A Randomized Trial of Pessary and Progesterone for Preterm Prevention in Twin Gestation with a Short Cervix
PROSPECT

Protocol

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1 Introduction

1.1 Study Abstract

Multiple gestation increases the risk of preterm delivery. Babies born preterm have increased rates of neonatal mortality and long-term neurodevelopmental morbidities. Short cervical length is known to be an important risk factor for spontaneous preterm birth and to occur more frequently in women with a twin gestation. Although there is no evidence that progesterone reduces the risk of preterm birth in multifetal gestation, there is evidence that progesterone reduces the risk of prematurity in singleton gestations complicated with a short cervix. The Arabin pessary has also been shown to reduce the risk of preterm birth among singletons with a short cervix, and in a secondary subgroup analysis of a recent study of the use of pessary in multiple gestations, women with a cervical length < 25th percentile had a significantly reduced risk of the primary composite neonatal adverse outcome. Secondary analysis of studies of vaginal progesterone in multiple gestation with a short cervix also suggest a possible beneficial effect on preterm delivery.

This protocol outlines a randomized trial of 630 women evaluating the use of micronized vaginal progesterone or pessary versus control (placebo) to prevent early preterm birth in women carrying twins and with a cervical length of less than 30 millimeters.

1.2 Primary Hypotheses

In women with twin gestations who show ultrasound evidence of short cervical length,

1. Placement of an Arabin cervical pessary reduces the risk of preterm birth less than 35 weeks.
2. Use of vaginal progesterone reduces the risk of preterm birth less than 35 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

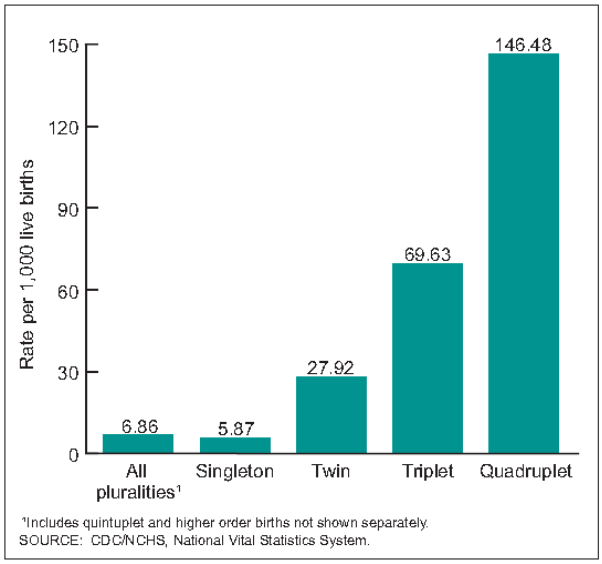
2.1 Introduction

Multiple gestations are complicated by myriad maternal and fetal conditions in excess of those encountered by singleton gestations, but the most significant of potential risks is preterm birth. Preterm birth is fraught with potential complications for the mother related to treatment modalities such as tocolysis and surgical delivery. With preterm delivery there is a higher probability of needing a classical incision, due to fetal malpresentation, increasing the risk for complications such as hemorrhage in the index pregnancy, but also increasing the risk of complications in future pregnancies. Preterm birth is also one of the most powerful predictors for neonatal morbidity and mortality. Moreover, prematurity is associated with long-term morbidities including adverse neurodevelopmental outcomes such as cerebral palsy. This serious public health issue is augmented by the fact that the rate of multiple gestation, and hence preterm birth associated with multiple gestation, has increased dramatically in recent years, driven in large part by advanced reproductive technologies. From 1980-2009, the rate of twin births rose 76% among all women, and more than doubled in women 35-39 years of age, such that in 2009 one in 30 infants born in the U.S. was a twin.[1]

2.1.1 Morbidity and Mortality Associated with Multifetal Gestation

In 2006, the infant mortality rate for twins was nearly 5 times higher than that for singleton births. While multiple gestations (predominantly twins) accounted for only 3% of all live births, multiples were responsible for 15% of all infant deaths.

