Study protocol:

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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Abstract:

Background: Women with a history of preterm delivery or second trimester abortion have a distinctly increased risk to deliver preterm in a subsequent pregnancy. This applies also for women with a previous cervical surgery. Interventions to prevent preterm birth are necessary for this high-risk population. We compare preventive cervical pessary and prevention of preterm birth in women with a singleton pregnancy at high risk of spontaneous preterm birth (sPTB).

Methods: We plan a randomized controlled trial among women with a singleton pregnancy with a history of at least one previous preterm delivery before 34+0 weeks and/or a history of previous cervical surgery.

Eligible women will be randomized and allocated to either pessary treatment or expectant management. In the control group serial cervix length measurements will be performed every 4 weeks from 12 weeks. In this group, if a cervical shortening ≤ 25 mm develops a McDonald cerclage should be performed. In the pessary group the cervical pessary will be left in situ until 37 completed weeks or earlier if necessary.

The primary outcome measure will be the children's long-term survival (3yrs) without neurodevelopmental disability. Key safety endpoints will include the composite neonatal outcome as well as preterm birth before 34 weeks. Secondary endpoints assess the impact of the preventive pessary placement on the prevention of preterm birth and its resulting risk on mortality and morbidity for the neonates. 310 women will be included in parallel groups (pessary vs. control group) in order to demonstrate a 18.6% higher survival rate of children without neurodevelopmental disability at the age of 3 in the pessary-group with an alpha-error of 0.05 and 80% power.

Discussion: 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. In accordance with the results by van ´t Hooft et al. 2018 we expect an approximately 20% higher percentage of children's long-term survival without neurodevelopmental disability for the pessary group in comparison with usual management (=control group) on basis of a reduction of prematurity < 34 week of gestation.

Trial Registration: ClinicalTrials.gov Identifier: NCT03418012. Registered on 31st[rd] January 2018.

Keywords: Preterm Birth, Recurrent PTB, Conisation, Preventive Pessary Placement, Arabin Cervical Pessary, Children´s Long-Term Outcome

Background

Background and rational:

Preterm birth complicates 9% of all pregnancies in Germany [1] and up to 13 % worldwide [2] 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 abortion who show an increased risk of 12% for preterm birth in a subsequent pregnancy [6]. 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]. Morbidity and mortality are strongly related to gestational age; of those infants born <30 weeks of gestation, only 25% are free of disabilities at the age of five years [4,8] whereas only 8% of children born after 32 weeks of gestation have a risk for neurodevelopmental delay [9]. Also, late preterm (> 32 WoG) neonates have a 10-fold increased mortality risk compared to full-term neonates [1]. Apart from the personal tragedies involved PTB generates tremendous healthcare costs[10]. 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 [11] and the Society for Maternal-Fetal Medicine Publications Committee [12] 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 [13, 14,15,16] or in RCTs where the risk factor previous PTB was combined with the risk factor cervical shortening (vaginal

progesterone [17,18]; cerclage [19], 17-OHP [20]). 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 [17, 18] but effectively reduced PTB in women with a short cervix [21,22]. For cervical pessary therapy there is up to now only one cohort analysis [23] 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 [24].

Cervical shortening develops in approximately 1/3 [25] of all PTB-pregnancies. Here the placement of a cervical pessary is a therapeutic option. For this risk factor, evidence is available for cervical pessary treatment in singleton [26] and twin pregnancies [27,28]. A Cochrane review [29] 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).

Cervical pessary treatment is a non-invasive, well-tolerated and cost-effective treatment option [30] which could be easily implemented in daily practice if it proves to have a preventive effect on sPTB in this high-risk-group. This especially applies for developing countries, where for example serial cervix length measurements to detect cervical shortening are not feasible.

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. This Trial is a multicentre, open-label, prospective, randomised, controlled trial in parallel groups; it might be considered as a part of the first worldwide prospective metaanalysis in medicine conducted by the Global Obstetrics Network (Go-Net)[31].

Methods: Participants, interventions, and outcomes

Study setting

This is a multicenter study to be conducted in 6 hospitals in Germany and in 2 hospitals in Greece. All hospitals are academic hospitals providing an obstetrical department along with a tertiary perinatal unit.

The following centres will be considered: Medical School of the Aristotle-University of Thessaloniki, University Hospital of Athens and in Germany, Vivantes Klinikum im Friedrichshain Berlin, Charité-Universitätsmedizin Berlin, Asklepios Kliniken Hamburg, Universitätsklinikum des Saarlandes Homburg, Universitätsfrauenklinik und Poliklinik am Klinikum Südstadt Rostock, Klinikum Darmstadt, Klinikum rechts der Isar Technische Universität München. All participating centres will file their own EC approval.

The trial was registered on January 23rd in 2018 in ClinicalTrials.gov (https://clinicaltrials.gov/ct2/results?term=NCT03418012&Search=Search); the trial number is NCT03418012.

