A Randomized Trial of Pessary in Singleton Pregnancies with a Short Cervix (TOPS)

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Protocol

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1 Introduction

1.1 Study Abstract

Preterm birth is the primary driver of perinatal morbidity and mortality affecting approximately 11% of all newborns in the United States.[1] Of the 4 million neonatal deaths that occur annually around the world, more than a quarter are the result of preterm birth.[2] A short cervix by ultrasound has been noted to be one of the strongest predictors of subsequent preterm birth and investigators have focused efforts in finding a treatment for women with a short cervix that will reduce the risk of preterm delivery. Although vaginal progesterone and cerclage have been shown to reduce the risk, results have not been uniformly positive, and a low-cost, simple and effective method would be of great value, especially globally. The cervical pessary is such a treatment. This randomized trial will evaluate whether a cervical pessary can reduce the risk of preterm birth before 37 weeks in women with a short cervix.

1.2 Primary Hypothesis

In women with a singleton gestation who show ultrasound evidence of short cervical length, placement of a cervical pessary reduces the risk of preterm birth less than 37 weeks.

1.3 Purpose of the Study Protocol

This protocol describes the background, design and organization of the randomized clinical trial and may be viewed as a written agreement among the study investigators. The Data and Safety Monitoring Committee (DSMC) and the Network Advisory Board review the protocol. Before recruitment begins, the protocol is approved by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Maternal-Fetal Medicine Units (MFMU) Network Steering Committee, and the Institutional Review Board (IRB) of each clinical center. Any changes to the protocol during the study period require the approval of the Steering Committee and the IRBs; major changes also require the approval of the DSMC.

A manual of operations supplements the protocol with detailed specifications of the study procedures.

2 Background

2.1 Introduction

Preterm birth remains the paramount clinical challenge in obstetrics and continues to be a major cause of infant mortality. Despite the scale of this issue, effective treatments for women presenting with preterm labor beyond administering corticosteroids for fetal lung maturation have remained elusive. Historically, efforts have focused on ameliorating the consequences of prematurity rather than preventing its occurrence.[3] Although this approach has improved neonatal outcomes, tremendous economic burden occurs as a direct result of the hospitalization of these neonates as well as the long-term costs associated with caring for these children.

The failure of these efforts has led researchers to explore interventions earlier in pregnancy and to identify women at increased risk for preterm delivery in whom such interventions could be beneficial. Success in preventing preterm birth has been achieved by identifying women with a history of prior preterm birth and providing exogenous progesterone.[4,5] However, while history of a prior spontaneous preterm birth remains one of the most powerful predictors of recurrent preterm birth, its utility is limited. First, 40% of pregnancies occur in nulliparous women who do not have an obstetrical history. An additional 50% of women are multiparous with only prior term birth. Although their risk of preterm birth is low, they still represent a significant percentage of the women who deliver prematurely. Petrini and colleagues in an analysis of the impact of universal screening for a history of prior preterm birth and treatment with progesterone noted that the impact on the overall preterm delivery rate was limited as it would only change by 0.3%.[6]

2.2 Cervical Length and the Risk of Preterm Birth

A short cervix during pregnancy, as measured by endovaginal ultrasound, was first reported to be a significant risk factor for preterm delivery by Andersen et al. in 1990.[7] This study found that in an unselected population of 113 gravidas, a cervix of less than 39 mm before 30 weeks gestation was a significant risk factor for early delivery. Moreover, the authors found the risk of preterm delivery to be inversely proportional to cervical length and that the risk increased significantly with shorter cervical measurements.

Subsequently, multiple studies have confirmed this finding, including the Preterm Prediction Study conducted by the MFMU Network from 1992-1995. The Prediction Study was a prospective observational cohort study evaluating associations between various markers and subsequent spontaneous preterm delivery. A total of 2915 women with a singleton gestation and 151 with a twin gestation had a cervical length measurement at 22-24 weeks of gestation by trained and certified sonographers. In the singleton cohort, the mean cervical length was 35 mm with a standard deviation of 8 mm.[8] A cervical length of 25 mm was approximately the 9th percentile for singletons and has now become the adopted cutoff for the diagnosis of short cervical length in singleton gestations. In an unselected population, short cervical length ($\leq$ 20 mm) at 23 weeks of gestation demonstrated a sensitivity of 58% with a false positive rate of 7% and a positive predictive value of 11% for spontaneous preterm birth $\leq$ 32 weeks.[9]

After the success of progesterone in women with previous preterm birth, the next logical step was to evaluate whether progesterone would prevent preterm delivery in women with a short cervix.

2.3 Progesterone for Short Cervix

In 2007, Fonseca et al. reported a randomized trial of 413 women with a short cervix (<15 mm) who were assigned to either 200-mg capsules of micronized progesterone administered vaginally daily or placebo. Vaginal progesterone was associated with a reduction in the primary outcome, spontaneous preterm birth

less than 34 weeks, (Relative Risk [RR] 0.56, 95% Confidence Interval [CI] 0.36 to 0.86).[10] The rate of preterm birth < 37 weeks was not reported.

In a randomized multinational trial of 659 women with a prior preterm birth, O'Brien et al. found no overall difference in the rate of preterm birth between progesterone and placebo.[11] However, in a small pre-specified subgroup analysis of 46 women with a cervical length of < 28 mm, the investigators found that there was a reduction in the rate of preterm birth < 32 weeks (0% vs. 29.6%, P = 0.014). There was no difference in preterm birth at any other gestational age cutoff.

Hassan et al. randomized 465 women with a short cervix (10 - 20mm) to either vaginal progesterone gel or placebo in a multinational trial of progesterone to prevent preterm delivery.[12] This study demonstrated a relative risk of 0.55 for the primary outcome, preterm birth <33 weeks (95% CI, 0.33–0.92) but there was no difference in the rate of preterm birth <37 weeks (RR 0.89, 95% CI 0.68 to1.16).

An individual participant data meta-analysis that included these trials of vaginal progesterone showed a significant reduction in preterm birth < 35 weeks (RR, 0.69; 95% CI, 0.55–0.88).[13]

In contrast with these positive findings, the MFMU Network examined the impact of 17-α hydroxy-progesterone caproate in nulliparous women with a short cervix (< 30 mm) and found no difference in the rate of preterm birth less than 37weeks.[14] Moreover, the FDA did not approve a New Drug Application for vaginal progesterone used to prevent preterm birth. In their reanalysis of the Hassan trial, the FDA concluded that there was considerable heterogeneity and a lack of efficacy among the US participants such that the data did not support the efficacy of progesterone gel.[15] Most recently the OPPTIMUM trial of vaginal progesterone conducted in the UK and Sweden did not show a benefit for women at high risk of preterm delivery. The definition of high risk included short cervix ≤ 25 mm as well as previous spontaneous preterm birth ≤ 34 weeks, or fetal fibronectin positive in conjunction with obstetrical risk factors.[16] Approximately one-third of the women had short cervical length. There was no differential effect between women with or without a short cervix as evidenced by a negative interaction test.

Nevertheless, the strategy of routine screening of cervical length and treatment with vaginal progesterone if the cervix is found to be short has been adopted by many in the obstetrical community. The American College of Obstetricians and Gynecologists (ACOG) Practice Bulletin stated that universal cervical length screening in women without a prior preterm birth may be considered.[17] The Society for Maternal-Fetal Medicine (SMFM) made a similar statement in 2012.[18] Several decision analyses have suggested that routine screening coupled with treatment with progesterone will result in a marked decreases in the rates of preterm birth < 34 weeks and substantial cost savings.[19,20] From a survey of the MFMU Network in 2014, 17 of the component 35 sites (at 14 centers) at that time (49%) were not measuring cervical length as part of the routine prenatal ultrasound, 7 sites were doing universal transvaginal cervical length screening and the remainder were measuring cervical length abdominally, with reflexive transvaginal cervical length measurement if the abdominal cervical length was below a cutoff of 30-35 mm.

2.4 Cervical Support for Short Cervix in Singleton Pregnancies - Cerclage

Besides progesterone, another strategy to prevent preterm delivery in high-risk women with a short cervix is to provide cervical support by means of a cerclage or pessary. The cerclage has been shown to be effective in preventing preterm delivery. In a meta-analysis of four prior randomized controlled trials of women with prior preterm birth and a short cervix (< 25 mm), Berghella noted a decrease in the rate of preterm birth < 35 weeks.[21] Owen, in a prospective randomized trial of cerclage in women with a prior preterm birth, found a decrease in the rate of preterm birth < 35 weeks in the subgroup of women with cervical length less than 15 mm.[22]

2.5 Cervical Support for Short Cervix in Singleton Pregnancies - Pessary

Vaginal pessaries have been used for many decades to treat uterine or vaginal vault prolapse but their use to prevent preterm birth dates back to the original case series reported by Cross in 1959.[23] In the late 1970s, a German doctor, Hans Arabin, designed a pessary made of flexible silicone.[24] The Arabin pessary has some theoretical benefits over cerclage in that the insertion is non-surgical and may mechanically tilt the cervix lowering mechanical stresses rather than a cerclage which simply encloses the cervix. Subsequent case reports and series have suggested that the Arabin pessary may offer benefit amongst women at risk for preterm birth.[25]

In the Spanish trial (PECEP) published in 2012, 385 women with a singleton pregnancy and a short cervix (< 25 mm) were randomized to either pessary or expectant management. A significant reduction was observed in the primary outcome, spontaneous preterm birth < 34 weeks (OR 0.18; 95% CI 0.08 to 0.37).[26] A similar difference was seen in spontaneous preterm birth < 37 weeks (OR 0.19; 95% CI 0.12 to 0·30) and in a composite of adverse neonatal outcomes (OR 0.14; 95% CI 0.04-0.39).

However, an international trial published by Nicolaides et al. showed that the Arabin pessary was not effective in preventing preterm birth < 34 weeks or < 37 weeks in 935 singleton pregnancies with cervical length less than or equal to 25 mm (OR 1.12; 95% CI 0.75 to 1.69). Preterm birth < 37 weeks was not reported.[27]

A small trial from Hong Kong in 108 women also showed no difference for preterm birth < 34 weeks (OR 1.04; 95% CI 0.94–1.12) or < 37 weeks (OR 0.96; 95% CI 0.81–1.14).[28] However, this trial was stopped before 10% of the planned sample size had accrued without a pre-specified stopping rule or conditional power analysis.

2.6 Safety and Acceptability of the Arabin Pessary

In the PECEP trial, 192 women were treated with the Arabin pessary.[26] While all women reported an increase in the amount of vaginal discharge, there were no serious adverse effects associated with the use of the pessary, including no increase in infection, rupture of membranes, or need for removal due to discomfort. Only 14% of patients required pessary repositioning at any point during pregnancy and only one patient (0.5%) requested pessary removal. There was no increase in the occurrence of adverse neonatal outcomes.

In the trial by Nicolaides et al., the pessary group had a higher rate than the control group of increased or new vaginal discharge (46.8% vs. 13.8%, P<0.001) and pelvic discomfort (11.4% vs. 3.4%, P<0.001). Ten percent (47 women) asked for the pessary to be removed, approximately half (25) because of discomfort and the remainder because of discharge (19) and vaginal bleeding (3). There appeared to be no provision in the protocol for replacing or repositioning the pessary. There was no difference in vaginal infection between the groups.[27]

In the Hong Kong trial, 53 women were treated with the Arabin pessary.[28] Women in the pessary group experienced significantly more side effects (55.6% versus 27.3%) than in the expectant management group. Nearly all of the side effects reported were vaginal discharge and this accounted for the difference between the groups (25 women versus 12). There were no differences in vaginal infection, ruptured membranes or adverse neonatal outcomes. The pessary dislodged in 2 patients and required replacement.

2.7 Rationale for a Randomized Clinical Trial

Although the rate of preterm birth among singleton pregnancies has slowly declined since its peak in 2005,[29] it remains the single largest cause of perinatal mortality and reduction of the preterm birth rate remains a public health priority. While short cervical length is one of the most powerful predictors of

subsequent preterm birth, the best treatment to reduce subsequent preterm birth remains unknown. Although some studies have shown a benefit to vaginal progesterone, some clinicians feel that the data are less than conclusive. In addition, some women may be reluctant to use a hormone-based treatment due to fear with regard to unknown, long-term effects. The Arabin pessary is a promising low–cost, non-surgical intervention that appears to be well-tolerated. Since it is not associated with hormone exposure, if shown effective it may offer a safe, simple and medication-free intervention. To date, however, the two larger trials to date have conflicting results. The results of an adequately powered and appropriately conducted trial from the United States will be important in determining whether the Arabin pessary is a useful intervention for the prevention of subsequent preterm birth in women with singleton gestation.