Figure 1. Infant Mortality by Plurality, 2006



The mortality rate was highest for the very preterm neonates and decreased with advancing gestational age. At 32-33 weeks, the mortality rate was 16.2 per 1000 births, nearly seven times that of a term singleton infant.[2] However, even birth at 34-36 weeks was associated with a three-fold higher infant mortality rate. This disproportionate share is not limited to mortality; similar patterns are seen with regard to morbidities, both those associated with prematurity and those related to the twinning process itself. For example, the rate of cerebral palsy is increased in twin gestations, in large part due to the higher rate of prematurity, but even after controlling for the earlier gestational age at birth, the risk remains 2-3 fold higher than in singletons.[3] The rate of structural birth defects is also increased in

multiple gestations and is approximately 25% higher in twins than in singletons which can further contribute to preterm birth and cerebral palsy.[4] Because of the cumulative and ongoing nature of such conditions, the public health burden is potentially immense.

2.1.2 Previous Studies of Interventions to Prevent Preterm Birth in Twin Gestations

Based on the salutary effects of progesterone in singletons, various progesterone-based therapies have been studied as preventative treatments for twin and triplet gestations. Unfortunately, in multiple studies progesterone, whether 17α-hydroxyprogesterone caproate, micronized progesterone, or vaginal suppositories, has failed to demonstrate a prolongation of pregnancy, a decrease in the rate of preterm birth, or a decrease in neonatal morbidity when administered to all women, regardless of risk status, with a twin gestation.[5-10]

Cerclage placement for ultrasound-diagnosed cervical shortening does not lower the risk of preterm birth in twins.[11] Patient-level meta-analysis data from multiple gestations suggests that cerclage placement due to ultrasound-identified cervical shortening may actually increase the rate of preterm birth prior to 35 weeks by two-fold.[12] Moreover, a policy of routine cervical length surveillance was not associated with improvement in perinatal outcomes, given the lack of effective interventions.[13]

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.[14] 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 in both singleton and twin pregnancies, 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 and in the twin cohort the mean was 33 mm with a standard deviation of 10 mm. In the singleton cohort, women with cervical length at or below a particular percentile were compared with those who had cervical length values above the 75th percentile. The relative risk for spontaneous preterm delivery at less than 35 weeks was 3.8 with a 95% confidence interval (CI) of 2.3 – 6.2 at or below the 25th percentile, 6.2 (95% CI: 3.8 – 10) at or below the 10th percentile and 9.5 (95% CI: 6.0 – 15.2) at or below the 5th percentile.[15] A cervical length of 25 mm was approximately the 9th percentile for singletons and has become the adopted cutoff for the diagnosis of short cervical length in singleton gestations.

In the twin cohort, as in singletons, women with a short cervix were at increased risk for preterm birth (53.9% versus 26.5% in the group with cervical length >25 mm, p=0.01). After adjusting for other factors, a short cervix was associated with a nearly 8-fold increase in the odds of a spontaneous preterm birth <32 weeks.[16] Similarly, a meta-analysis demonstrated that asymptomatic women with twin gestations and cervical length ≤ 20 mm at 20-24 weeks had a nearly 10-fold increase in the risk of preterm birth prior to 34 weeks.[17]

2.2.1 Cervical Length Measurement Distribution in Twin Gestation

In addition to the Preterm Prediction Study, an analysis was conducted of the Twin Stratum of the MFMU Network Randomized Trial of 17-α Hydroxyprogesterone Caproate for Prevention of Preterm Birth in Multifetal Gestation (STTARS). In this study, cervical length measured prior to randomization for

clinical purposes was collected. Thirty-three percent of the patients enrolled had a transvaginal cervical length measurement for clinical reasons prior to enrollment. For this (unpublished) analysis, cervical lengths acquired at less than 14 weeks were excluded. The cervical length percentiles are shown below.