Eligibility criteria:

Women presenting with a singleton pregnancy in week of gestation (WoG) 12+0 - 16+0 and a history of at least one previous preterm delivery before 34+0 weeks and/or a history of cervical surgery are eligible for this study. Gestational age will be determined through menstrual history and first trimester scan. Women with major congenital abnormalities and uterine malformations will be excluded. Women with active vaginal bleeding, spontaneous rupture of membranes, painful regular uterine contractions or a cervical cerclage in situ at the time of randomization will also be excluded. Silicone allergy and a current participation in another RCT are exclusion criteria as well. All women will have to be older than 18 years and capable of giving consent.

Interventions:

Pessary-Group-participants will receive management as usual except for placement of the cervical pessary (non-invasive) at enrolment including a transvaginal ultrasound to verify its correct fit and removal of the cervical pessary (non-invasive) in a regular preventive examination at WoG 37. The Arabin cervical pessary will be used in this trial; it is CE-certified for preventing SPB (CE 0482 / EN ISO 13485: 2012 + AC: 2012 annex III of the council directive 93/42 EEC [32].

Further surveillance of the pregnancy will not be influenced by the participation in the study.

Control-group-women receive management as usual; i.e. expectant management with interventions only in terms of a tertiary prevention of PTB according to guidelines for premature rupture of membranes, premature labour or other pregnancy complications[33]. Serial cervix length measurements will be performed every 4 weeks as asymptomatic women with a cervical length ≤ 25 mm are at an increased risk of PTB [26]. In the control group, if a cervical shortening ≤ 25 mm develops a McDonald cerclage [34] (invasive) is to be done.

Outcomes

The primary outcome is the children`s survival without neurodevelopmental disability at 3 years of corrected age: neurodevelopmental disability is an issue of great concern regarding preterm new-borns. As such, the core outcome of the Impetus trial is to assess not only the survival but also the neurological status of the children as implemented by the CROWN Initiative[35]. This outcome measure focuses on whether the surviving children will be impaired by a mental disability in life or not; the exact potential disability is not object of the study.

Secondary outcomes will be related to the pregnancy, delivery and the short-term outcome of the neonates. The outcome measures for pregnancy and delivery will be: hospitalisation for threatened preterm labour before 31+6 weeks (days hospitalisation, tocolytic treatment (type, days, dose); premature rupture of membranes (PRoM) before 31+6 weeks; infection / inflammation; physical or psychological intolerance to pessary; rate of significant maternal adverse events (heavy bleeding, cervical tear due to pessary placement, uterine rupture); maternal death; preterm birth as rate of delivery before weeks of gestation: 36+6 / 33+6 / 31+6 / 29+6 / 27+6; time to birth; birth weight (g).

As short-term neonatal outcome will be assessed: fetal or neonatal death within the first 24 hours; neonatal morbidity as rate of major adverse neonatal outcomes before discharge from the hospital (intraventricular haemorrhage III-IV, retinopathy of prematurity, respiratory distress syndrome II-IV, need for ventilation > 72 h, necrotising enterocolitis, proven or suspected sepsis (antibiotics >5 days), need (days) for neonatal special care, harm from intervention.

Our outcome measures meet the core-outcome set for the evaluation of interventions to prevent PTB published by the crown-initiative in 2016[35].

Participant timelines

Fig 1

We expect patient recruitment to take approximately 1 year. The study duration of the entire trial is estimated to be 58 months, whereas the intervention duration for the clinical trial will take approximately 19 months and the intervention duration per patient max. 29 weeks.

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 [36]. 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 25%, sample size of 155 in each group, overall n=310 women will be recruited. The reported response rate of the ProTwin*Kids*[36] study served as a basis for the assumed drop-out rate of 25 % for the primary outcome measure children`s survival without neurodevelopmental disability at the age of 3 as for both studies the follow-up time was 3 years.

Recruitment

The obstetric departments of the participating centres will counsel all women being referred for the regular preventive ultrasound examination or for the first trimester screening from 11 to 14 WoG. The obstetrical specialist will confirm that the patient fulfils the inclusion criteria and the study will be

proposed. The patients will be informed about the intended therapeutic effect and possible side effects. The patient will be given an information sheet and the requisite time to reflect on participation. In case of participation and after having obtained their informed consent, they will be randomised in two groups either control group with usual management or pessary group with immediate placement of the cervical pessary. We expect patient recruitment to take approximately 1 year.

Randomization and masking

After providing written informed consent all women will be randomly allocated to the cervical pessary group or the control-group in a 1:1 ratio. The randomization sequence is computer generated with variable block sizes using a web-based e-CRF (Online-Software Castor[37] is a fully GCP compliant system) stratified for centers. The allocation code will be disclosed after the patient´s initials will be confirmed. The investigators or the trial coordinator will not have access to the randomization sequence. Neonatologists and pediatricians assessing the children will not be aware of the allocated treatment. The study is open label since masking the intervention is not possible.

Methods: Data collection, management and analysis

Data collection

The primary outcome measure “children´s survival without neurodevelopmental disability at the age of 3 years” will be collected by the standardized screening questionnaire Ages & Stages Questionnaire ASQ-3 (at 36 month of corrected age). The ASQ-3 is a parental questionnaire which is frequently used for screening developmental delay in problem solving, communication, fine- and gross motor skills and personal-social behaviour of preschool aged children [38,39]. Additionally the results of a regular preventive examination at paediatrician for children aged 34-36 month (in Germany ‘*Vorsorgeuntersuchung U7a’* or equivalent examination in Greece) are recorded.
All data for the secondary endpoints will be routinely collected during the course of the pregnancy and birth in the data management system of the caregiving hospital.

