at least one cold knife conisation' for PTB was up to now only addressed in a pilot study investigating the effect of pessary treatment in asymptomatic women with a singleton pregnancy along with a short sonographic cervix and it suggested a beneficial effect on the prolongation of the pregnancy [7].
A cervical pessary to support the cervix in pregnant women with cervical insufficiency was introduced in 1960. It is a silicone ring with a smaller diameter to be fitted around the cervix and a larger diameter to fix the device against the pelvic floor. This effectively rotates the cervix toward the posterior vaginal wall and corrects the cervical angle [20].
In approximately 1/3 [21] of pregnancies leading to PTB cervical shortening develops. Here the placement of a cervical pessary is a good therapeutic option. For this risk factor good evidence is available for cervical pessary treatment in singleton [22] and twin pregnancies [23, 24]. A Cochrane review [25] detailed a significant decrease in the incidence of spontaneous PTB in women with a short cervix when compared with expectant management: PTB less than 37 weeks' gestation (22% versus 59 %; RR 0.36, 95% CI 0.27 to 0.49) and PTB less than 34 weeks´ gestation (6% and 27% resp. RR 0.24; 95% CI 0.13 to 0.43).

This is the first RCT aiming to investigate the impact of a preventive cervical pessary therapy for the prevention of recurrent PTB in women with a history of PTB and/or history of at least one conisation.
Furthermore this RCT is a part of the first worldwide prospective metaanalysis in the medicine Global Obstetrics Network http://www.globalobstetricsnetwork.org/projects/
The primary outcome "Children´s survival without neurodevelopmental disability at the age of 3 years" measures the long-time outcome of the intervention according to the CROWN [26] criteria.
Cervical pessary treatment is a non-invasive, well-tolerated and cost-effective treatment option [20] which could be easily implemented in daily practice if it proves to have a preventive effect of PTB. This especially applies for developing countries, where for example serial cervix length measurements to detect cervical shortening are not feasible.

2.2. Description of the study population.

Women with a singleton pregnancy at 12 – 16 weeks of gestation and a history of at least one previous preterm delivery before 34+0 weeks and/or a history of previous cervical surgery attending the reference hospital and who do not fulfil the exclusion criteria the study will be proposed. The patients will be informed of the intended therapeutic effect and possible side effects. If they agree and after obtaining their informed consent, they will be randomised according to either usual management with rescue cerclage placement only when (and as soon as possible) a cervical shortening below 25 mm occurs (=control group) or cervical pessary placement (= pessary group).
Pessaries or cerclage shall be placed up to 37+0 weeks of gestation. In the control group serial cervical length measurements shall be conducted every 4 weeks in order to diagnose cervical shortening as soon as possible.

2.3. Name and description of the device under investigation.

The Arabin cervical pessary, which is CE-certified for preventing SPB (CE 0482 / EN ISO 13485: 2012 + AC:2012 annex III of the council directive 93/42 EEC).
See annex I.

2.4. Statement that testing will be performed according to protocol, GCP and applicable legal requirements.

The Clinical Trial will be conducted following the protocol, the GCP, and all legal requirements.

3. Objective

This study aims to investigate the benefit of a prophylactic cervical pessary treatment in women at high risk of PTB due to a history of at least one previous preterm delivery before 34+0 weeks and/or a history of previous cervical surgery on the children´s long-term survival without neurodevelopmental disability.
Hereby, a standardized and validated test called ‘Ages and Stages 3rd edition’[27] should evaluate the children’s neurodevelopment. The test should be conducted by the parents and takes approximately 12 minutes. The questionnaires will be provided by the sponsor.