3 Study Design

3.1 Primary Research Question

This randomized trial will address the primary research question:

In women with a singleton gestation and short cervical length less than or equal to 20 mm at 16 weeks 0 days to 23 weeks 6 days of gestation, does treatment with a cervical pessary reduce the risk of preterm birth prior to 37 weeks of gestation?

3.2 Secondary Research Questions

Secondary research questions that this study will address are:

- Does treatment with the Arabin cervical pessary for women with a short cervix (≤ 20mm) compared with usual care alter any of the secondary outcomes listed in Section 4.6, including:
    - Preterm birth less than 28 weeks, 32 weeks, or 35 weeks?
    - Neonatal morbidity or mortality?
    - Special care nursery admission?
    - Lower genital tract or urinary tract infection?
    - Physician interventions including labor inhibition, cerclage, and bed rest?
    - Alter the rates of inflammatory markers in cervicovaginal fluid?
- What is the acceptability of and compliance with the Arabin pessary as an adjunctive with vaginal progesterone?
- Are there specific subgroups in which treatment with the pessary is more efficacious? (See Section 5.5 for a discussion of subgroup analyses.)
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3.3 Design Summary

The study is an unblinded randomized controlled multi-center clinical trial of 850 women with a singleton gestation and ultrasound evidence of short cervical length, defined as less than or equal to 20 mm, randomized to one of two arms at participating MFMU Network clinical centers.

- Usual care. Women will receive vaginal progesterone if they meet the criteria per local standard of care.
- Arabin cervical pessary. If the local usual care is to receive vaginal progesterone for a short cervix, women randomized to the pessary will also receive progesterone.

3.4 Eligibility Criteria

3.4.1 Inclusion Criteria

1. Singleton gestation. Twin gestation reduced to singleton either spontaneously or therapeutically, is not eligible unless the reduction occurred before 13 weeks 6 days project gestational age (see below). Higher order multifetal gestations reduced to singletons are not eligible.

2. Gestational age at randomization between 16 weeks 0 days and 23 weeks 6 days based on clinical information and evaluation of the earliest ultrasound as described in Gestational Age Determination in Section 3.4.2 below.
3. Cervical length on transvaginal examination of less than or equal to 20 mm by a study certified sonographer. There is no lower cervical length threshold.

3.4.2 Gestational Age Determination

Gestational age is determined using criteria proposed by the American Congress of Obstetrics and Gynecology, the American Institute of Ultrasound in Medicine and the Society for Maternal-Fetal Medicine and is denoted as the "project gestational age".[30] The "project EDC", which is based on the project gestational age, cannot be revised once a determination has been made. If the pregnancy is conceived by in-vitro fertilization, project gestational age is calculated from the date of embryo transfer and the embryo age at transfer. If the pregnancy is conceived spontaneously (including ovulation induction and artificial insemination) information from the earliest dating ultrasound and the last menstrual period are used to determine project gestational age. If no dating ultrasound has been performed previously, one must be performed before the patient can be randomized.

Table 1. Cutoffs for Using LMP to Determine Gestational Age for Sure LMP

Gestational age at first ultrasound by LMP	Ultrasound method of measurement	Ultrasound agreement with LMP
Up to 8 weeks 6 days	CRL	± 5 days
9 weeks 0 days to 13 weeks 6 days	CRL	± 7 days
14 weeks 0 days to 15 weeks 6 days	Per institution	± 7 days
16 weeks 0 days to 21 weeks 6 days	Per institution	± 10 days
22 weeks 0 days to 23 weeks 6 days	Per institution	± 14 days

3.4.3 Cervical Length Determination

The length of the cervix will be measured according to the transvaginal ultrasound method described by Iams et al.[31] With a real-time ultrasound probe placed in the anterior fornix of the vagina while the woman's bladder is empty, the appropriate sagittal view will be obtained by the location of the triangular area of echodensity at the external os, a V-shaped notch at the internal os, and a faint line of echodensity or echolucency between the two. After the initial image is obtained once the probe is in place, the probe will be withdrawn until the image blurs, and then the probe will be reapplied with only enough pressure to restore the image. The cervix will be measured three times along the line made by the interface of the mucosal surfaces, with calipers placed at the external and internal os. Dynamic change in cervical length will be considered by observing for spontaneous dynamic change or by applying mild fundal pressure for 15-30 seconds and then re-measuring the cervical length. The final cervical measurement reported will be the shortest best measure that clearly meets the above criteria – an averaging approach will not be used.

All cervical length measurements employed for enrollment will be performed by a sonographer who has been trained and certified in transvaginal cervical length measurement. If the initial screening measurement has been obtained by a non-accredited sonographer it will need to be repeated by a credentialed sonographer. Credentialed sonographers will have documentation of education and proficiency in appropriate technique and competency in cervical assessment. Required documentation includes a Fetal Medicine Foundation Certificate of Competence in cervical assessment, or certification

through the Perinatal Quality Foundation's Cervical Length Education and Review (CLEAR) program, or sonographer participation in a previous NICHD study.

An advisory committee of ultrasound experts will be assembled to review a random sampling of approximately 10-15% of enrollment vaginal ultrasound cervical length measurements as validation of appropriate imaging techniques.

3.4.4 Exclusion Criteria

1. Cervical dilation (internal os) 3 cm or greater on digital examination or evidence of prolapsed membranes beyond the external cervical os either at the time of the qualifying cervical ultrasound examination or at a cervical exam immediately before randomization.
2. Fetal anomaly or imminent fetal demise. This includes lethal anomalies, or anomalies that may lead to early delivery or increased risk of neonatal death e.g., gastroschisis, spina bifida, serious karyotypic abnormalities. An ultrasound examination from 14 weeks 0 days to 23 weeks 6 days by project EDC must be performed prior to randomization to evaluate the fetus for anomalies.
3. Previous spontaneous preterm birth between 16 weeks 0 days and 36 weeks 6 days. This includes induction for pPROM in a prior pregnancy.
4. Planned treatment with intramuscular 17-α hydroxy-progesterone caproate
5. Placenta previa, because of risk of bleeding and high potential for indicated preterm birth. A low lying placenta is acceptable.
6. Active vaginal bleeding greater than spotting at the time of randomization, because of potential exacerbation due to pessary placement.
7. Symptomatic, untreated vaginal or cervical infection because of potential exacerbation due to pessary placement. Patients may be treated and if subsequently asymptomatic, randomized.
8. Active, unhealed herpetic lesion on labia minora, vagina, or cervix due to the potential for significant patient discomfort or increasing genital tract viral spread. Once lesion(s) heal and the patient is asymptomatic, she may be randomized. History of herpes is not an exclusion.
9. Rupture of membranes due to likelihood of pregnancy loss and preterm delivery as well as the risk of ascending infection which could be increased with pessary placement.
10. More than six contractions per hour reported or documented prior to randomization. It is not necessary to place the patient on a tocodynamometer.
11. Known major Mullerian anomaly of the uterus (specifically bicornuate, unicornuate, or uterine septum not resected) due to increased risk of preterm delivery which is unlikely to be affected by progesterone.
12. Any fetal/maternal condition which would require invasive in-utero assessment or treatment, for example significant red cell antigen sensitization or neonatal alloimmune thrombocytopenia.
13. Major maternal medical illness associated with increased risk for adverse pregnancy outcome or indicated preterm birth (treated hypertension requiring more than one agent, treatment for diabetes prior to pregnancy, chronic renal insufficiency defined by creatinine >1.4 mg/dL, carcinoma of the breast, conditions treated with chronic oral glucocorticoid therapy). Lupus, uncontrolled thyroid disease, and NYHA stage II or greater cardiac disease are also excluded. Patients with seizure disorders, HIV, and other medical conditions not specifically associated with an increased risk of indicated preterm birth are not excluded. Prior cervical cone/LOOP/LEEP is not an exclusion criterion.
14. Planned cerclage or cerclage already in place since it would preclude placement of a pessary.

15. Planned indicated delivery prior to 37 weeks.
16. Allergy to silicone
17. Participation in another interventional study that influences gestational age at delivery or neonatal morbidity or mortality.
18. Participation in this trial in a previous pregnancy. Patients who were screened in a previous pregnancy, but not randomized, may be included.
19. Prenatal care or delivery planned elsewhere unless the study visits can be made as scheduled and complete outcome information can be obtained.

3.5 Informed Consent Criteria

Written informed consent must be obtained from patients before they can be screened for the study by cervical ultrasound unless the ultrasound is clinically indicated or part of routine clinical care. Patients who are eligible for the study because of the ultrasound results will be asked to sign another consent form to participate in the trial. Full disclosure of the nature and potential risks of participating in the trial is to be made.

Each center will develop its own consent form(s) according to the requirements of its own institutional review board using the model screening and study consent forms in Appendix B. Each center will also develop its own patient research authorization documents, as required by the HIPAA Privacy Rule, following the guidelines of its own institution. A copy of the signed screening consent form and, if applicable, the consent form for the study will be provided to the patient.

Women who are not fluent in English will be enrolled by a person fluent in their language, if possible. Both verbal and written informed consent and authorization will be obtained in that language; if this is not possible the patient will be excluded.

3.6 Randomization Method and Masking

Consenting women will be assigned to one of the two arms by using an internet based randomization system maintained centrally by the Biostatistical Coordinating Center (BCC).

The simple urn method will be used to generate the randomization sequences because it provides a high probability of balance in treatment assignments, it is unpredictable, and it allows an explicit randomization analysis to be conducted with relative ease. Randomization will be stratified by clinical site to assure balance between the two arms with respect to anticipated differences in the clinic populations and possible differences in patient management.

4 Study Procedures

4.1 Screening for Eligibility and Consent

All women with singleton gestation presenting for prenatal care before approximately 24 weeks gestational age are potentially eligible for screening. Women, who are identified with a short cervix through clinical or research screening will be approached for inclusion into this trial. The measurement must have been made by a certified sonographer. Patients who have had a documented short cervical length (≤ 20 mm) by non-study certified personnel are eligible for inclusion in the study but would still have to undergo cervical length screening by an official study sonographer.

If the cervical length is 20 mm or less, consent for the trial will be obtained and the patient will be screened for eligibility. If an obstetrical ultrasound examination to evaluate the fetus for anomalies has not been performed at 14 weeks of gestation or later, one must be performed before randomization. The results of this ultrasound must be reviewed to check for exclusion criteria, and if it is the patient's first ultrasound with dating parameters, gestational age. The results of the dating and/or anatomy ultrasounds may be made available to the patient's physician.

Immediately prior to randomization a speculum examination will be performed (followed by a digital exam if necessary) to rule out cervical dilation and cervical infection, as well as an evaluation of preterm premature rupture of the membranes (pooling, nitrazine, ferning). A cervicovaginal fluid sample, vaginal Gram stain, and vaginal pH will be collected to assess for local inflammation and vaginitis.

4.2 Randomization

Eligible and consenting patients will be randomized by certified research staff using an internet based randomization system maintained by the BCC. The patient will be assigned either to pessary or usual care.

4.3 Baseline Procedures

In addition to information collected for eligibility, project gestational age, and project EDC determination, the following information will be obtained at randomization from a patient interview followed by a review of her chart:

- Demographic information: age, race, insurance status
- Medical history: pre-pregnancy weight, current weight, height, chronic disease history
- Obstetrical history including outcome of all prior pregnancies and history of vaginal bleeding in the current pregnancy
- Social history: marital status, years of education, alcohol use, tobacco use and other maternal drug use
- Complications during this pregnancy including sexually transmitted infections and vaginal infections.
- Current and planned progesterone treatment per usual care at the participating site.

Women randomized to pessary will be evaluated by an accredited obstetric care provider (nurse, nurse practitioner, nurse midwife, or physician) who has been trained in the proper technique of pessary sizing and placement. The provider will fit the patient for and place an Arabin pessary according to standard techniques so that it encircles the cervix and rests in the anterior and posterior fornices. Care to ensure

that the entirety of the cervix is contained within the pessary will be assessed through a vaginal digital examination. Women will be provided with written education regarding anticipated symptoms with a pessary and indications for physician assessment. The patient will be instructed to present to the research center on the next business day if the pessary should be spontaneously expulsed.

All women will be provided with education regarding the warning symptoms of preterm labor.

4.4 Patient Management and Follow-up

All patients will receive a phone call from a research nurse to assess compliance and symptoms within one week of randomization. If a patient in the pessary group is experiencing discomfort she will be asked to come in to assess the pessary for fit and possible replacement with a different size.