Table 1. Cervical Length Measurement Percentiles from the MFMU Prediction Study and the MFMU STTARS Trial

Percentile	Gestational age 14-20 weeks (STTARS) - Twins	Gestational age 22-24 weeks (Preterm Prediction) - Twins	Gestational age 22-24 weeks (Preterm Prediction)- Singletons
5th	30 mm	17 mm	22 mm
10th	32 mm	21 mm	26 mm
25th	36 mm	28 mm	30 mm
50th	40 mm	33 mm	35 mm

The 25th percentile of cervical length at 16-20 weeks observed in twin pregnancies enrolled in a Dutch trial was somewhat higher: 38mm.[18] In a secondary analysis of a micronized progesterone trial, the 10th percentile of cervical length measured in 448 women at approximately 20-24 weeks was 30 mm while in a report by Souka et al. of 215 twin pregnancies assessed in clinic at 22 to 24 weeks of gestation, the median was 38 mm and 5th percentile was 19 mm.[5,19]

The table also shows the 5th, 10th, 25th and 50th percentile in the singleton cohort of the Preterm Prediction Study, which were uniformly longer at 22-24 weeks. Thus, cervical shortening appears to occur more commonly in multiple gestation than singleton gestations and to be more evident as gestation progresses.

2.2.2 Implications of a Short Cervix in Twin versus Singleton Gestation

The risk of preterm birth differs for cervical length measurement between singletons and twins with a higher risk for preterm birth with a longer cervix in twins. For example, 15 mm is associated with a 50% risk of preterm birth <32 weeks in singletons whereas 25 mm conveys approximately the same risk in twins.[19,20] In the Preterm Prediction Study a short cervix ≤ 30 mm, the 25th percentile at 22-24 weeks, was associated with a 9% rate of preterm delivery < 35 weeks whereas in the twin cohort, cervical length less than 30 mm was associated with a 56% rate of preterm delivery < 35 weeks (unpublished). In the analysis of the STTARS study, measurements below 30 mm at 14-20 weeks were associated with a preterm birth rate < 35 weeks of 50%.

2.3 Pessary for Preterm Birth Prevention in Women with a Short Cervix

Over the last half-century, numerous studies have suggested benefit to the use of pessary in women with a history of cervical insufficiency, cervical shortening, or prior cervical excision procedure.[21-23] The exact mechanism of beneficial effect with a cervical pessary is uncertain. Mechanical effects due to changes in the angle of the cervix-uterus junction to a more posterior position and shift of the weight of the pregnancy to the lower uterine segment have been postulated. Both of these mechanisms may be especially pertinent in twin gestations. In addition, decreasing exposure of the intact membranes to the vagina, especially with the Arabin pessary that encircles the cervix holding it closed, has been proposed as a potential mechanism.

The recently published "Pesario Cervical para Evitar Prematuridad (PECEP)" study is the largest randomized trial to examine the use of cervical pessary for preterm birth prevention.[24] Greater than 16,000 low-risk women with singleton pregnancies were screened at five hospitals in Spain; those with cervical length 25 mm or less were randomized to the Arabin pessary or expectant management.

Figure 2. The Arabin Pessary[1]

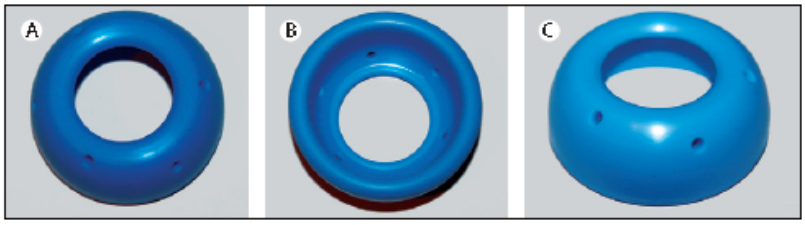


Figure 1: Photograph of the silicone cervical pessary
(A) Inner diameter. (B) Outer diameter. (C) Lateral view.

A total of 385 women were randomized; the odds of preterm birth prior to 34 weeks was reduced 82% (OR 0.18; 95% CI 0.08-0.37). There was a similar reduction in adverse neonatal outcomes (OR 0.14; 95% CI 0.04-0.39).