4. Design

4.1. Specific description of primary and secondary variables.

4.1.1. Primary outcome:

- Children`s long-term survival without neurodevelopmental disability

4.1.2. Secondary outcomes:

- Offspring
  - Time to birth
  - Preterm birth before 37 weeks: rate of delivery before 36+6 weeks
  - Preterm birth before 34 weeks: rate of delivery before 33+6 weeks

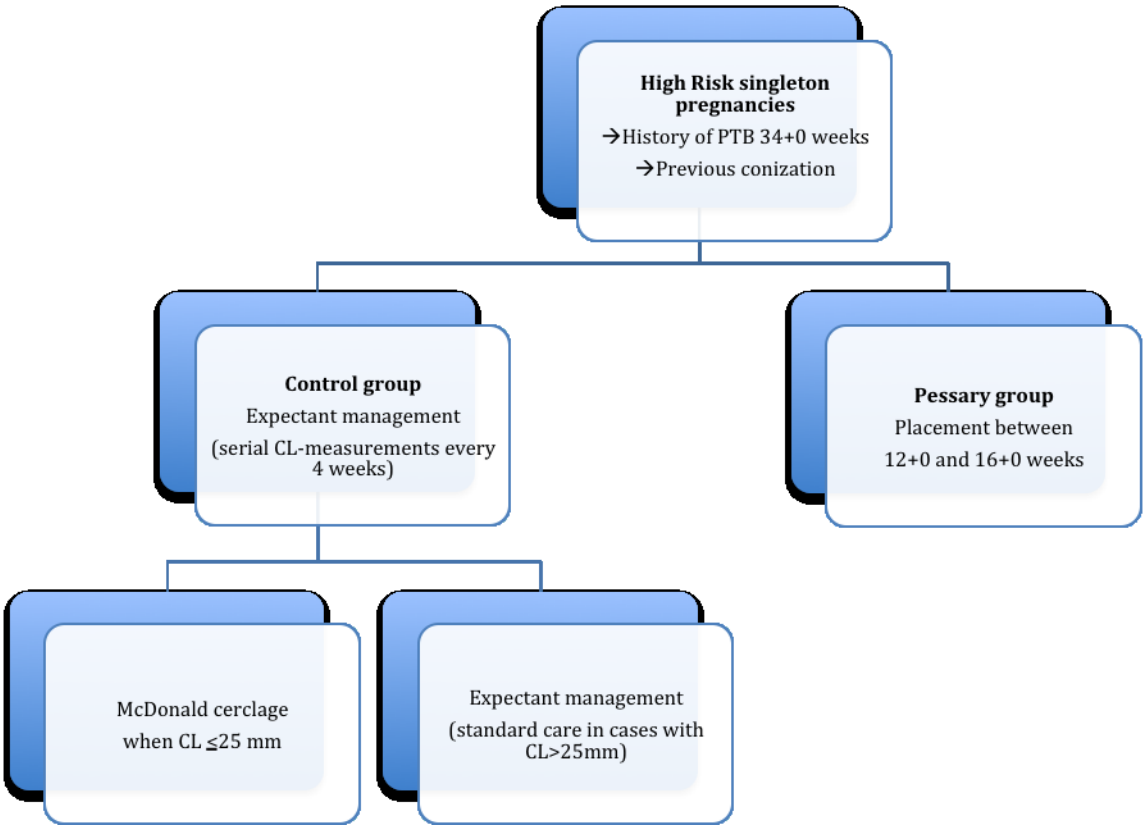
- Preterm birth before 32 weeks: rate of delivery before 31+6 weeks
- Preterm birth before 30 weeks: rate of delivery before 29+6 weeks
- Preterm birth before 28 weeks: rate of delivery before 27+6 weeks
- Birth weight: median weight (g) of the newborns at birth
- Fetal or neonatal death: rate of intrauterine demise or neonatal death during the first 24 hours
- Neonatal morbidity: rate of major adverse neonatal outcomes before discharge from the hospital
    - Intraventricular Haemorrhage (IVH): grades III-IV
    - Retinopathy of prematurity
    - Respiratory Distress Syndrome (RDS): grades II-IV,
    - Need for ventilation > 72 h
    - Necrotising enterocolitis
    - Proven or suspected sepsis, antibiotics (>5 days)
    - Need (Duration in days) for neonatal special care (NICU)
- Harm from intervention