All patients will have monthly study visits (in-person or virtual) with a research nurse/provider for compliance, symptoms related to treatment, review of recent hospitalization(s), and any additional treatment received for preterm labor, such as corticosteroids or tocolytics since their last visit. Data on ongoing progesterone treatment will be collected.

A second set of cervicovaginal fluid samples will be collected if an in-person study visit occurs between 24 to 32 weeks by project gestational age. The second samples will include a cervicovaginal fluid sample, vaginal Gram stain and vaginal pH (without a speculum exam) to assess for local inflammation and vaginitis. The samples will be evaluated not only for their potential individual association with outcomes, but also to examine any potential interval changes that may be associated with the assigned treatment arm. Women randomized to pessary will have at least one in-person visit to undergo a digital examination to ensure appropriate pessary placement.

At the second study visit after randomization, patients randomized to pessary will be asked to complete a questionnaire summarizing their experience with the pessary. The questionnaire will be administered again at 37 weeks gestation.

Therapy will be continued until 36 weeks 6 days, at which time all patients should have a final study visit scheduled. Women in the pessary arm will have the device removed at this visit.

The pessary may be removed as necessary to evaluate vaginal bleeding contractions, preterm labor, or other conditions. The pessary will be reinserted if symptoms resolve and the cervix is less than 3 cm dilated. A patient will be instructed to call if the pessary comes out (fully or partially), becomes dislodged or if she removes it herself so that arrangements for a replacement pessary can be made. If the patient is uncomfortable, a replacement pessary may be inserted or the original pessary may be reinserted or repositioned.

Indications for pessary removal are as follows:

1. Painful, regular uterine contractions occurring at least every 10 minutes in order to facilitate accurate assessment of cervical dilation and effacement, especially if cervical examination with the pessary in place suggests dilation or progressive cervical shortening.
2. Confirmed rupture of membranes — the initial assessment for rupture can be performed with the pessary in place, but once confirmed, the pessary should be removed.
3. Confirmed diagnosis of clinical chorioamnionitis.
4. Active vaginal bleeding greater than spotting — if the bleeding ceases and there are no other contraindications, the pessary can be replaced.
5. Development of significant cervical edema with a cervical herpetic lesion.
6. Cervical laceration or significant edema.

7. At the patient's request because of significant discomfort or other reasons.

If a patient presents with symptoms of vaginitis, she should be treated as per local clinical standards. No attempt will be made to alter or mandate clinical management of the subjects, which includes corticosteroids, tocolytics and magnesium sulfate. In rare instances an exam-indicated rescue cerclage may be placed at the discretion of the provider. Sexual intercourse is not expressly prohibited in this study. However, the use of serial cervical length ultrasounds, prophylactic tocolytic drugs or cerclage is discouraged.

Neonates will be followed to 28 days after the expected date of delivery or to discharge, whichever is longer. Maternal and neonatal records will be reviewed and a follow-up telephone interview conducted to capture neonatal and maternal outcomes.

4.5 Adverse Event Reporting

Detailed information concerning adverse events will be collected and evaluated throughout the conduct of the protocol.

The NICHD Program Scientist and the BCC will be notified within seventy-two hours of any maternal or neonatal death by email/phone/fax, if the event occurred in a MFMU Network hospital. For any maternal or neonatal death occurring outside a MFMU Network hospital, the adverse event must be reported to the NICHD and the BCC within twenty-four hours of being notified. These and other adverse events deemed serious, unexpected and definitely, possibly or probably related, will be immediately (within twenty-four hours of notification) forwarded by the BCC to the DSMC Chair, NIH representative, and any other DSMC member who requests notification. If a death is reported, a copy of the patient's medical record will be made.

Adverse events which do not qualify under the above definition must be reported to the BCC within 7 days of being notified. These adverse events will be collected and sent to the Chair, NIH representative, and any other requesting DSMC member on a monthly basis. The Chair decides whether the adverse event reports should be disseminated to the rest of the committee and whether a follow-up call or meeting is required. NICHD representatives may also request follow-up of specific events. All adverse events will be considered along with other interim safety data in the DSMC deliberations.

An IDE safety report will be completed for any suspected adverse reaction to the pessary that is both serious and unexpected.

4.6 Study Outcome Measures and Ascertainment

4.6.1 Primary outcome

The primary outcome is delivery or fetal demise prior to 37 weeks 0 days (as determined by the project gestational age).

4.6.2 Maternal Secondary Outcomes

1. Interval from randomization to delivery or fetal demise
2. Gestational age at delivery
3. Preterm delivery or fetal demise prior to 28 weeks, 32 weeks or 35 weeks
4. Preterm premature rupture of membranes (pPROM)
5. Spontaneous preterm delivery (following preterm labor or pPROM)
6. Indicated preterm delivery

7. Cesarean delivery
8. Chorioamnionitis
9. Maternal antepartum hospitalization days
10. Maternal antibiotic or antifungal use for vaginal infection
11. Vaginal infection as assessed by local clinical diagnosis
12. Treatment for preterm labor, including cervical cerclage
13. Side effects including symptomatic vaginal discharge or discomfort
14. Discontinuation of pessary treatment and reason

4.6.3 Fetal and Neonatal Secondary outcomes

1. Fetal or neonatal death
2. Duration of ventilator support
3. Duration of supplemental oxygen
4. Seizures requiring treatment
5. Small for gestational age defined as < 5^{th} percentile weight for gestational age, assessed specifically by sex and race of the infant based on United States birth certificate data
6. Intraventricular hemorrhage (IVH) grades III or IV as determined by cranial ultrasounds performed as part of routine clinical care and classified based on the Papile classification system
7. Retinopathy of prematurity (ROP). This diagnosis will be reached when an ophthalmologic examination of the retina has been performed and ROP is diagnosed at Stage I (demarcation line in the retina) or greater.
8. Respiratory distress syndrome (RDS) defined as the presence of clinical signs of respiratory distress (tachypnea, retractions, flaring, grunting, or cyanosis), with an oxygen requirement and a chest x-ray that shows hypoaeration and reticulogranular infiltrates.
9. Bronchopulmonary dysplasia (BPD) defined as oxygen requirement at 28 days of life or at 36 weeks project gestational age for infants born before 32 weeks.
10. Necrotizing Enterocolitis (NEC), defined as modified Bell Stage 2 or 3 where stage 2 represents clinical signs and symptoms with pneumatosis intestinalis on radiographs and stage 3 is defined as advanced clinical signs and symptoms, pneumatosis, impending or proven intestinal perforation.
11. Hyperbilirubinemia. Peak total bilirubin of at least 15 mg% or the use of phototherapy
12. Neonatal infectious morbidity
    - Sepsis (within 72 hours and > 72 hours after birth). The diagnosis of sepsis will require the presence of a clinically ill infant in whom systemic infection is suspected with a positive blood, CSF, or catheterized/suprapubic urine culture; or, in the absence of positive cultures, clinical evidence of cardiovascular collapse or an unequivocal radiograph confirming infection.
    - Suspected sepsis. The diagnosis of suspected sepsis will include infants with suspicious clinical findings of infection, but no positive cultures or radiographs.
    - Pneumonia. The diagnosis of pneumonia will be confirmed by radiograph or positive blood culture.

13. Composite neonatal outcome comprised of fetal or neonatal death or RDS, Grade 3 or 4 IVH, PVL, Stage 2 or 3 NEC, BPD, Stage III or higher ROP, or early onset sepsis. Occurrence of any of the individual components is considered indicative of the outcome
14. Length of hospital stay, need for NICU or intermediate care admission and length of stay

5 Statistical Considerations

5.1 Data Relevant to the Primary Outcome

Hassan, who used a screening cervical length of between 10-20 mm, found a rate of preterm birth < 37 weeks of 26.7% in women treated with progesterone.[12] Because of the exclusion of women with cervical lengths between 0-9 mm it is highly plausible that the rate will be higher in the current trial. In an individual patient data meta-analysis of vaginal progesterone trials by Romero et al., the pooled preterm birth rate for singleton pregnancies was 34.7% for women with a short cervix of < 25 mm. However, Conde-Agudelo et al. in a systematic review and indirect comparison meta-analysis that contained overlapping but not exactly the same trials reported a rate of preterm birth<37 weeks of 45.3%.[32] Goya et al reported a 59% rate of spontaneous preterm delivery < 37 weeks for women with short cervix ≤ 25 mm in the expectant management group.[33]

5.2 Sample Size and Power

A one-third reduction in preterm birth < 37 weeks was selected as being clinically meaningful. If it is conservatively assumed that the rate of preterm birth <37 weeks in the progesterone arm is between 28% and 35%, then a sample of 850 women is sufficient to detect a 33% reduction in preterm birth at 90% power. In addition this sample size yields more than 80% power to detect a 30% reduction, assuming a type 1 error of 5% 2-sided.

Table 2. Sample Size for Various Outcome Rates and Effect Sizes

PTB rate in Usual care arm (%)	Total sample size for 30% reduction	Total sample size for 33.3% reduction
Power=80% (α=0.05; β=0.2)		
28	810	640
30	740	590
32	680	540
35	600	480
Power=90% (α=0.05; β=0.1)		
28	1080	850
30	990	790
32	900	720
35	800	640

5.3 Feasibility

The feasibility of answering the primary research question will be addressed after the first 150 patients have been randomized and delivered. The primary outcome rate in the usual care group will be presented to the Data and Safety Monitoring Committee (DSMC) without any comparison by group. The DSMC would be charged with making a recommendation regarding potential revision of the sample size in addition to addressing the feasibility of answering the primary research question.

5.4 Interim Analysis

The DSMC meets in person at least once per year and more often if recommended by the committee. Before each of the annual meetings, a formal detailed report will be written by the Biostatistical Coordinating Center (BCC) which presents all baseline variables, protocol adherence, side effects, all adverse events reported, as well as center performance in terms of recruitment, data quality, loss to follow-up and protocol violations.

Once sufficient patients have been accrued into the trial, the report will also include a formal interim analysis evaluating the primary outcome by treatment group. For this evaluation, a cohort of patients is chosen consisting of all patients randomized before a certain date so that the analysis cohort does not depend on gestational age at delivery.

The main statistical issue relevant to interim analysis is the problem of performing multiple tests of significance on accumulating data. For this trial, the group sequential method of Lan and DeMets will be used to characterize the rate at which the type I error is spent.[34] This method is flexible with regard to the timing of the interim analyses. It is expected that an interim analysis will be conducted at approximately 50% of the final sample size of 850.

Asymmetric stopping boundaries will be used for the Lan-DeMets procedure. The upper boundary which describes the stopping rule for benefit will be based on 1-sided type I error of .025 and the Lan-DeMets generalization of the O'Brien-Fleming boundary. The lower boundary will be based on a less stringent stopping rule: 1-sided type I error of .05 and the Lan-DeMets generalization of the Pocock type boundary.

It is often useful to calculate conditional power given the observed data to date, and conditional on the future data showing the originally assumed design effect. If this conditional power is low (under 10 percent) the DSMC may consider termination for futility if the accrual rate is slow with confidence that the Type II error is not greatly inflated.[35]

It is recognized that any decision to terminate the study would not be reached solely on statistical grounds but on a number of complex clinical and statistical considerations.

5.5 Analysis Plan

All statistical analyses will be based upon the total cohort of patients randomized into the trial. Although data on some patients may be missing, all relevant data available from each patient will be employed in the analyses. Patients will be included in the treatment group to which they were randomly assigned regardless of compliance.

The primary analysis will consist of a simple comparison of binomial proportions. The relative risk and confidence interval will be reported. The individual components of the composite outcome will also be examined. If the treatment groups are found to differ on a pre-treatment factor known to be a risk factor for the outcome, the statistical analysis will adjust for these differences. An evaluation of treatment by center interaction will be included. An analysis adjusting by center also will be performed to ensure that center differences do not change the conclusion.

If the two groups show a difference in the incidence of the primary outcome, interactions will be evaluated and subgroup analyses conducted to determine whether the effect prevails throughout particular subgroups of patients. Indeed, NIH guidelines require investigators to evaluate consistency between the genders and across racial subgroups (see Section 5.5.1). It should be noted, however, that subgroup analyses have been greatly abused, particularly when there is no overall treatment difference.[36] There is a strong temptation to search for a specific subpopulation in which the therapy is nevertheless effective. Yusuf et al. concluded "the overall 'average' result of a randomized clinical trial is usually a more reliable estimate of the treatment effect in the various subgroups examined than are the observed effects in individual subgroups."[37] Thus subgroup analyses will be interpreted with care.