Few studies have examined the effect of pessary placement in multiple gestations. In a study that included seven twin pregnancies with cervical length <15mm identified prior to 24 weeks, those treated with pessary delivered at 35 6/7 weeks compared with matched controls who delivered at 33 2/7 weeks. The rate of preterm birth was 52% in controls compared with 35% in those treated with a pessary.[23] One observational study that included nine twin and two triplet pregnancies with cervical length of 25 mm or less reported a mean interval between pessary placement and delivery of 10.4 weeks and a mean delivery gestational age of 34 weeks.[22]

The results of the Dutch ProTWIN Trial reinforce the need to evaluate pessary in multiple pregnancies with a shortened cervix.[18] The risks of the primary composite adverse neonatal outcome or preterm birth were not reduced by pessary in twins overall (N=808). However, a secondary analysis of the subgroup (N=133) with a cervical length < 25th percentile (38 mm in this population), showed that the risk of the primary composite neonatal outcome was reduced: 12% vs. 29% in the pessary group; relative risk 0.40 (95% CI 0.19-0.83). Preterm birth < 32 weeks was similarly reduced: 14% vs. 29%, relative risk 0.49 (95% CI 0.24-0.97).

2.3.1 Safety and Acceptability of the Arabin Pessary

The Arabin cervical pessary, named after the German scientist who developed it, is a soft, flexible silicone pessary with no rigid metal framework or inflexible edges that put increase pressure on the vaginal wall. This design is quite different than that of many pessaries used in the U.S. for the treatment of pelvic prolapse and the soft, flexible nature may be an explanation for the acceptability and tolerability of the Arabin pessary in European clinical trials. In the PECEP trial, 192 women were treated with the Arabin pessary.[24] 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.

While few studies have examined the effect of pessary placement in multiple gestations, the Dutch trial reported no increase in the risk of adverse maternal or neonatal outcomes in the 401 women with twin

[1] From Goya et al, Lancet, 2012

gestations randomized to pessary.[18] However vaginal discharge was more frequent in the pessary group as 104 women reported vaginal discharge as compared with 0 women (out of 407) in the control group.

2.4 Progesterone for Preterm Birth Prevention in Women with a Short Cervix and Multiple Gestation

The benefit of progesterone, especially vaginal progesterone, specifically for short cervix in twin pregnancies remains an unresolved question. Although when studied in twins overall, progesterone does not appear to convey maternal or neonatal benefit, no published studies have focused primarily on high risk twin gestations vis à vis cervical shortening. Moreover, only about 113 women with a short cervix have been included in the trials published to date and not only have different definitions of short cervix been applied but also different formulations of progesterone utilized. When summarized using meta-analysis, the odds ratio for preterm birth <34 or 35 weeks was 1.07 (95% CI 0.52 – 2.19).[5] This meta-analysis included data on women treated with either vaginal or intramuscular progesterone.

Although STTARS failed to demonstrate any effect of progesterone in twins overall or in those with cervical shortening, by any definition, questions remained regarding dosing and interval of administration.[9] However, in a study presented at the 2013 SMFM meeting, Senat and colleagues randomized 165 women with twin gestations and a cervical length <25 mm to 500 mg 17-α hydroxyprogesterone caproate twice weekly or no treatment.[25] Not only did they find no difference in the interval to delivery, but they also saw a statistically significant increase in preterm birth <32 weeks and a trend to increased neonatal morbidity in women treated with progesterone. Given these data, there remains little doubt that intramuscular 17-α hydroxyprogesterone caproate is ineffective in preventing preterm birth in twins regardless of cervical length or dosing regimen.