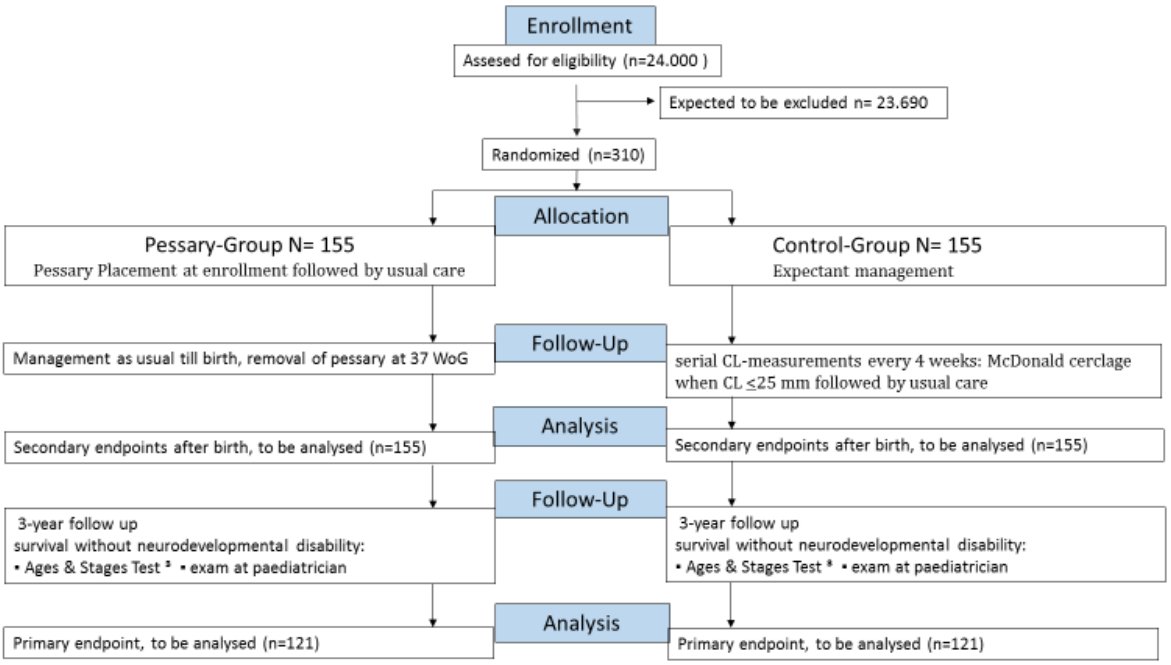
- Mother:
    - Maternal death
    - Significant maternal adverse events (rate):
        - Heavy bleeding: bleeding that requires a medical intervention
        - Cervical tear: cervical rupture due to the pessary placement
        - Uterine rupture: rupture of the uterus due to contractions or surgery
    - Physical or psychological intolerance to pessary: discomfort or pain due to the pessary that makes daily life uncomfortable (number of cases)
    - Rupture of membranes before 32 weeks: rate of–rupture of amniotic membranes before 31+6 weeks
    - Infection/inflammation
    - Hospitalisation for threatened preterm labour before 32 weeks: requirement of hospitalisation due to preterm contractions that need medical treatment to try to stop them before 31+6 weeks (rate)
        - Mean hospital stay duration: number of days of admittance at the hospital
        - Use of tocolytic treatment: Type of tocolytic, days of treatment, dose

4.2. Description of the trial design.

Open Multicentre International Collaborative Randomized Controlled Trial, in parallel groups, based on intention-to-treat analysis comparing the placement of a prophylactic cervical pessary with usual management in singleton pregnancies at high-risk of PTB due to a history of at least one previous preterm delivery before 34+0 weeks and/or a history of previous cervical surgery.