It is generally acknowledged that subgroup analysis that is pre-specified in the protocol has more validity than ad-hoc comparisons. The following factors will be considered for subgroup analysis, if there is a significant interaction between the factor of interest and the treatment effect.

- Race/ethnicity (see below)
- Gestational age at randomization (< 20 weeks and ≥ 20 weeks)
- Cervical length at randomization (< 15 and ≥ 15 - 20 mm)
- Treatment with vaginal progesterone (as planned per usual care locally)
- Screening to randomization interval
- Debris/funneling on randomization ultrasound
- Obesity by BMI category
- Parity
- Bacterial vaginosis/Nugent score at enrollment—Nugent ≥ 7 with pH > 4.4
- Prior cervical surgery including LOOP/ LEEP

Loss to follow-up will be defined as no information regarding pregnancy prior to 37 weeks. Those defined as lost to follow-up will not be included in the primary analysis. It is expected that the loss to follow-up rate will be very low. For trials conducted by the MFMU Network, the loss to follow-up rate has typically been under 2 percent. However, a sensitivity analysis will be performed including patients lost to follow-up with different assumptions regarding their outcome, to determine whether the results are robust.

Since many of the secondary endpoints are dichotomous variables like the primary outcome, standard statistical methods for rates and proportions will be appropriate. The Wilcoxon rank sum test will be used to compare continuous variables, and survival analysis methodology may be used to compare time-to-event variables.

In general, analyses of data will be conducted to address the primary and secondary research questions of the trial, and other interrelationships among elements of study data of interest to the investigators and of relevance to the objectives of the study.

5.5.1 Racial/Ethnic Subgroup Analysis

The racial/ethnic composition of women recruited into the MFMU Network trials varies. Assuming for this trial that the composition is 50% African-American and 15% Hispanic, similar to the SCAN trial there is >90% and approximately 50% power respectively to detect a 50% reduction in the primary outcome in the separate subgroups.

6 Data Collection

6.1 Data Collection Forms

Data will be collected on standardized forms on which nearly all responses have been pre-coded. Each form is briefly described below:

- TO01 Screening Log.
- TO01A Eligibility Checklist
- TO02 Eligibility and Randomization Form is completed for all patients eligible for the study.
- TO03A Pessary Accountability Log lists the specific pessary(ies) given to each patient.
- TO04 Baseline Form is completed for all randomized patients. This form includes detailed demographic and social data, medical and obstetrical history, and current pregnancy complications.
- TO04A Previous Pregnancy Outcome Form.
- TO05 Study Visit Form documents monthly study visits, possible side effects and compliance
- TO07 Unscheduled Visit or Hospitalization Form is completed for all patients who had an unscheduled emergency room, Labor & Delivery, clinic visit or hospitalization between the scheduled monthly visits, including the delivery admission.
- TO08 Maternal Delivery and Outcome Form documents specific pregnancy complications since randomization, in addition to labor, delivery and postpartum information.
- TO09 Neonatal Baseline Form records date and time of birth, delivery data and status at delivery, for each fetus/infant.
- TO10 Neonatal Outcome Form records outcome data for all infants admitted to the NICU or special care nursery.
- TO11 Patient Status Form documents loss to follow up/withdrawal status, last date of contact for lost to follow-up patients, side effects since the last dose.
- TO12 Adverse Event Form records serious and non-serious adverse events.
- TO13A Women's Views on the Arabin Pessary, a patient questionnaire.
- TO14 Pessary Removal Form documents the position of the pessary at the time of removal.

6.2 Web Data Entry System

For this protocol, web data entry screens corresponding to the study forms listed above will be developed and maintained by the staff of the BCC. Clinical center staff will enter data into the MySQL database located at the BCC through a web data management system (MIDAS). The data are edited on-line for missing, out of range and inconsistent values. A Users' Manual documenting this system is provided to the centers by the BCC.

6.3 Centralized Data Management System

Daily data conversions from the MySQL database create up-to-date SAS datasets. Data are reviewed weekly using edit routines similar to those implemented on-line during data entry, as well as additional checks for data consistency within or across forms. A database of resulting potential data problems is generated in MIDAS for initial review by BCC staff who then evaluate the comments keyed in association with edits on missing or unusual values. Valid edits will be flagged in MIDAS for resolution at the clinical centers.

At regular intervals, specialized data reviews comparing data availability and consistency across forms are run by the BCC staff on the entire database or on a specific subset of data. These reports are also submitted to the centers for correction or clarification.

An audit trail, consisting of all prior versions of each data form as entered in the computer for each patient, is maintained so that the succession of corrections can be monitored.

6.4 Performance Monitoring

The BCC will present regular reports to the TOPS Subcommittee, the Steering Committee, and the Data and Safety Monitoring Committee. These include:

- Monthly Recruitment Reports - reports of the number of women screened and enrolled by month and by clinical center are provided monthly to the TOPS Subcommittee and all other members of the Steering Committee. Weekly or bi-weekly reports are provided electronically if needed.
- Quarterly Steering Committee Reports - reports detailing recruitment, baseline patient characteristics, data quality, incidence of missing data and adherence to study protocol by clinical center, are provided quarterly to the TOPS Subcommittee and all other members of the Steering Committee.
- Data and Safety Monitoring Committee Reports - for every meeting of the DSMC, a report is prepared which includes patient recruitment, baseline patient characteristics, center performance information with respect to data quality, timeliness of data submission and protocol adherence (in addition to safety and efficacy data). The reports also include adverse events, loss to follow-up and all outcome variables as described previously in this protocol.

7 Study Administration

7.1 Organization and Funding

The study is funded by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD). The study is conducted by the NICHD Maternal-Fetal Medicine Units (MFMU) Network, consisting of twelve clinical centers, the Biostatistical Coordinating Center (BCC) and the NICHD, and is administered under cooperative agreements between each of the centers and the NICHD. Each of the funded institutions is represented by a Principal Investigator. A complete description of the organization of the MFMU Network is provided in the MFMU Network Policy Manual.

7.1.1 Participating Clinical Centers

The participating Principal Investigators of the clinical centers have agreed to abide by the study protocol, to have comparable staff, facilities and equipment and to ensure the proper conduct of the study at each of their centers including: recruitment and treatment of patients as specified in the protocol, accurate data collection and the transmission of information to the Steering Committee.

7.1.2 Biostatistical Coordinating Center

The BCC is responsible for all aspects of biostatistical design, data management, interim and final statistical analyses, and preparation of publications based on the study results. The Principal Investigator of the BCC reports to the Steering Committee and the Data and Safety Monitoring Committee.

7.1.3 NICHD

In addition to its role as funding agency, the NICHD participates in the activities of the Network, including the development of protocols, administration and conduct of the studies and preparation of publications.

7.1.4 Network Advisory Board

Appointed by the NICHD, the members of the Network Advisory Board consist of a group of experts who are not affiliated with research being conducted by the Network and represent the disciplines of maternal-fetal medicine, neonatology and biostatistics/epidemiology. The role of the board includes the review and prioritization of proposed studies, in addition to the identification of scientifically and clinically important questions and ideas that might be conducted by the Network. The NICHD Project Scientist convenes and attends the meetings.

7.2 Committees

7.2.1 Steering Committee

This committee consists of fifteen members. The Principal Investigator from each of the twelve clinical centers, the BCC, and the NICHD MFMU Network Project Scientist are all voting members. The Chair of the Steering Committee may vote to break a tie. The Chair, a person independent of the participating institutions, is appointed by NICHD. The Steering Committee has the responsibility for identifying topics for Network studies, designing and conducting study protocols and monitoring study implementation, recruitment and protocol adherence. The committee receives recommendations from the Data and Safety Monitoring Committee and the Network Advisory Board.

7.2.2 Protocol Subcommittee

The subcommittee consists of a chair (who is an investigator from one of the clinical centers), investigators from one or more other clinical centers, BCC staff, nurse coordinators, outside consultants

(if appropriate), and the NICHD Network Project Scientist. The Protocol Subcommittee is responsible for the preparation and conduct of the study, and reporting the progress of the study to the Steering Committee.

7.2.3 Publications Committee

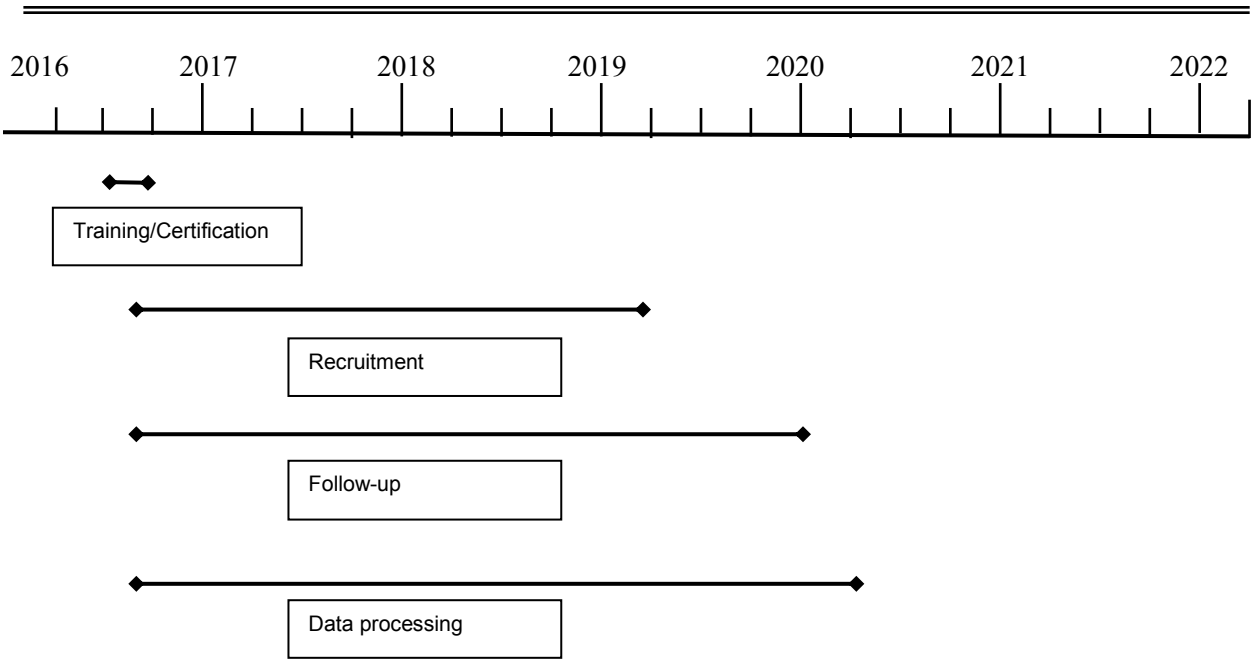
The Publications Committee is a standing committee of the Steering Committee. The functions of this committee are to develop publication policies and to review all manuscripts and abstracts prior to submission. The goals of this committee are fair and appropriate authorship credit and high quality publications.

7.2.4 Data and Safety Monitoring Committee

The Data and Safety Monitoring Committee (DSMC), a group of individuals not affiliated with any of the participating institutions, was established by the NICHD. Before the trial can begin, the protocol must be approved by the committee. During the conduct of the study, the committee is charged with monitoring the emerging results for efficacy and safety, in addition to center performance and protocol adherence. Recommendations by the committee can include protocol modification, early termination for efficacy, or for unexpected safety problems. Recommendations are made to the NICHD and disseminated to the Steering Committee.

8 Study Timetable

Figure 1. Timetable



8.1 Training and Certification

A preliminary training with the nurse coordinators was held on January 2016 and a final training was conducted for research staff in July 2016, in addition to CLEaR or Fetal Medicine Foundation certification of individual sonographers not previously certified. Physicians and staff at each study site will also have to undergo training in the appropriate techniques of pessary sizing and placement prior to receiving approval to begin enrollment. Each participating center must be certified to start the trial before recruitment at that center can begin. The certification requirements are designed to ensure that personnel involved in the trial are committed to the study and proficient in study procedures, and that the center has satisfied regulatory requirements. Each center is required to obtain IRB approval for the study before they are certified to begin the trial. The trial is expected to start in August/September 2016, if approved.