Data on the effect of vaginal progesterone, albeit limited, is however more encouraging. In a subanalysis of the larger parent trial, Fonseca et al. reported an odds ratio of 0.49 (95% CI, 0.09 – 2.53) for spontaneous preterm birth <34 weeks in 24 twins with a cervical length < 15 mm.[26] In a secondary analysis of a trial of women with twin gestations, 47 were identified to have transvaginal cervical length <30 mm between 20-24 weeks. Vaginal progesterone inserts (200 mg) starting at 20-24 weeks and continued until 34 weeks produced a nominal reduction in preterm birth <34 weeks (29% vs. 40%; RR 0.63; 95% CI 0.18 –2.23) compared with placebo, although not statistically significant likely due to the small number of subjects.[6] Data in one individual patient data meta-analysis suggests the potential, with adequate power, for vaginal progesterone to be beneficial in preventing preterm birth <33 weeks (RR 0.70; 95% CI 0.34–1.44) and composite neonatal morbidity and mortality (24 vs. 40%; RR 0.56; 95% CI 0.3-0.97).[27] This analysis involved 52 twin gestations with cervical length <25 mm at <24 weeks. An individual patient data meta-analysis of progesterone in twin gestation conducted in the Netherlands (which included STTARS) reports a reduction in a composite neonatal morbidity outcome with vaginal progesterone in women with short cervix 27% vs. 37%, RR 0.57; 95% CI 0.47- 0.70.[28]

The response to vaginal progesterone in singletons varies as a function of the cervical length measurement such that even though women with a short cervix are at increased risk for preterm birth, those who receive progesterone have a lower rate of preterm birth and neonatal morbidity.[26,29]

2.4.1 Safety of Vaginal Progesterone

The use of progesterone, in its various formulations, has been well-studied over the last decade. Several studies have now shown that use of vaginal progesterone, in both 200 mg capsule form and the 90 mg gel formulation, is not associated with an increase in the occurrence of adverse events in the mother or the neonates.[26,29,30] Moreover, one of the trials that was being conducted in preparation for FDA submission, demonstrated no potential safety signals.[30]

2.5 Rationale for a Randomized Clinical Trial

The rising rate of multiple gestations and the associated risk of preterm birth and the sequelae of prematurity, especially when a short cervical length is present, constitute an important clinical and public health problem. To date, no screening or intervention strategy has proven effective in reducing the risk of preterm birth in multiple gestations. The recent ACOG Practice Bulletin on Prediction and Prevention of Preterm Birth concludes that there is insufficient evidence to assess the effect of progestogens in women with both multiple gestation and short cervical length.[31] Furthermore, a recent commentary from Romero highlights the lack of convincing evidence and the need for well designed studies to investigate the role of vaginal progesterone in the setting of a short cervix in twin gestations.[32] Given the fact that a short cervix may identify those most likely to benefit from vaginal progesterone, there is compelling reason to investigate further the role of vaginal progesterone for the prevention of preterm birth in women with twins and a short cervix. In addition, the promising data on the use of the Arabin pessary in the presence of a short cervix emphasize the need for further investigation on the use of this well-tolerated, low-cost, non-surgical intervention to tackle the problem of preterm birth in multiple gestations.

In summary, the lack of an effective, but urgently-needed intervention for women with a twin gestation, particularly those with a short cervix, underscores the need for a randomized trial.

3 Study Design

3.1 Primary Research Question

The randomized trial will address the primary research question:

In women with twin gestations and short cervical length less than 30 mm at 16 weeks 0 days to 23 weeks 6 days of gestation, does treatment with either a) an Arabin cervical pessary or b) vaginal progesterone prevent preterm birth prior to 35 weeks of gestation?

3.2 Secondary Research Questions

Secondary research questions this study will address are:

- Does treatment with either Arabin cervical pessary or vaginal progesterone compared with only placebo alter any of the secondary outcomes listed in Section 4.7 , including:
    - Neonatal morbidity or mortality?
    - Preterm birth less than 32 weeks?
    - Preterm birth less than 37 weeks?
    - Lower genital tract or urinary tract infection?
    - Physician interventions including labor inhibition, cerclage, and bed rest?
- What is the acceptability of and compliance with the Arabin pessary compared with vaginal progesterone?
- Is treatment with pessary or progesterone superior in preventing preterm delivery or other maternal or neonatal adverse outcomes?
- Does treatment with either the Arabin cervical pessary or vaginal progesterone increase the risk of vaginitis compared with vaginal placebo?
- Does treatment with vaginal progesterone change the profile of inflammatory mediators present in the cervicovaginal fluid compared with baseline and with vaginal placebo?
- Is the presence of fetal fibronectin in the cervicovaginal fluid (qualitative and/or quantitative) at randomization associated with primary or secondary outcomes and does this differ by treatment group?
- Do changes in fetal fibronectin concentrations between randomization and the 26-30 week follow-up visit predict subsequent preterm birth?
- What is the distribution of cervical length in twin gestation by gestational week in the second trimester as measured by certified sonographers?
- What risk factors, including cervical length, debris or funneling, predict preterm birth or other maternal and neonatal outcomes in twins?
- Are there specific subgroups in which treatment (either pessary or progesterone) is more efficacious? (See Section 5.5 for a discussion of the potential concerns with subgroup analysis.)