4.3. Flowchart.





4.4. Description of the medical device and the treatment regimen.

The cervical pessary is a vaginal device (silicone ring) that is used to treat pregnant women for preventing spontaneous preterm birth. This device can be easily placed around the uterine cervix without pain (see annex I).

Women with a singleton pregnancy at 12+0 – 16+0 weeks of gestation and a history of at least one previous preterm delivery before 34+0 weeks and/or a history of previous cervical surgery attending the reference hospital for a preventive examination will be informed of the ongoing trial. The patient will be advised of the intended therapeutic effect and possible side effects. If they agree and after obtaining their informed consent, they will be randomised according to either usual management (=control group) or cervical pessary placement up to 37+0 weeks (= pessary group).
If the pregnant woman is assigned to the pessary group and after having excluded a vaginal infection the pessary will be inserted directly. This procedure does not need anaesthesia and it does not need to be done in a surgery room. After the insertion of the pessary the correct fit of the pessary is verified by transvaginal ultrasound and in case it does not fit perfectly, it can easily be adjusted.
In the control-group the cervical length of the women will be evaluated by transvaginal ultrasound scan started from randomization and every 4 weeks; if a cervical shortening below 25mm is detected a Mc Donald cerclage will be placed.
The pessary will be removed at 37+0 weeks of gestation, or before if any unexpected event occurs (see 4.6). After insertion of the pessary the obstetrical management during the remainder of the pregnancy will be usual management.
Further surveillance of the pregnancy will not be influenced by the participation on the study.

4.5. Expected duration of subject's participation.

Starting recruitment: June, 1st, 2018
Finishing recruitment and follow-up: est. June 1st, 2023.
Final report: Sept. 1st, 2023

4.6. Completion and interruption criteria of the study or the subjects.

The pessary will be removed at 37+0 weeks of pregnancy. The indications to remove them before this time will be: active bleeding stronger than period bleeding, persistent contractions after tocolysis and premature rupture of the membranes after 34+0 weeks.
After removing the pessary, the obstetrical management will be done as usual and will not be influenced by the study.

4.7. Maintenance of the randomisation codes and test procedures of the trial.

Every participating centre will have its own randomisation list.
We have created a database in a website so it can be accessed worldwide, that every hospital will be able to randomize their patients.
Every center will receive a password and a username in order to access the database for recruitment, randomization and documentation of patient data. Hereby, a personal identification number will be assigned for every patient. Patient names will not appear in the databases.
This database will be supervised and coordinated by PD Dr. Ioannis Kyvernitakis, Bürgerhospital Frankfurt/M. (Webmaster).

4.8. Identification of data to be collected in the case report files (CRF) that should be considered as data source.

Data will be collected in E-CRF, provided by >Dr. Olaf Hars Wissenschaft, Berlin< on study software "Castor".

4.9. Definition of what is considered to be the end of the study.

The study will be finished after the 3 year-follow up examination of the surviving children focusing on neurodevelopmental disabilities.

5. Selection and withdrawal of subjects

5.1. Inclusion criteria.

- Women with a singleton pregnancy and a history of at least one previous preterm delivery before 34+0 weeks and/or a history of previous cervical surgery
- 12+0 -16+0 weeks of gestation
- Minimal age of 18 years
- Informed consent signature

5.2. Exclusion criteria.

- Major fetal abnormalities (requiring surgery or leading to infant death or severe handicap)
- Cerclage prior to randomisation
- Uterine malformation
- Placenta previa totalis
- Active vaginal bleeding at the moment of randomization
- Spontaneous rupture of membranes at the time of randomization
- Silicone allergy
- Painful regular uterine contractions
- Current participation in another RCT

5.3. Withdrawal criteria.

If a participant may voluntarily withdraw from treatment or if it is necessary to remove the pessary due to the conditions described before, the patients will be followed as usual until delivery (intention-to-treat analysis).
Replacement of patients is not applicable in this trial.