8.2 Recruitment and Data Collection Period

Approximately 160,000 women deliver at MFMU Network centers annually. It is conservatively hypothesized that that 1.5% of the women will have a short cervix $\leq$ 20 mm. In the MFMU SCAN trial of nulliparous singletons, 2 % of those screened had a cervical length $\leq$ 20mm before 23 weeks. In an analysis of the MFMU Network Prediction Study, 2.2% of parous women with a low–risk history had cervical length $\leq$ 20mm at 22-24 week ultrasound.[38] In Hassan et al., 2.3% of women had a cervical length between 10 and 20 mm.[12]

A survey of the MFMU Network sites in 2014 showed that in approximately 50% of the delivery population the cervix is not routinely measured, in 20% of the population universal routine transvaginal cervical length screening is conducted and in 30% the cervix is measured or evaluated by abdominal scan with reflexive transvaginal screening if it is short. If it is assumed that 80% of women receive an ultrasound at 16-23 weeks, and that there is a 20% detection rate for short cervix where cervical length is not measured routinely, 100% detection with routine transvaginal cervical length screening and a 90% rate when there is abdominal scan with reflexive transvaginal cervical length measurement, then with 160,000 deliveries per year approximately 1100 potentially eligible women would be available for recruitment annually.

Table 3. Calculation of Potential Number of Women with Short Cervix Detectable per Year

Approach (% detection)	Percent of Delivery Population	Short Cx (1.5%)	With Ultrasound (80%) at 15-23 wks	Detected
No Screening (detection rate 20%)	50	1200	960	192
Cervical Measurement (detection rate 100%)	20	480	384	384
Abdominal Measurement (detection rate 90%)	30	720	576	518
				1094

Assuming that only 75% of these women are accessible and eligible and that only 50% consent to the study, this would translate to an enrollment rate of 410 women per year, or 34 per month. Thus enrollment could be achieved within 30 months, even assuming a gradual start-up. If the percentage of women accessible and eligible cervix is only 50%, enrollment could still be achieved in just over 3 years.

8.3 Final Analysis

After a three-month period for completion of data entry for the trial and close-out of the delivery and primary outcome, the data set will be locked and available for the primary and other main analysis.

Appendix A Design Summary

A Randomized Trial of Pessary in Singleton Pregnancies with a Short Cervix

OBJECTIVE: To determine whether pessary reduces the risk of preterm birth in women with a singleton gestation and a short cervix.

ORGANIZATION

Clinical Centers: Magee, UAB, Ohio State, Utah, Brown, Columbia, Case Western, UT-Houston, UNC, Northwestern, UTMB-Galveston, UPenn

Subcommittee: Matthew Hoffman, MD (Chair)

DESIGN

Major Eligibility Criteria:
- Singleton gestation
- Gestational age 16^0 to 23^6 wks
- Cervical length ≤ 20.0 mm

Groups:
- Usual Care (may include vaginal progesterone)
- Arabin Pessary + Usual Care

Random Allocation: Standard urn design; 1:1 allocation

Level of Masking: Unmasked

Stratification:
- Clinical site

Sample Size:
- 850

Assumptions:
- Outcome event=delivery < 37^0 weeks gestation or fetal loss
- Usual care group event rate =28%
- Pessary group event rate =18.67% (33.3% reduction)
- Type I error = 2.5% (two sided with one comparison)
- Power =90%

Interim Analysis:
- Lan-DeMets group sequential method

SCHEDULED EVALUATIONS / DATA COLLECTION

Pre-Randomization:
- Cervical length measurement by trained sonographer
- Pregnancy, exposure and medical history

Randomization:
- Vaginal sample, vaginal Gram stain and vaginal pH

Post-randomization:
- Phone call to assess patient symptoms and compliance within 7 days of randomization
- Every four weeks: study visit to assess symptoms and compliance
- Study visit between 24 and 32wks: vaginal sample, vaginal Gram stain and vaginal pH
- Digital exam to ensure appropriate pessary placement (pessary group)

Delivery:
- Patient questionnaire 8 weeks after randomization and again at 37 wks gestation.
- Pessary group: assessed for fit or replacement, as needed
- Delivery and neonatal data

MANAGEMENT PROTOCOL

Both Groups:
- Vaginal progesterone per usual care and rescue cerclage if needed

Pessary Group:
- Placement management from randomization to < 37 wks

OUTCOME MEASURES

Primary:
- Delivery or fetal loss prior to 37 wks

Secondary:
- Randomization to delivery interval
- Gestational age at delivery
- Neonatal morbidity and mortality
- Lower genital tract or urinary tract infection
- Physician interventions including bedrest, cerclage, labor inhibition therapy

TIMETABLE

Enrollment: September 2016 to October 2019

Data Collection: September 2016 to October 2019

Closeout/Analysis: October 2019 to September 2021

Appendix B Sample Informed Consent Forms

B.1. Sample Informed Consent Form for Screening (without Common Rule 2018 changes)

Research Study Title: A Randomized Trial of Pessary in Singleton Pregnancies with a Short Cervix (TOPS)

Sponsor: *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) of the National Institutes of Health (NIH)

Principal Investigator: ***Phone ( ) -***

Introduction

You are invited to be screened to see if you are eligible to take part in a research study. This consent form provides the information about the risks and benefits of being screened for this research study. You can choose whether or not you will take part in the study. If you agree to be screened for this study, you will need to sign this consent form. This process is known as informed consent. Please tell the study doctor or study staff if you are taking part in another research study.
This consent form may contain words that you do not understand. Please ask the study staff to explain any words or information that you do not clearly understand.

Research Purpose

Women who have a short cervix (which is the lower, narrow part of the womb) are more likely to deliver preterm. Babies born preterm have a greater chance of having serious, long-term health problems or dying.

The purpose of this research study is to find out whether a pessary lowers the risk of a baby being born too soon to women with a short cervix. One study has been done to date in the US to find out if placing a pessary in women with a short cervix helps the pregnancy to last longer. That study did not show that the pessary delayed or prevented preterm birth but the study was too small to have a reliable result. Studies done in other countries have had differing results. A pessary is a soft silicone device that goes around the cervix to give the cervix support.

Procedures

If you consent to screening for this study, your cervix will be measured by a vaginal ultrasound. The ultrasound exam will take about 10 minutes. If the length of your cervix measures 20 mm (about ¾ of an inch) or less, a member of the research staff may contact you to talk about taking part in a study in which you will be randomized (like flipping a coin) into one of two treatment groups: 1) pessary or 2) non-pessary. The pessary group will have a pessary placed around the cervix. The non-pessary group will continue to receive the standard obstetric care provided by the doctor or nurse. You and your doctor or nurse will be informed of the results of your screening ultrasound examination.

Possible Risks

Vaginal ultrasounds have been used in pregnancy for many years and have not been shown to cause any harm to the mother or the unborn baby. It is widely used to look at the cervix. A vaginal ultrasound is like having a pelvic exam. Therefore, you may have mild discomfort during the exam.

Benefits

The screening may not benefit you directly. If your ultrasound shows that you have a short cervix, you may be eligible for the randomized study.

Alternatives

The alternative is not to participate in the screening.

Costs

There will be no additional cost to you for taking part in the screening.

Right to Withdraw From the Research Study

You are free to withdraw your consent and stop participating at any time.

Confidentiality

You have the right to privacy. All information obtained from this research that can identify you will remain confidential within the limits of the law. The results of your vaginal ultrasound will be sent to the data coordinating center, the George Washington University Biostatistics Center in Rockville, Maryland, with a unique code. Only the research study staff at this medical center for this study will have access to the key to the code that can identify you.

Certificate of Confidentiality

This research is covered by a Certificate of Confidentiality from the NIH. The researchers with this Certificate may not disclose or use information, documents, or biospecimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless you have consented for this use. Information, documents, or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except, if there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases but not for federal, state, or local civil, criminal, administrative, legislative, or other proceedings); if you have consented to the disclosure or if it is used for other scientific research, as allowed by federal regulations protecting research subjects.

The Certificate cannot be used to refuse a request for information from personnel of the United States federal or state government agency sponsoring the project that is needed for auditing or program evaluation by the NIH or to meet the requirements of the Food and Drug Administration (FDA). If you want your research information released to an insurer, medical care provider, or any other person not connected with the research, you must provide consent to allow the researchers to release it.

Questions

If you have questions about the procedures of this research study, please contact _____ by telephoning (___) ___-____ during the workday.

If you have any questions about the informed consent process or any other rights as a research subject, please contact _____, Director of the Office of Human Research, at (____) ___-____. _____ who is your representative.

Signatures

By signing this form you show that you have read this informed consent form, the study has been explained to you, your questions have been answered, and you agree to take part in the screening for this study.

_____	_____	_____
Participant (*Print Name*)	Signature	Date

_____ _____ _____

Person Obtaining Consent Signature Date

(Print Name)

ASSENT FOR FEMALES UNDER 18 YEARS of AGE **(if required by Center IRB):**

I agree _____ I do not agree_____ to participate in this study.

This has been explained to me by _____

_____ _____

Signature of Minor Date

_____ _____

Print Name of Subject Age

Please provide either one or both parental signatures as instructed by your IRB.

_____ _____

Signature of Mother/Guardian Date

_____ _____

Signature of Father/Guardian Date

A witness unrelated to the study is necessary if the participant can comprehend but cannot read (i.e., blind), or cannot sign (e.g., unable to use hands) the consent form.

_____ _____ _____

Witness' Name Signature Date

(Print Name)

B.2. Sample Informed Consent Form for Screening (with Common Rule changes)

Research Study Title: A Randomized Trial of Pessary in Singleton Pregnancies with a Short Cervix (TOPS)

Sponsor: *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) of the National Institutes of Health (NIH)

Principal Investigator: _____ ***Phone (___) ___ - ____***

Key Information

This screening study is being done to find out whether you have a short cervix which may make you eligible for a research study. Women with a short cervix have an increased risk of a baby being born too soon.

If you consent, your cervix will be measured by transvaginal ultrasound between 16,0 and 23,6 weeks of pregnancy. You and your doctor or nurse will be informed of the results of your screening ultrasound examination. If you have a short cervix, research staff may contact you to talk about taking part in a research study.

This screening may not benefit you directly. A possible risk of the vaginal ultrasound is mild discomfort during the exam. Participation in this research study is voluntary and if you do not take part, you will receive the routine care usually provided to pregnant women.

Introduction

You are invited to be screened to see if you are eligible to take part in a research study. This consent form provides the information about the risks and benefits of being screened for this research study. You can choose whether or not you will take part in the study. If you agree to be screened for this study, you will need to sign this consent form. This process is known as informed consent. Please tell the study doctor or study staff if you are taking part in another research study.

This consent form may contain words that you do not understand. Please ask the study staff to explain any words or information that you do not clearly understand.

Research Purpose

Women who have a short cervix (which is the lower, narrow part of the womb) are more likely to deliver preterm. Babies born preterm have a greater chance of having serious, long-term health problems or dying.

The purpose of this research study is to find out whether a pessary lowers the risk of a baby being born too soon to women with a short cervix. One study has been done to date in the US to find out if placing a pessary in women with a short cervix helps the pregnancy to last longer. That study did not show that the pessary delayed or prevented preterm birth but the study was too small to have a reliable result. Studies done in other countries have had differing results. A pessary is a soft silicone device that goes around the cervix to give the cervix support.

Procedures

If you consent to screening for this study, your cervix will be measured by a vaginal ultrasound. The ultrasound exam will take about 10 minutes. If the length of your cervix measures 20 mm (about ¾ of an inch) or less, a member of the research staff may contact you to talk about taking part in a study in which you will be randomized (like flipping a coin) into one of two treatment groups: 1) pessary or 2) non-pessary. The pessary group will have a pessary placed around the cervix. The non-pessary group will continue to receive the standard obstetric care provided by the doctor or nurse. You and your doctor or nurse will be informed of the results of your screening ultrasound examination.

Possible Risks

Vaginal ultrasounds have been used in pregnancy for many years and have not been shown to cause any harm to the mother or the unborn baby. It is widely used to look at the cervix. A vaginal ultrasound is like having a pelvic exam. Therefore, you may have mild discomfort during the exam.

Benefits

The screening may not benefit you directly. If your ultrasound shows that you have a short cervix, you may be eligible for the randomized study.

Alternatives

The alternative is not to participate in the screening.

Costs

There will be no additional cost to you for taking part in the screening.

Right to Withdraw From the Research Study

You are free to withdraw your consent and stop participating at any time.

Confidentiality

You have the right to privacy. All information obtained from this research that can identify you will remain confidential within the limits of the law. The results of your vaginal ultrasound will be sent to the data coordinating center, the George Washington University Biostatistics Center in Rockville, Maryland, with a unique code. Only the research study staff at this medical center for this study will have access to the key to the code that can identify you.