All investigators will be trained in pessary application and cerclage placement. Quality protocols will be submitted according to the Clara-Angela Foundation requirements for pessary placement.

Data management:

Prometheus Trial will be conducted according to standard operating procedures (SOP) of the Sponsor. These SOPs describe the processes during planning, conduct and evaluation as well as the quality management. It includes a predefined Data Management Plan (DMP), Data Validation Plan (DVP) and statistical analysis plan (SAP) including a description how to handle missing or implausible data. Source data verification will be performed in randomly selected centres (5%) as well as in randomly selected patients (5%) N=35

An electronic archiving of all reports and documents will be done for at least 10 years.

All data will be collected and processed in standardized electronic case report forms (eCRF) specially designed for Prometheus Trial (=eCRF-Prometheus). A feasibility assessment of the eCRF-Prometheus will be done before start of the RCT, regular electronic checks for completeness and plausibility will be carried out. All AE reporting is done in eCRF. Castor EDC[37] is the Prometheus eCRF software/database which complies with all applicable laws and regulations (Good Clinical Practice, 21 CFR Part 11, EU Annex 11; General Data Protection Regulation, HIPAA (US) ISO 9001 and ISO 27001). Castor is a validated system and approved by external auditors.

Safety: All SAR/SAE/AE will be reported to Sponsor who will notify Ethics Committee of the *Landesärztekammer Hessen*, all SAR/SAE (life-threatening or resulting in death) within 24 hours, all not life-threatening AE within 15 days, all AE will be recorded.

Statistics

The primary statistical aim is to compare the primary combined outcome “children´s long-term survival without neurodevelopmental 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≤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 dropout rate of up to 25% due to the long follow-up time (3 years) of the study based on ProTwin*Kids*[36]; 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 (time to birth) only.

Interim analysis

After birth of 150 neonates the key safety parameters • rate of preterm birth ≤ 32WoG • death before discharge • rate of SAR/SAE • maternal death will be assessed by a one-sided test with alpha=2,5%. 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.

Discussion

Evidence based treatment guidelines for these high-risk pregnancies are not available in Germany/Europe, expectant management is the usual care for these patients. Bearing in mind the evidence for cervical pessary treatment on preventing PTB for the risk factor cervical shortening [26-28] a potential benefit on recurrent PTB should be investigated.

Cervical pessary treatment is a non-invasive therapy and is generally well tolerated [30].

Cervival pessaries have a very low risk profile: in several RCT [26-28,40] investigating cervical pessaries in singleton and twin pregnancies no severe adverse events were reported. Increased vaginal discharge was the only statistically significant side effect [26,28] but no increased risk [40] of vaginal infection and no difference in pelvic discomfort were reported. For the neonates, no adverse events have been reported [26-28,40].

If a preventive cervical pessary treatment is proven to be effective for these patients at high risk of sPTB, the outcome of their newborns would be tremendously enhanced considering that even one week of prolonged pregnancy [41,42] is favourable for the outcome of the neonate.

This RCT might be considered as a part of the prospective metaanalysis of pessary trials (PROMPT); a project by Global Obstetrics Network[31] (GONet) summarizing registered RCTs in pregnancies using cervical pessaries on basis of CORE[35] outcome parameters.

Abbreviations

PTB: Preterm Birth; RCT: Randomised Controlled Trial; WoG: Week of Gestation; 17-OHPC: 17-alpha hydroxyprogesterone caproate; CL: Cervical length; ASQ-3: Ages and Stages Questionnaire-3 (36 month), EC: Ethics Committee; SAR/SAE: Serious Adverse Reaction/ Serious Adverse Event, AE: Adverse Event

Ethics approval and consent to participate☑

The sponsor, participating centers and investigators ensure that this study will be conducted in accordance with the protocol, the principles of the Declaration of Helsinki, ICH Guidelines for Good

Clinical Practice and in full conformity with relevant regulations as well as applicable national laws 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 were submitted to the reference Ethics Committee (*Ethik-Kommission der Landesärztekammer Hessen*, Frankfut/M, Germany) (EC) and written approval has been obtained (Reference number FF 33/2017). All substantial amendments to the originally approved documents will also be sent to the respective authorities for approval. All participating centers will file their own EC approval. Per study site the study will not begin until the approval of the EC and their director's consent will be obtained.

Consent for publication

Provided.

Availability of data and material

All data will be recorded in an eCRF; the database is located on a website so it can be accessed worldwide by the participating centres. Every centre 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. Every participating centre will have its own randomisation list.

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.

Competing interests

The authors declare that they have no competing interests

Funding

No funding was obtained for this study.

Authors' contributions

IK from Frankfurt/M conceived the study and participated in its design and coordination. EH from Frankfurt compiled the statistics and power analysis. All authors participated in the acquisition of data. All authors read and approved the final manuscript.

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