5.4. Rescue treatment criteria.

Regarding the control group, a McDonald cerclage may be indicated if there is a cervical shortening below 25 mm during the follow-up scans according to the current guidelines and expert recommendations[11].

6. Treatment of Subjects

6.1. Treatments to be administered.

The pessary will be inserted during a preventive examination in pregnancy in the examination room. This procedure does not need anaesthesia and it does not need to be done in a surgery room. After the insertion of the pessary the correct fit of the pessary is verified by transvaginal ultrasound and in case it does not fit perfectly, it can easily be adjusted. In the control-group the cervical length of the women will be evaluated by transvaginal ultrasound scan: if a cervical shortening below 25 mm is

detected a cervical cerclage will be placed. The pessary or cerclage will be removed at 37+0 weeks of gestation, or before if any unexpected event occurs (see 4.6).
After insertion of the pessary the obstetrical management during the pregnancy will be usual management.
Further surveillance of the pregnancy will not be influenced by the participation on the study.

7. Efficacy assessment

7.1. Specification of efficacy parameters: Primary and secondary endpoints.

This study aims to investigate the benefit of a prophylactic cervical pessary treatment in women at high risk of PTB due to a history of at last one previous preterm delivery before 34+0 weeks and/or a history of previous cervical surgery on the perinatal outcome and on the children´s long-term survival without neurodevelopmental disability.
The effect of the pessary treatment will be assessed in women independent of the cervical length at 12 -16 weeks of gestation compared to standard care treatment.

7.2. Methods and timing to assess records and analyze the efficacy parameters.

The pregnant women will be assessed according to usual obstetrical management in a high-risk pregnancy.

	Regular Preventive Exam	Serial CL measurements after randomization	Regular Preventive Exam 37 WoG	Postnatal evaluation	3 years follow up (corrected age)
Study procedure	study inclusion 12+0-16+0 WoG				
Informed consent	x				
randomisation	x				
Control-group		x			
Pessary/cerclage placement	Pessary-Group: Pessary at enrollment	Control-Group: Cerclage when CL ≤25mm			
Pessary/cerclage removal	WoG 37+0		x		
physical exams					
Abdominal US	x	x	x		
Vaginal US		x			
pH-Value	pH < 4,4	pH < 4,4			
Neonatal examination				x	
Ages & Stages test					x
Exam at paediatrician					x

8. Assessment of Safety

8.1. Procedures to record and report adverse events.

If a serious and unexpected adverse effect occurs during pessary treatment, it will be notified to the study Sponsor. The Department of Obstetrics and Gynecology of the Sponsor will fill the side effects document to notify it to the *Landesärztekammer Hessen.*
The patient affected by the adverse effect will be followed more intensively during the first days and if nothing else occurs, she will return to the standard control.

8.2. Definitions.

Adverse Event (AE): Any untoward medical occurrence in a patient or clinical investigation participants administered a medicinal product, which does not necessarily have to have a causal relationship with this treatment (the study medication). An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of the study medication/procedure, whether or not considered related to the study medication.

Adverse Reaction (AR): All untoward and unintended responses to a medicinal product related to any dose. The phrase "responses to a medicinal product" means that a causal relationship between a study medication and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out.
All cases judged by either the reporting medically qualified professional or the sponsor as having a reasonable suspected causal relationship to the study medication / procedure qualify as adverse reactions.

Serious Adverse Event (SAE): A serious adverse event is any untoward medical occurrence that at any dose: Results in death; is life-threatening, NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe; Requires inpatient hospitalization or prolongation of existing hospitalization; Results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.

Other important medical events: Other events that may not result in death, are not life threatening, or do not require hospitalization, may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.
To ensure no confusion or misunderstanding of the difference between the terms "serious" and "severe", which are not synonymous, the following note of clarification is provided:
The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a participant's life or functioning as defined in the bullet points above. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

Serious Adverse Reaction (SAR): An adverse event (expected or unexpected) that is both serious and, in the opinion of the reporting investigator, believed with reasonable probability to be due to one of the study treatments, based on the information provided.