Certificate of Confidentiality

This research is covered by a Certificate of Confidentiality from the NIH. The researchers with this Certificate may not disclose or use information, documents, or biospecimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless you have consented for this use. Information, documents, or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except, if there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases but not for federal, state, or local civil, criminal, administrative, legislative, or other proceedings); if you have consented to the disclosure or if it is used for other scientific research, as allowed by federal regulations protecting research subjects.

The Certificate cannot be used to refuse a request for information from personnel of the United States federal or state government agency sponsoring the project that is needed for auditing or program evaluation by the NIH or to meet the requirements of the Food and Drug Administration (FDA). If you want your research information released to an insurer, medical care provider, or any other person not connected with the research, you must provide consent to allow the researchers to release it.

Questions

If you have questions about the procedures of this research study, please contact _____ by telephoning (___) ___-____ during the workday.

If you have any questions about the informed consent process or any other rights as a research subject, please contact _____, Director of the Office of Human Research, at (____) ___-____. _____ who is your representative.

Signatures

By signing this form you show that you have read this informed consent form, the study has been explained to you, your questions have been answered, and you agree to take part in the screening for this study.

_____	_____	_____
Participant (*Print Name*)	Signature	Date
_____	_____	_____
Person Obtaining Consent *(Print Name)*	Signature	Date

ASSENT FOR FEMALES UNDER 18 YEARS of AGE **(if required by Center IRB):**

I agree _____ I do not agree_____ to participate in this study.

This has been explained to me by _____

_____	_____
Signature of Minor	Date
_____	_____
Print Name of Subject	Age

Please provide either one or both parental signatures as instructed by your IRB.

_____	_____
Signature of Mother/Guardian	Date
_____	_____
Signature of Father/Guardian	Date

A witness unrelated to the study is necessary if the participant can comprehend but cannot read (i.e., blind), or cannot sign (e.g., unable to use hands) the consent form.

_____	_____	_____
Witness' Name	Signature	Date
(Print Name)		

B.3. Sample Informed Consent Form for RCT (without Common Rule 2018 changes)

Research Study Title: A Randomized Trial of Pessary in Singleton Pregnancies with a Short Cervix (TOPS)

Sponsor: *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) of the National Institutes of Health (NIH)

Principal Investigator: _____*Phone* (____) ___ - ____

Introduction

You are invited to take part in a research study. Before you decide to be a part of this study, you need to understand the risks and benefits. This consent form provides information about the research study. A member of the research team will be available to answer your questions. Please ask the study staff to explain any words or information that you do not clearly understand. You can choose whether or not you will take part in the study. If you agree to take part, you need to sign this consent form. This process is known as informed consent.

You have been asked to take part in this research study because you are between 16 weeks 0 days and 23 weeks 6 days pregnant with one baby and a vaginal ultrasound showed that your cervix is shorter than usual (less than or equal to 20 mm, which is about ¾ of an inch). The cervix is the lower, narrow part of your womb.

Please tell the study doctor or study staff if you are taking part in another research study.

Research Purpose

Women who have a short cervix are more likely to deliver preterm. Babies born preterm have a greater chance of having serious, long-term health problems or dying.

The purpose of this research study is to find out whether a pessary lowers the risk of a baby being born too soon to women with a short cervix. One study has been done to date in the US to find out if placing a pessary in women with a short cervix helps the pregnancy to last longer. That study did not show that the pessary delayed or prevented preterm birth but the study was too small to have a reliable result. Studies done in other countries have had differing results. A pessary is a soft silicone device that goes around the cervix.

The Arabin pessary has not been approved by the FDA for treating pregnant women who have a short cervix and are at risk for preterm delivery. For this reason, the pessary is considered to be an 'investigational' device and is being used for research purposes only**.**

You will be in the study from the time of randomization (between 16-23 weeks of pregnancy) until one month after your expected date of delivery or until your baby is discharged from the hospital, whichever is the longest.

This research study is funded by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD). Twelve medical centers across the country are part of this research study, and in all, 850 women with singleton pregnancies who have a short cervix will be enrolled.

Procedures

If you are eligible and decide to participate in this study, you will be asked to sign this consent form. If you consent, you will be randomized (like tossing a coin) to one of two treatment groups: 1) pessary or 2)

non-pessary. The pessary group will have a pessary placed around the cervix. The non-pessary group will continue to receive the standard obstetric care provided by the doctor or nurse.

All study participants will receive standard obstetric care should they develop symptomatic preterm labor. This care may include the following:

- Corticosteroids which helps preterm babies breathe easier
- Magnesium sulfate which may prevent cerebral palsy in preterm babies
- Certain medications that may decrease contractions

Just before being randomized into one of the two treatment groups, an exam will be done with a "speculum", a device which allows the doctor to look at the inside of your vagina and to look at your cervix to find out if it is opening or if you have an infection. You have had a similar exam earlier in your pregnancy. Opening of the cervix may allow the membranes (your bag of waters) to be exposed to the vagina which could increase the chances of infection, rupture of the membranes and preterm delivery. If you have significant opening of your cervix, you do not qualify for this study. Some infections of the cervix or vagina can increase the risk of complications, such as preterm birth, during pregnancy so it is important that we determine if an infection is present before beginning any treatment. If you have an infection you will be treated before you can join the study. You will need to have another speculum exam at that time. If necessary, a digital exam (an exam where the physician uses his/her fingers) of the cervix may follow the speculum examination to better determine if your cervix is opening.

During the exam, three vaginal samples will be collected. The samples will be taken by placing a swab in your vagina and holding it there for about 30 seconds. All vaginal swabs taken during the study will be tested at a later time to look at factors that may be linked to preterm birth. You will not get results from these tests since they are for research purposes only.

If you are randomized to the pessary group, a pessary will be placed around your cervix at your first study visit. This will be done by a member of the research staff who will make sure that it fits around your cervix and is comfortable. You will also be given information to take home with you about any symptoms you may have while the pessary is in place.

No matter which treatment group you were randomized to a research nurse will call you within one week of your randomization visit to see how you are doing.

If you are randomized to the pessary and feel discomfort in the pelvic area, you will be asked to come into the clinic. You will have an exam to find out if the pessary should be moved or changed so that it feels better.

After the first study visit, you will meet (either in-person or by video or phone) with a member of the research staff every four weeks until the 37th week of your pregnancy. At each study visit, the research nurse will ask questions about your pregnancy, if you have had any symptoms, and if you are taking any medication.

If you have an in-person study visit between 24 and 32 weeks of pregnancy, a second set of vaginal swabs will be taken at that time. If you are in the pessary group, a vaginal exam will be done at an in-person visit to check that the pessary is in place.

If you are randomized to the pessary group, during your second study visit after randomization (about 8 weeks after randomization) you will be asked to complete a questionnaire about your feelings on the pessary. You may be asked to answer these questions again around the 37th week of your pregnancy.

If you were randomized to pessary, an in-person study visit will take place around the 37th week of your pregnancy to remove the pessary.

You will continue to receive standard care from your doctor while you are in this research trial. There is a very small chance that your doctor may decide to place a rescue cerclage if your cervix opens too early in pregnancy. A rescue cerclage is a stitch that is used to close the cervix when the membranes are bulging into the vagina. About one month after your expected date of delivery or at the time your baby is discharged from the hospital, whichever is the longest, we will collect information about your pregnancy, labor, delivery, and the health of your baby. We will review your medical records and your baby's medical records and will contact you by telephone.

After the study is done, researchers may want to contact you to do another follow-up study on you and your baby.

Possible Risks

If you are randomized to pessary, you may feel discomfort during the placement, or when it is taken out at the last visit, or if the pessary has to be moved or changed. After placement, the pessary may become displaced or dislodged; should you experience any pain or discomfort please contact your provider. You may have light vaginal bleeding or spotting at the time of pessary placement. Vaginal intercourse may also be uncomfortable with the pessary in place. The pessary may not reduce the risk of preterm birth.

In studies of women pregnant with one baby, no serious side effects were associated with the pessary, including infection or rupture of membranes. In one study some women (about 5%) asked for the pessary to be removed because of discomfort but it is not known if they were offered a replacement. In the other two studies no women asked for the pessary to be removed because of discomfort. Women did report an increase in vaginal discharge. No risks from the pessary to the baby were found in either study.

You may have vaginal itching, vaginal irritation, vaginal odor or vaginal burning, no matter which group you are randomized to. If any of these symptoms occur, you can come into the clinic and your health care provider can determine if treatment is necessary.

Although unlikely, it is possible that participating in this study may involve risks to you or your baby that are not expected.

There is a risk of improper release or misuse of your personal information or specimens. The chance of this happening is very small. We have many protections in place to lessen this risk.

Benefits

If you decide to take part in this research study, you and your baby may or may not directly benefit from your participation. If the study shows that treatment is successful, you and your baby may benefit if you are assigned to receive the pessary. If the pessary is successful it may delay or prevent preterm delivery. In addition, if the study shows benefit, ultrasound testing and/or pessary may be made available to other women. Therefore, your participation can potentially benefit mothers and their babies in the future.

Consent for Use/Disposal of Biospecimens

By signing this consent form, you agree to have vaginal samples taken before receiving the pessary and/or usual care and at a later study visit between 26 and 30 weeks of pregnancy. These samples may be used in the future to find out if there was an infection or other condition, such as the presence of certain substances in the fluid from your cervix, which may increase the risk of delivering a preterm baby.

If you agree, any samples leftover after the study is finished may be used for future research. The samples will be sent to a National Institutes of Health sample storage facility, where they will be kept indefinitely and without information identifying you. The samples will only be shared with researchers approved by the National Institutes of Health. An Institutional Review Board must also approve any future research using your samples.

However if the researchers decide that there is no more use for your samples, you agree that they may be discarded.

Alternative Procedures

The alternative to this study is not to participate and to continue receiving standard monitoring and care during pregnancy, labor and delivery.

Costs

There will be no cost to you to take part in the research study. All research study related procedures will be provided at no cost to you or your insurance company. The costs of your standard medical care will be billed to you or your insurance company in the usual manner.

Compensation

By signing this consent form, you acknowledge and agree that in the event that this research project results in the development of any marketable product, you will have no ownership interest in the product and no right to share in any profits from its sale or commercialization.

(THIS SECTION WILL BE CENTER SPECIFIC.) You will be paid $XX to compensate you for the time and travel associated with the research study.

Payment for Injury or Harm

(THIS SECTION WILL BE CENTER SPECIFIC.) This medical institution and the NICHD have not made any provision for monetary compensation in the event of injury resulting from the research. In the event of such injury, treatment will be provided, but it is not provided free of charge. Since this is a research study, payment for any injury resulting from your participation in this research study may not be covered by some health insurance plans.

Right to Withdraw From the Research Study

Your participation in this research study is voluntary. You are free to withdraw your consent and stop taking part in this research study at any time. Refusal to take part will involve no penalty or loss of benefits to which you are otherwise entitled. Neither will your refusal affect your legal rights or quality of health care that you will receive at this hospital. All of the information that has already been collected about you as part of the research study will continue to be used. No new information about you will be collected for research study purposes unless the information concerns an adverse event (bad effect) related to the research study.

Any significant new information which becomes available during your participation in this research, and which may affect your health, safety, or willingness to continue in this research study, will be given to you.

Right of the Investigator to Withdraw

The researchers of this institution or the National Institutes of Health can withdraw you from this study without your approval. A possible reason for withdrawal could be the early termination of the study by the National Institutes of Health.

Confidentiality

You have the right to privacy. All information obtained from this research that can be identified with you will remain confidential within the limits of the law.

The medical information collected on you for this research study will come from your medical record and from information you give the nurse, such as your previous pregnancies, height, weight, and whether you drink or smoke. Other information collected about you includes marital status, your level of education, type of medical insurance, and current pregnancy complications. When your baby is born, data will be collected on your labor (such as when it starts) and delivery. Information will also be collected on your

baby at delivery and on your baby's hospital stay. If we lose track of you, study staff may collect information from the internet including social network sites in order to find your contact information.

The information collected for this research study will be submitted to the data coordinating center (George Washington University Biostatistics Center in Rockville, Maryland). There the information will be put into a database with information from all of the participants. Your information in the database will only be used for statistical analysis and may appear in scientific publications but will not identify you. The information sent to the data coordinating center does **not** include your name, address, social security number, hospital number, date of birth or any other personal identifiers. Instead, the data center will use a unique code for each person consisting of a number and the first letter of your first name. All vaginal samples will be labeled with a unique barcode consisting of a series of numbers. The key to the code linking the data and samples to you will be kept here in a locked file. Only the research study staff employed for this study at this hospital will have access to the key to the code.