3.3 Design Summary

The study is a randomized controlled multi-center clinical trial of 630 women with a twin gestation and ultrasound evidence of short cervical length, defined as less than 30 mm, randomized to one of three arms at participating MFMU Network clinical centers.

- 200 mg micronized progesterone daily in the form of a gelatin capsule administered vaginally. This dose was chosen because it has previously been shown to have benefit in women (mainly singletons) with a short cervix < 15mm.[26]
- Identical appearing daily placebo capsule administered vaginally
- Arabin cervical pessary

3.4 Eligibility Criteria

3.4.1 Inclusion Criteria

1. Twin gestation with cardiac activity in both fetuses. Higher order multifetal gestations reduced to twins, either spontaneously or therapeutically, are not eligible unless the reduction occurred by 13 weeks 6 days project gestational age (see below).
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 30 mm by a study certified sonographer. Cervical length must be measured no earlier than 16 weeks 0 days as determined by the project gestational age (refer to Section 3.4.2 below). 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 Obstetricians and Gynecologists, the American Institute of Ultrasound in Medicine and the Society for Maternal-Fetal Medicine and is denoted "project gestational age".[33] 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.

The following algorithm is used:

- The first day of the last menstrual period (LMP) is determined, and a judgment made as to whether or not the patient has a "sure" LMP date.
- If the LMP date is unsure, ultrasound measurement(s) of the larger twin obtained at the patient's first dating ultrasound examination is used to determine the project gestational age. If the first dating ultrasound was conducted before 14 weeks 0 days, the measurement must be based on crown rump length (CRL).
- If the LMP date is sure, project gestational age is determined by a comparison between the gestational age by LMP and by ultrasound measurement of the larger twin based on the earliest dating ultrasound. If the ultrasound confirms the gestational age by LMP as in the table below,

the LMP-derived gestational age is used to determine the project gestational age. Otherwise, project gestational age will be determined based upon the ultrasound measurement of the larger twin.

Table 2. 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.[15] 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 screening and enrollment will be performed by a sonographer who has been trained and certified in the appropriate technique. Documentation of education and proficiency in appropriate technique and competency in cervical assessment will be required. 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. Monoamniotic gestation, due to increased risk of adverse pregnancy outcome.
3. Twin-twin transfusion syndrome, due to increased risk of adverse pregnancy outcome.
4. Evidence of severe IUGR (<5th percentile for gestational age) in either fetus.

5. Fetal anomaly in either twin 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 fetuses for anomalies.
6. Placenta previa, because of risk of bleeding and high potential for indicated preterm birth.
7. Active vaginal bleeding greater than spotting at the time of randomization, because of potential exacerbation due to pessary placement.
8. Symptomatic, untreated vaginal or cervical infection, also because of potential exacerbation due to pessary placement. Patients may be treated and if subsequently asymptomatic, randomized.
9. 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.
10. 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.
11. More than six contractions per hour reported or documented prior to randomization. It is not necessary to place the patient on a tocodynamometer.
12. 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.
13. Any fetal/maternal condition which would require invasive in-utero assessment or treatment, for example significant red cell antigen sensitization or neonatal alloimmune thrombocytopenia.
14. 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, conditions treated with chronic oral glucocorticoid therapy, conditions requiring anti-coagulation therapy). Specifically, 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.
15. Planned cerclage or cerclage already in place since it would preclude placement of a pessary.
16. Planned indicated delivery prior to 35 weeks.
17. Planned or actual progesterone treatment of any type or form after 15 weeks 6 days during the current pregnancy.
18. Allergy to progesterone, silicone, or excipients in the study drug, including peanuts or peanut oil.
19. Known, suspected or history of breast cancer because breast cancer is a contraindication to the active study medication.
20. Known liver dysfunction or disease because liver disease is a contraindication to the active study medication.
21. Participation in another maternal/fetal interventional study that influences gestational age at delivery or neonatal morbidity or mortality.
22. Participation in this trial in a previous pregnancy. Patients who were screened in a previous pregnancy, but not randomized, do not have to be excluded.