Suspected Unexpected Serious Adverse Reaction: A serious adverse reaction, the nature or severity of which is not consistent with the applicable product information

(e.g. Investigator's Brochure for an unapproved investigational product or summary of product characteristics for an approved product).

8.3. Procedures for immediate notification of serious or unexpected adverse events.

All AEs occurring during the study /or observed by the investigator or reported by the participant, whether or not attributed to study medication, will be recorded on the CRF.
The following information will be recorded: description, date of onset and end date, severity, and assessment of relatedness to study medication, other suspect drug or device and action taken. Follow-up information should be provided as necessary.
AEs considered related to the sanitary device, as judged by a medically qualified investigator, will be followed until resolution or the event is considered stable. All related AEs that result in a participant's withdrawal from the study or are present at the end of the study, should be followed up until a satisfactory resolution occurs.
It will be left to the investigator's clinical judgment whether or not an AE is of sufficient severity to require the participant's removal from treatment. A participant may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable AE. If either of these occurs, the participant must undergo an end of study assessment and be given appropriate care under medical supervision until symptoms cease or the condition becomes stable.
A medically qualified investigator will assess the relationship of AEs to the study medication.

All SAEs must be reported to the main investigator. He will perform an initial check of the report, request any additional information, and he will notify it to the Ethics Committee. All SAE information will be recorded. It may be appropriate that some SAEs do not require immediate reporting but this must be justified. Justification might be determined, for example, by admission to hospital, or prolongation of hospitalization, where this is to be expected in the underlying disease or condition.
All adverse events (AE) life-threatening or resulting in death will be notified within 24 hours. All AE that are not life-threatening will be notified within 15 days. The rest of AE will be recorded and analyzed at the end of the study.

9. Statistics

9.1. Description of statistical methods.

A descriptive analysis by preterm birth will be carried out calculating means and medians for quantitative variables and proportions for categorical variables.
The primary statistical aim is to compare the primary combined outcome "long-term survival without neuro-developmental disability at 3 years follow up" between the two treatment groups with a two-sided chi-square test. In general, statistical comparisons will be two-sided and use appropriate tests according to the scale of the outcome. A multivariate logistic regression will be fitted to control for possible confounders. Relative risks and 95% confidence interval as well as adjusted odds ratios will be calculated for the binary outcomes. Statistical significance will be accepted in all cases with a $p \leq 0.05$.
The main statistical evaluation will be performed at two time points.
(1) The complete data set for the secondary endpoints will be available after the last women enrolled in this study has delivered her neonate, so the analysis of these outcome parameter will be done right after this event.
(2) The primary outcome will be evaluated 3 years after the last woman enrolled in this study has delivered her neonate.

A descriptive analysis by preterm birth will be carried out calculating means and medians for quantitative variables and proportions with 95% confidence intervals for categorical variables.
Additionally we will perform an explorative subgroup analysis of the study collective comparing the efficacy of the cervical pessary treatment in women with a normal cervical length at 12 -16 weeks of gestation and in women who have developed a cervical shortening (< 25 mm) as an additional risk factor.
For the primary endpoint we expect to have a drop out rate of up to 25% due to the long follow-up time (3 years) of the study; but we do not expect to have lost data for the secondary endpoints because for these parameters the study has a short follow-up time till time to birth only.
An interim analysis shall be conducted on key safety parameters after birth of 150 neonates: the following safety endpoints will be assessed by a one-sided test with alpha=1%
• on level of the neonates:
rate of preterm birth, time to birth, birth weight, death, neonatal morbidity, harm of intervention
• and on the maternal level:
rate of hospitalisation for threatened preterm labour < 32 weeks, rate of PRoM <32 weeks, rate of infection / inflammation, rate of physical or psychological intolerance to pessary, rate of SAR/SAE, death.