The following individuals and/or agencies will be able to look at and copy your research records:

- The investigator, study staff and other medical professionals who may be evaluating the study.
- Authorities from this institution, including the Institutional Review Board (IRB) which is a group of people who are responsible for making sure the rights of participants in research are respected. Members or staff of the IRB at this medical center may also contact you about your experience with this research. You do not have to answer any questions the representative(s) of the board may ask.
- The United States Food and Drug Administration (FDA) and/or the Office for Human Research Protections (OHRP).
- The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) which sponsors this study, including persons or organizations working with the sponsors, such as the data coordinating center, the George Washington University Biostatistics Center in Rockville, Maryland.

A copy of your medical chart or your baby's medical chart also may be sent to research investigators at one of the other enrolling centers or the data coordinating center for review. If your chart is sent, all identifying information, such as your name, address, social security number, hospital number, and date of birth first will be removed. The results of this research study will be provided to the sponsor, NICHD (and/or their representatives).

In addition, data from this study will be put in a public data set that will be available to other research investigators. This public data set will not contain any identifying patient data.

A description of this clinical trial will be available on http://www.clinicaltrials.gov, as required by U.S. Law. This web site will not include information that can identify you. At most, the web site will include a summary of the results. You can search this web site at any time.

Once the study is finished, you may request to have and review a copy of your personal health information collected during this study and placed in your medical record. This right to review and copy your personal health information only extends to information that is placed in your medical record; it does not extend to information that is placed in your research record.

We may want to use or share your biologic samples and data with other investigators either within or outside our institution so that other research studies can be done now or in the future. Your samples and data will be de-identified (all identifying information removed) before being released to other researchers within or outside of this institution. Such future testing and research may also lead to the development and use of information, products, tests, and treatments having commercial value. You will not receive any financial compensation that may result from this testing or research as the specimens used have been de-identified and it will not be possible to determine if your specimen was used.

If you agree to let us keep your samples for future research, the samples will be stored until they are used up, or for as long as deemed useful for research purposes and may be stored in off-site facilities. There will be no cost to you for any data or sample collection and storage.

This permission does not end unless you cancel it, even if you withdraw from the study. You can cancel this permission any time except where a healthcare provider has already used or released your health information, or relied on your permission to do something. Even if you cancel this authorization, the researchers may still use and disclose protected health information (PHI) they already have obtained about you as necessary to maintain the integrity or reliability of the research. However, no new PHI or new biological specimens will be collected from you after you revoke your authorization.

To cancel your authorization, you will need to send a letter to Dr. _____ of the _____ stating that you are canceling your authorization. This letter must be signed and dated and sent to this address:_____. If you are unable to write a letter ask one of the research staff to provide you with a letter that must be signed, dated, and sent to the above address. A copy of this cancellation will be provided to the Study Doctor and his or her research team. Not signing this form or later canceling your permission will not affect your health care treatment outside the study, payment for health care from a health plan, or ability to get health plan benefits.

Your protected health information will be treated confidentially to the extent permitted by applicable laws and regulations. Federal law may allow someone who gets your health information from this study to use or release it in some way not discussed in this section and no longer be protected by the HIPAA Privacy Rule.

By signing this form you authorize the Study Doctor and members of the research team to use and share with others (disclose) your PHI for the purpose of this study. If you do not wish to authorize the use or disclosure of your PHI, you cannot participate in this study because your PHI is necessary to conduct this study.

Certificate of Confidentiality

This research is covered by a Certificate of Confidentiality from the National Institutes of Health (NIH). The researchers with this Certificate may not disclose or use information, documents, or biospecimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless you have consented for this use. Information, documents, or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except, if there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases but not for federal, state, or local civil, criminal, administrative, legislative, or other proceedings); if you have consented to the disclosure, including for your medical treatment; or if it is used for other scientific research, as allowed by federal regulations protecting research subjects.

The Certificate cannot be used to refuse a request for information from personnel of the United States federal or state government agency sponsoring the project that is needed for auditing or program evaluation by the NIH or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA). You should understand that a Certificate of Confidentiality does not prevent you from voluntarily releasing information about yourself or your involvement in this research. If you want your research information released to an insurer, medical care provider, or any other person not connected with the research, you must provide consent to allow the researchers to release it.

Questions

The researchers are available to answer your questions about this research. A representative of the Institutional Review Board is also available to answer questions about your rights as a participant in

research or to answer your questions about an injury or other complication resulting from your participation in this research study.

If you have questions or are hurt while taking part in this research study, you should contact _____ at (___) ___-____.

If you have any questions about the informed consent process or any other rights as a research subject, please contact _____, at (____) ___-____. _____ .

Signatures

By signing below, you indicate that you have read this consent form, the study has been explained to you, your questions have been answered, and you agree to take part in this study. You do not give up any of your legal rights by signing this form. A copy of this consent form will be given to you.

Please initial below to indicate whether or not you give permission for future research of your samples.

YES (initials)_____ I **agree** to have my samples, which will be kept confidential, stored and shared with other investigators doing research which is related to the health of mothers and children.

NO (initials)_____ I **do not agree** to have my samples, which will be kept confidential, stored and shared with other investigators doing research which is related to the health of mothers and children.

The investigator or study team may wish to contact you in the future to request permission for additional research. Please initial the appropriate statement to indicate whether or not you give permission for future contact.

YES (initials)_____ I **give** permission to be contacted in the future for follow-up research.

NO (initials)_____ I **do not give** permission to be contacted in the future for follow-up research.

_____	_____	_____
Signature of Mother	Signature	Date
(Print Name)		
_____	_____	_____
Signature of Father	Signature	Date
(Print Name)		
_____	_____	_____
Person Obtaining Consent	Signature	Date
(Print Name)		

ASSENT FOR FEMALES UNDER 18 YEARS of AGE (if required by Center IRB):

I agree _____ I do not agree_____ to participate in this study.

This has been explained to me by _____.

_____ _____

Signature of Minor Date

_____ _____

Print Name of Subject Age

Please provide either one or both parental signatures as instructed by your IRB.

_____ _____

Signature of Mother/Guardian Date

_____ _____

Signature of Father/Guardian Date

A witness unrelated to the study is necessary if the participant can comprehend but cannot read (e.g., blind), or cannot sign (e.g., unable to use hands) the consent form.

_____ _____ _____

Witness' Name Signature Date

(Print Name)

Investigator Statement

I certify that the research study has been explained to the above individual by me or my research staff including the purpose, the procedures, the possible risks and the potential benefits associated with participation in this research study. Any questions have been answered to the Individual's satisfaction.

_____ _____ _____

Investigator Signature Date

(Print Name)

B.4. Sample Informed Consent Form for RCT (with Common Rule 2018 changes)

Research Study Title: A Randomized Trial of Pessary in Singleton Pregnancies with a Short Cervix (TOPS)

Sponsor: *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) of the National Institutes of Health (NIH)

Principal Investigator: _____*Phone* (____) ___ - ____

Key Information

This research is being done to find out whether a pessary lowers the risk of a baby being born too soon to women who have a short cervix. A pessary is a soft, round, silicone device that is placed into the vagina to support the cervix. The cervix is the lower, narrow part of your womb.

If you consent, you will be in the study from randomization (between 16,0 and 23,6 weeks of pregnancy) until one month after your expected date of delivery or until your baby is discharged from the hospital, whichever is the longest. Just before randomization, an exam will be done with a speculum (a device which allows the doctor to look at the inside of your vagina and to look at your cervix) and vaginal samples will be collected. You will be randomly assigned (like tossing a coin) to pessary or no pessary.

You will have monthly study visits (in-person or by video or phone) until the 37th week of pregnancy or delivery, whichever comes first. After delivery, the research staff will collect medical information about you and your baby until you leave the hospital. Around four weeks after your expected date of delivery, the research staff will give you a phone call to see how you and your baby are doing.

There are risks to the study that are described in this consent. If you are in the pessary group, likely risks include discomfort during pessary placement, or when the pessary is removed or changed, light vaginal bleeding or spotting at the time of placement, or discomfort during vaginal intercourse. For all groups, risks include vaginal itching, vaginal irritation, vaginal odor or vaginal burning.

There are no known benefits from participating in this study. Participation in this research study is voluntary and if you do not take part, you will receive the routine care usually provided to pregnant women.

Introduction

You are invited to take part in a research study. Before you decide to be a part of this study, you need to understand the risks and benefits. This consent form provides information about the research study. A member of the research team will be available to answer your questions. Please ask the study staff to explain any words or information that you do not clearly understand. You can choose whether or not you will take part in the study. If you agree to take part, you need to sign this consent form. This process is known as informed consent.

You have been asked to take part in this research study because you are between 16 weeks 0 days and 23 weeks 6 days pregnant with one baby and a vaginal ultrasound showed that your cervix is shorter than usual (less than or equal to 20 mm, which is about ¾ of an inch). The cervix is the lower, narrow part of your womb.

Please tell the study doctor or study staff if you are taking part in another research study.

Research Purpose

Women who have a short cervix are more likely to deliver preterm. Babies born preterm have a greater chance of having serious, long-term health problems or dying.

The purpose of this research study is to find out whether a pessary lowers the risk of a baby being born too soon to women with a short cervix. One study has been done to date in the US to find out if placing a pessary in women with a short cervix helps the pregnancy to last longer. That study did not show that the pessary delayed or prevented preterm birth but the study was too small to have a reliable result. Studies done in other countries have had differing results. A pessary is a soft silicone device that goes around the cervix.

The Arabin pessary has not been approved by the FDA for treating pregnant women who have a short cervix and are at risk for preterm delivery. For this reason, the pessary is considered to be an 'investigational' device and is being used for research purposes only**.**

You will be in the study from the time of randomization (between 16-23 weeks of pregnancy) until one month after your expected date of delivery or until your baby is discharged from the hospital, whichever is the longest.

This research study is funded by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD). Twelve medical centers across the country are part of this research study, and in all, 850 women with singleton pregnancies who have a short cervix will be enrolled.

Procedures

If you are eligible and decide to participate in this study, you will be asked to sign this consent form. If you consent, you will be randomized (like tossing a coin) to one of two treatment groups: 1) pessary or 2) non-pessary. The pessary group will have a pessary placed around the cervix. The non-pessary group will continue to receive the standard obstetric care provided by the doctor or nurse.

All study participants will receive standard obstetric care should they develop symptomatic preterm labor. This care may include the following:

- Corticosteroids which helps preterm babies breathe easier
- Magnesium sulfate which may prevent cerebral palsy in preterm babies
- Certain medications that may decrease contractions

Just before being randomized into one of the two treatment groups, an exam will be done with a "speculum", a device which allows the doctor to look at the inside of your vagina and to look at your cervix to find out if it is opening or if you have an infection. You have had a similar exam earlier in your pregnancy. Opening of the cervix may allow the membranes (your bag of waters) to be exposed to the vagina which could increase the chances of infection, rupture of the membranes and preterm delivery. If you have significant opening of your cervix, you do not qualify for this study. Some infections of the cervix or vagina can increase the risk of complications, such as preterm birth, during pregnancy so it is important that we determine if an infection is present before beginning any treatment. If you have an infection you will be treated before you can join the study. You will need to have another speculum exam at that time. If necessary, a digital exam (an exam where the physician uses his/her fingers) of the cervix may follow the speculum examination to better determine if your cervix is opening.

During the exam, three vaginal samples will be collected. The samples will be taken by placing a swab in your vagina and holding it there for about 30 seconds. All vaginal swabs taken during the study will be tested at a later time to look at factors that may be linked to preterm birth. You will not get results from these tests since they are for research purposes only.

If you are randomized to the pessary group, a pessary will be placed around your cervix at your first study visit. This will be done by a member of the research staff who will make sure that it fits around your

cervix and is comfortable. You will also be given information to take home with you about any symptoms you may have while the pessary is in place.

No matter which treatment group you were randomized to a research nurse will call you within one week of your randomization visit to see how you are doing.

If you are randomized to the pessary and feel discomfort in the pelvic area, you will be asked to come into the clinic. You will have an exam to find out if the pessary should be moved or changed so that it feels better.

After the first study visit, you will meet (either in-person or by video or phone) with a member of the research staff every four weeks until the 37th week of your pregnancy. At each study visit, the research nurse will ask questions about your pregnancy, if you have had any symptoms, and if you are taking any medication.

If you have an in-person study visit between 24 and 32 weeks of pregnancy, a second set of vaginal swabs will be taken at that time. If you are in the pessary group, a vaginal exam will also be done at an in-person visit to check that the pessary is in place.

If you are randomized to the pessary group, during your second study visit after randomization (about 8 weeks after randomization) you will be asked to complete a questionnaire about your feelings on the pessary. You may be asked to answer these questions again around the 37th week of your pregnancy.