23. 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 forms 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 initially be assigned to progesterone, pessary or placebo in a 1:1:1 ratio according to a randomization sequence prepared and maintained centrally by the Biostatistical Coordinating Center (BCC). The two study medication arms of the study (progesterone or placebo) are double masked; neither the patient nor the clinical staff will be aware of the treatment assignment.

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.[34,35] Randomization will be stratified by clinical site to assure balance between the two treatment groups 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 twin gestation presenting for prenatal care before approximately 24 weeks gestational age are potentially eligible for screening. If a patient appears to meet the criteria for screening, she will be told about the study and asked to sign an informed consent form for screening (see Appendix B.1 for the model screening consent form) unless she has already been identified as having cervical length less than 30 mm from a transvaginal ultrasound conducted by a study certified sonographer as part of clinical care. Cervical length is assessed with a transvaginal ultrasound conducted in a standardized fashion described in Section 3.4.3. All measurements will be conducted by a sonographer who has been previously certified for this or one of the previous studies. If the patient has a cervical length of 30 mm or more, but less than 35 mm she may be rescreened once within a one to four week window, if the patient is still less than 24 weeks gestation.

Patients who have had either a transabdominal or transvaginal ultrasound that has a documented short cervical length by non-study certified personnel are eligible for inclusion in the study but would still have to grant informed consent for cervical length screening followed by an official study ultrasound.

Inclusion/exclusion criteria will be reviewed with the patient's chart. Eligible patients will be asked for written informed consent to participate in the trial (see Appendix B.2 for the model consent to study form). If an obstetrical ultrasound examination to evaluate the fetuses 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 each patient will also undergo a speculum examination (followed by a digital exam if necessary) to rule out cervical dilation and cervical infection. A cervicovaginal fluid sample, vaginal Gram stain, and vaginal pH will be collected to assess for local inflammation, vaginitis, and fetal fibronectin (quantitative).

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 to a study drug code number corresponding to a blinded study medication kit.

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

- Current pregnancy complications including sexually transmitted infections and vaginal infections.

Women randomized to pessary will be evaluated by an obstetric care provider (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 technique so that it encircles the cervix and rests in the anterior and posterior fornices.

Women randomized to vaginal progesterone or placebo will place the first dose of study product under supervision in the clinic. The patient will receive instruction on daily use of the study product and will receive a month's supply of study product.

4.4 Study Procedures

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 assessments (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. Patients who are receiving vaginal progesterone or placebo will receive a monthly supply of study drug and compliance will be assessed monthly by a capsule count.

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, vaginitis, and fetal fibronectin (quantitative). 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 will be asked to complete a questionnaire summarizing their experience with the pessary (if randomized to pessary) or study medication (if randomized to the study medication group). The questionnaire will be administered again at 36 weeks gestation.

Therapy will be continued until 34 weeks, 6 days to 36 weeks, 0 days of gestation, at which time all patients should have a final study visit scheduled. Women in the pessary arm will have the device removed.

4.5 Patient Management and Follow-up

If a patient experiences rupture of the membranes, the study treatment should be stopped.

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.

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. Vaginal bleeding greater than menses — 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. If the patient has a pessary, it should be left in place; if she is in one of the study medication arms, she should be instructed to continue her daily use of study medication while she is being treated.