The trial will be terminated as negative if a disadvantage for the pessary-treatment can be found in one of these tests. To guarantee a high safety level the significance level is chosen more conservatively than in a Bonferroni correction. All analysis will be carried out with SPSS® version 19.0 or later (IBM Company SPSS Inc. Headquarters, Chicago, Illinois. USA) and R version 3.2.3 or later (R Foundation for Statistical Computing, Vienna, Austria).

Primary Outcome	**Statistical Test**
Children`s Long-Term Survival without Neurodevelopmental Disability (3-Years-follow up)	Chi-Square test
Secondary Outcome	**Statistical Test**
Birth before 34 Weeks of Gestation	Chi-Square test or Fisher test
Time to Birth	Cox regression
Birthweight	t-test or Wilcoxon-Mann-Whitney test
Fetal / Neonatal Death	Chi-Square test or Fisher test
Neonatal Morbidity	Chi-Square test or Fisher test
Need for Hospitalization	Chi-Square test or Fisher test
Days of Hospitalzation	t-test or Wilcoxon-Mann-Whitney test
Maternal Adverse Events	Chi-Square test or Fisher test
Pessary Intolerance	Chi-Square test or Fisher test
Vaginal Infections	Chi-Square test or Fisher test

9.2. Expected number of subjects to be included.

For sample size calculation, we assume a combined event rate for the primary outcome (long-term survival without neurodevelopmental disability at 3 years of follow up) of 8% for the pessary group (see van't Hooft, Pro Twin Trial[28]) and an event rate of 20% for the control group. Group sample size of 121 in both groups achieve 80% power to detect this difference using a two-sided chi-square test with significance level alpha=5%. To account for a drop out rate around 15%, sample size of 155 in each group, overall n=310 women will be recruited.

9.3. Criteria for termination of the trial.

A non-justified case of maternal death (temporary stop until complete evaluation of the case by an external committee).

9.4. Selection of subjects to be included in each analysis.

The analysis will include all the subjects that have been randomised.

10. Direct Access to Data Source

Direct access will be granted to the authorized monitor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

11. Quality and Control Assurance

Main investigator and collaborators: In order to ensure the Quality of the data they will provide instructions and training to the sites involved in the trial; review the CRF data; and detail of any other steps taken to ensure quality of research.
The main investigator will sign the study protocol and the "investigator's commitment; he will apply for the Ethics Committee and the Director's approval; and he will review the final report of the study.
The collaborators will assess patient's eligibility, they will inform the patients and ask for the informed consent; and they will be responsible of the CRF and obtaining and registering all data.

Monitor: he will perform regular monitoring according to ICH GCP. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents. Monitors will verify that the clinical trial is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable and local regulatory requirements.

Serious Breaches: A serious breach is defined as "A breach of GCP or the trial protocol which is likely to effect to a significant degree: (a) the safety or physical or mental integrity of the subjects of the trial; or (b) the scientific value of the trial". All serious breaches will be notified to the competent Regulatory Authority according to applicable legislation.

12. Ethical issues

The Sponsor, participating Centres and Investigator will ensure that this study is conducted in accordance with the Protocol, the principles of the Declaration of Helsinki (see annex III), ICH Guidelines for Good Clinical Practice and in full conformity with relevant regulations as well as applicable national laws, the German Law and in accordance with regulations and guidelines applicable to clinical trials relating to medical devices.
The protocol, informed consent form, participant information sheet and any applicable documents will be submitted to an appropriate Ethics Committee (EC) and Regulatory Authority for written approval. All substantial amendments to the original approved documents will be also sent to an appropriate Ethics Committee (EC) and

Regulatory Authority for written approval. The study will not begin until the approval of the EC and Director's consent.