If you were randomized to pessary, an in-person study visit will take place around the 37th week of your pregnancy to remove the pessary.

You will continue to receive standard care from your doctor while you are in this research trial. There is a very small chance that your doctor may decide to place a rescue cerclage if your cervix opens too early in pregnancy. A rescue cerclage is a stitch that is used to close the cervix when the membranes are bulging into the vagina. About one month after your expected date of delivery or at the time your baby is discharged from the hospital, whichever is the longest, we will collect information about your pregnancy, labor, delivery, and the health of your baby. We will review your medical records and your baby's medical records and will contact you by telephone.

After the study is done, researchers may want to contact you to do another follow-up study on you and your baby.

Possible Risks

If you are randomized to pessary, you may feel discomfort during the placement, or when it is taken out at the last visit, or if the pessary has to be moved or changed. After placement, the pessary may become displaced or dislodged; should you experience any pain or discomfort please contact your provider. You may have light vaginal bleeding or spotting at the time of pessary placement. Vaginal intercourse may also be uncomfortable with the pessary in place. The pessary may not reduce the risk of preterm birth.

In studies of women pregnant with one baby, no serious side effects were associated with the pessary, including infection or rupture of membranes. In one study some women (about 5%) asked for the pessary to be removed because of discomfort but it is not known if they were offered a replacement. In the other two studies no women asked for the pessary to be removed because of discomfort. Women did report an increase in vaginal discharge. No risks from the pessary to the baby were found in either study.

You may have vaginal itching, vaginal irritation, vaginal odor or vaginal burning, no matter which group you are randomized to. If any of these symptoms occur, you can come into the clinic and your health care provider can determine if treatment is necessary.

Although unlikely, it is possible that participating in this study may involve risks to you or your baby that are not expected.

There is a risk of improper release or misuse of your personal information or specimens. The chance of this happening is very small. We have many protections in place to lessen this risk.

Benefits

If you decide to take part in this research study, you and your baby may or may not directly benefit from your participation. If the study shows that treatment is successful, you and your baby may benefit if you are assigned to receive the pessary. If the pessary is successful it may delay or prevent preterm delivery. In addition, if the study shows benefit, ultrasound testing and/or pessary may be made available to other women. Therefore, your participation can potentially benefit mothers and their babies in the future.

Consent for Use/Disposal of Biospecimens

By signing this consent form, you agree to have vaginal samples taken before receiving the pessary and/or usual care and at a later study visit between 26 and 30 weeks of pregnancy. These samples may be used in the future to find out if there was an infection or other condition, such as the presence of certain substances in the fluid from your cervix, which may increase the risk of delivering a preterm baby.

If you agree, any samples leftover after the study is finished may be used for future research. The samples will be sent to a National Institutes of Health sample storage facility, where they will be kept indefinitely and without information identifying you. The samples will only be shared with researchers approved by the National Institutes of Health. An Institutional Review Board must also approve any future research using your samples.

However if the researchers decide that there is no more use for your samples, you agree that they may be discarded.

Alternative Procedures

The alternative to this study is not to participate and to continue receiving standard monitoring and care during pregnancy, labor and delivery.

Costs

There will be no cost to you to take part in the research study. All research study related procedures will be provided at no cost to you or your insurance company. The costs of your standard medical care will be billed to you or your insurance company in the usual manner.

Compensation

By signing this consent form, you acknowledge and agree that in the event that this research project results in the development of any marketable product, you will have no ownership interest in the product and no right to share in any profits from its sale or commercialization.

(THIS SECTION WILL BE CENTER SPECIFIC.) You will be paid $XX to compensate you for the time and travel associated with the research study.

Payment for Injury or Harm

(THIS SECTION WILL BE CENTER SPECIFIC.) This medical institution and the NICHD have not made any provision for monetary compensation in the event of injury resulting from the research. In the event of such injury, treatment will be provided, but it is not provided free of charge. Since this is a research study, payment for any injury resulting from your participation in this research study may not be covered by some health insurance plans.

Right to Withdraw From the Research Study

Your participation in this research study is voluntary. You are free to withdraw your consent and stop taking part in this research study at any time. Refusal to take part will involve no penalty or loss of benefits to which you are otherwise entitled. Neither will your refusal affect your legal rights or quality

of health care that you will receive at this hospital. All of the information that has already been collected about you as part of the research study will continue to be used. No new information about you will be collected for research study purposes unless the information concerns an adverse event (bad effect) related to the research study.

Any significant new information which becomes available during your participation in this research, and which may affect your health, safety, or willingness to continue in this research study, will be given to you.

Right of the Investigator to Withdraw

The researchers of this institution or the National Institutes of Health can withdraw you from this study without your approval. A possible reason for withdrawal could be the early termination of the study by the National Institutes of Health.

Confidentiality

You have the right to privacy. All information obtained from this research that can be identified with you will remain confidential within the limits of the law.

The medical information collected on you for this research study will come from your medical record and from information you give the nurse, such as your previous pregnancies, height, weight, and whether you drink or smoke. Other information collected about you includes marital status, your level of education, type of medical insurance, and current pregnancy complications. When your baby is born, data will be collected on your labor (such as when it starts) and delivery. Information will also be collected on your baby at delivery and on your baby's hospital stay. If we lose track of you, study staff may collect information from the internet including social network sites in order to find your contact information.

The information collected for this research study will be submitted to the data coordinating center (George Washington University Biostatistics Center in Rockville, Maryland). There the information will be put into a database with information from all of the participants. Your information in the database will only be used for statistical analysis and may appear in scientific publications but will not identify you. The information sent to the data coordinating center does **not** include your name, address, social security number, hospital number, date of birth or any other personal identifiers. Instead, the data center will use a unique code for each person consisting of a number and the first letter of your first name. All vaginal samples will be labeled with a unique barcode consisting of a series of numbers. The key to the code linking the data and samples to you will be kept here in a locked file. Only the research study staff employed for this study at this hospital will have access to the key to the code.

The following individuals and/or agencies will be able to look at and copy your research records:

- The investigator, study staff and other medical professionals who may be evaluating the study.
- Authorities from this institution, including the Institutional Review Board (IRB) which is a group of people who are responsible for making sure the rights of participants in research are respected. Members or staff of the IRB at this medical center may also contact you about your experience with this research. You do not have to answer any questions the representative(s) of the board may ask.
- The United States Food and Drug Administration (FDA) and/or the Office for Human Research Protections (OHRP).
- The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) which sponsors this study, including persons or organizations working with the sponsors, such as the data coordinating center, the George Washington University Biostatistics Center in Rockville, Maryland.

A copy of your medical chart or your baby's medical chart also may be sent to research investigators at one of the other enrolling centers or the data coordinating center for review. If your chart is sent, all identifying information, such as your name, address, social security number, hospital number, and date of birth first will be removed. The results of this research study will be provided to the sponsor, NICHD (and/or their representatives).

In addition, data from this study will be put in a public data set that will be available to other research investigators. This public data set will not contain any identifying patient data. When the data set is shared, it will be done without obtaining additional permission from you.

A description of this clinical trial will be available on http://www.clinicaltrials.gov, as required by U.S. Law. This web site will not include information that can identify you. At most, the web site will include a summary of the results. You can search this web site at any time.

Once the study is finished, you may request to have and review a copy of your personal health information collected during this study and placed in your medical record. This right to review and copy your personal health information only extends to information that is placed in your medical record; it does not extend to information that is placed in your research record.

We may want to use or share your biologic samples and data with other investigators either within or outside our institution so that other research studies can be done now or in the future. Your samples and data will be de-identified (all identifying information removed) before being released to other researchers within or outside of this institution. Such future testing and research may also lead to the development and use of information, products, tests, and treatments having commercial value. You will not receive any financial compensation that may result from this testing or research as the specimens used have been de-identified and it will not be possible to determine if your specimen was used. This future research will not include whole genome (DNA) sequencing.

If you agree to let us keep your samples for future research, the samples will be stored until they are used up, or for as long as deemed useful for research purposes and may be stored in off-site facilities. There will be no cost to you for any data or sample collection and storage.

This permission does not end unless you cancel it, even if you withdraw from the study. You can cancel this permission any time except where a healthcare provider has already used or released your health information, or relied on your permission to do something. Even if you cancel this authorization, the researchers may still use and disclose protected health information (PHI) they already have obtained about you as necessary to maintain the integrity or reliability of the research. However, no new PHI or new biological specimens will be collected from you after you revoke your authorization.

To cancel your authorization, you will need to send a letter to Dr. _____ of the _____ stating that you are canceling your authorization. This letter must be signed and dated and sent to this address:_____. If you are unable to write a letter ask one of the research staff to provide you with a letter that must be signed, dated, and sent to the above address. A copy of this cancellation will be provided to the Study Doctor and his or her research team. Not signing this form or later canceling your permission will not affect your health care treatment outside the study, payment for health care from a health plan, or ability to get health plan benefits.

Your protected health information will be treated confidentially to the extent permitted by applicable laws and regulations. Federal law may allow someone who gets your health information from this study to use or release it in some way not discussed in this section and no longer be protected by the HIPAA Privacy Rule.

By signing this form you authorize the Study Doctor and members of the research team to use and share with others (disclose) your PHI for the purpose of this study. If you do not wish to authorize the use or

disclosure of your PHI, you cannot participate in this study because your PHI is necessary to conduct this study.

Certificate of Confidentiality

This research is covered by a Certificate of Confidentiality from the National Institutes of Health (NIH). The researchers with this Certificate may not disclose or use information, documents, or biospecimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless you have consented for this use. Information, documents, or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except, if there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases but not for federal, state, or local civil, criminal, administrative, legislative, or other proceedings); if you have consented to the disclosure, including for your medical treatment; or if it is used for other scientific research, as allowed by federal regulations protecting research subjects.

The Certificate cannot be used to refuse a request for information from personnel of the United States federal or state government agency sponsoring the project that is needed for auditing or program evaluation by the NIH or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA). You should understand that a Certificate of Confidentiality does not prevent you from voluntarily releasing information about yourself or your involvement in this research. If you want your research information released to an insurer, medical care provider, or any other person not connected with the research, you must provide consent to allow the researchers to release it.

Questions

The researchers are available to answer your questions about this research. A representative of the Institutional Review Board is also available to answer questions about your rights as a participant in research or to answer your questions about an injury or other complication resulting from your participation in this research study.

If you have questions or are hurt while taking part in this research study, you should contact _____ at (___) ___-____.

If you have any questions about the informed consent process or any other rights as a research subject, please contact _____, at (____) ___-____. _____ .

Signatures

By signing below, you indicate that you have read this consent form, the study has been explained to you, your questions have been answered, and you agree to take part in this study. You do not give up any of your legal rights by signing this form. A copy of this consent form will be given to you.

Please initial below to indicate whether or not you give permission for future research of your samples.

YES (initials)_____ I **agree** to have my samples, which will be kept confidential, stored and shared with other investigators doing research which is related to the health of mothers and children.

NO (initials)_____ I **do not agree** to have my samples, which will be kept confidential, stored and shared with other investigators doing research which is related to the health of mothers and children.

The investigator or study team may wish to contact you in the future to request permission for additional research. Please initial the appropriate statement to indicate whether or not you give permission for future contact.

YES (initials)_____ I **give** permission to be contacted in the future for follow-up research.

NO (initials)_____ I **do not give** permission to be contacted in the future for follow-up research.

_____	_____	_____
Signature of Mother	Signature	Date
(Print Name)		
_____	_____	_____
Signature of Father	Signature	Date
(Print Name)		
_____	_____	_____
Person Obtaining Consent	Signature	Date
(Print Name)		

ASSENT FOR FEMALES UNDER 18 YEARS of AGE (if required by Center IRB):

I agree _____ I do not agree_____ to participate in this study.

This has been explained to me by _____.

_____	_____
Signature of Minor	Date
_____	_____
Print Name of Subject	Age

Please provide either one or both parental signatures as instructed by your IRB.

_____	_____
Signature of Mother/Guardian	Date
_____	_____
Signature of Father/Guardian	Date

A witness unrelated to the study is necessary if the participant can comprehend but cannot read (e.g., blind), or cannot sign (e.g., unable to use hands) the consent form.

_____	_____	_____
Witness' Name	Signature	Date

(Print Name)

Investigator Statement

I certify that the research study has been explained to the above individual by me or my research staff including the purpose, the procedures, the possible risks and the potential benefits associated with participation in this research study. Any questions have been answered to the Individual's satisfaction.

_____	_____	_____
Investigator	Signature	Date

(Print Name)

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