13. Data Management and Registry File

Patient's participation in the study will be annotated into the medical history.
The main investigator will perform a list with the participant's names, ID numbers and codes. He also will have a file with all the information referring to the study.
All the data will be collected in a database that will be accessed worldwide.
The randomisation will be done on a computer basis. Once entering in the website, if the patient fulfils the inclusion criteria, the computer generated list will randomise the patient to "pessary" or "control" group.
The excluded patients will be also collected in the database.
Every participating centre will have its own randomisation list, and it will be accessible with a username and password.
The trial staff will ensure that the participants' anonymity is maintained. Only a participant ID number on the CRF and in the electronic database will identify the participants. All documents will be stored securely and only accessible by trial staff and authorized personnel. The study will comply with the Data Protection Legislation that requires data to be anonymized as soon as it is mandatory to do so.

13.1. Data ownership

Sponsor and participating Center have expressly agreed that any and all data collected and prepared in the context of the study shall be the property of the Sponsor, provided that participating Center shall remain the owner of its source data and may utilize such data as it deems appropriate without the approval, but with the reliable communication of Sponsor. Furthermore, Sponsor will always have access to the Study data, in terms of good faith and cooperation, in order to improve their own knowledge and information.

14. Funds and Insurance

According to German legislation and Ethical Committee decisions, it is not necessary to enter into an insurance contract in order to cover patients while using this medical device in a clinical trial. Insofar as it has been issued with the appropriate certificate of the State Medicines Agency to the concrete use of the medical device.

Nevertheless, it will be mandatory to enter into a hedging insurance by any other participating centre of this clinical trial, in the case that it is mandatory according to the laws of their country.

No funding is provided for the study.

15. Publication policy

The Sponsor takes the commitment of publishing the results of the study; despite they are good or bad.

Promoter and participating Centre agree that publications or presentations of any of the results from the study shall be in accordance with accepted scientific practice, academic standards and customs.

Authorship and other related publications questions shall be addressed in accordance with the principles of the 'Uniform Requirements for Manuscripts Submitted to Biomedical Journals' and in accordance with the requirements of the respective medical journal.

Sponsor agrees to ensure co-authorship for clinical co-investigators on any proposed multicentre publication.

Sponsor and participating Centres agree that at first they will strive to make a joint publication. After such joint publication or one year after termination of the study the following shall be agreed:

As a general principle, the parties agree that prior to submission of a publication or any other dissemination of the results, including oral presentation, the Sponsor shall have the right to prior review and comment on the content of the material to be published or presented within sixty (60) days following the receipt of the publication or any other dissemination of the results, and Participating Centre ensures that it will take Promoter's comments into due consideration.

16. Legal Issues

Both the Promoter and the participating Centre will enter into a contract before they can start randomizing patients.
This contract will prevail in case of lack of agreement from any of the parts.

17. References

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18. Annex

Annex I. Technical details of the device.

The Arabin cervical pessary
CE-certified for preventing spontaneous preterm birth (CE 0482 / EN ISO 13485: 2012 + AC:2012 annex III of the council directive 93/42 EEC).

This pessary is used to treat pregnant women with cervical incompetence in order to support the cervix and sacralise it towards the sacrum.
It may be indicated in pregnancies with a history of premature labour, multiple pregnancies or mothers who are exposed to physical strain (e.g. standing for a long time). It may also be indicated in pregnant women suffering from prolapse of the genital organs.
The cerclage pessary can easily be folded and inserted without pain.

In general, cerclage pessaries should have a height of 21-25 mm in singleton pregnancies and a height of 25-30 mm in multiple pregnancies or pregnant patients with complaints of prolapse. The width of the upper and lower diameter should be chosen depending on the individual constitution of the pregnant patient.
Cerclage pessaries can be ordered in a non-perforated or perforated version. The perforations facilitate discharge to pass.

Sizes and Models: Cerclage pessaries are classified according to
- The lower larger diameter (65 or 70 mm)
- The height (17, 21, 25, 30 mm)
- The upper smaller diameter (32 or 35 mm)

Dr. Arabin online shop. http://www.dr-arabin.de/e/cerclage.html