No attempt will be made to alter or mandate clinical management of the subjects. Sexual intercourse is not expressly prohibited in this study. However, the use of serial cervical length ultrasounds, prophylactic tocolytic drugs or cerclage is discouraged. If a patient is hospitalized, the patient should be told to continue her study medication and additional supplies made available if necessary. Otherwise patients admitted to hospital for preterm labor should be managed according to institutional policy.

Infants will be followed to discharge or until 28 days after the expected date of delivery as determined by project gestational age, whichever is longest. Maternal and neonatal records will be reviewed and a follow-up telephone interview conducted to capture neonatal and maternal outcomes.

4.6 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 death, neonatal death, or life threatening maternal event by email/phone/fax, if the event occurred in a MFMU Network hospital. For any maternal death, neonatal death, or life threatening maternal event 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 DSMC Chair, NIH representative, and any other requesting DSMC member on a monthly basis. The DSMC Chair decides whether the adverse event reports should be disseminated to the rest of the committee, whether a follow-up call or meeting is required, and whether the treatment assignment should be unmasked. 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 FDA Investigational Device Exemption safety report will be completed for any suspected adverse reaction to the pessary that is both serious and unexpected. Likewise an FDA Investigational New Drug

safety report will be completed for any suspected adverse reaction to the study medication, whether active or placebo.

The only indication for breaking the randomization code is when it is medically necessary to unmask the study drug assignment to be able to treat the patient.

4.7 Study Outcome Measures and Ascertainment

4.7.1 Primary Outcome

The primary outcome is delivery or fetal demise of either twin prior to 35 weeks 0 days (as determined by the project gestational age).

4.7.2 Maternal Secondary Outcomes

- Randomization to delivery (or fetal demise) interval
- Gestational age at delivery
- Preterm delivery or fetal demise of either twin prior to 28 weeks, 32 weeks, and 37 weeks
- Delivery of at least one liveborn infant at $\geq$ 32 weeks, $\geq$ 35 weeks, and $\geq$ 37 weeks
- Preterm premature rupture of membranes (pPROM)
- Spontaneous preterm delivery (following preterm labor or pPROM) < 35 weeks and < 32 weeks
- Indicated preterm delivery < 35 weeks
- Cesarean delivery
- Chorioamnionitis
- Maternal antepartum hospitalization days
- Maternal antibiotic or antifungal use for vaginal infection
- Vaginal infection as assessed by local clinical diagnosis
- Side effects including symptomatic vaginal discharge or discomfort
- Discontinuation of treatment and reason

4.7.3 Fetal and Neonatal Secondary Outcomes

- Fetal or neonatal death
- Twin-twin transfusion syndrome
- Duration of ventilator support
- Duration of supplemental oxygen
- Seizures requiring treatment
- 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
- 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

- 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.
- 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.
- 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.
- 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.
- Hyperbilirubinemia. Peak total bilirubin of at least 15 mg% or the use of phototherapy
- 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.
- 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
- Length of hospital stay, need for NICU or intermediate care admission and length of stay if admitted

5 Statistical Considerations

5.1 Data Relevant to the Primary Outcome

For this trial as in the MFMU Network STTARS trial, the primary outcome is fetal death or preterm delivery before 35 weeks for either twin. In the STTARS trial the primary outcome rate in all twins (regardless of cervical length) was approximately 40% with no difference seen by treatment group. In the current trial, a higher incidence of the primary outcome is expected in the placebo group since these women will have a shorter cervical length.

This is confirmed by the data from the Network presented in Section 2.2.2. In the Preterm Prediction Twin Cohort, cervical length less than 30 mm at 22-24 weeks was associated with a 56% rate of preterm delivery or fetal loss < 35 weeks. In the STTARS study, there were very few (10) patients with cervical length less than 30 mm at 14-20 weeks, of which 5 (50%) had a preterm delivery or fetal loss before 35 weeks (the primary outcome for STTARS). However, 56% (10/18) of those with cervical length < 32 mm (10^{th} percentile) had the same outcome. Therefore, it is reasonable to assume that the primary outcome rate in the placebo group would be between 50 and 60%.

5.2 Sample Size and Power

A one-third reduction in preterm birth < 35 weeks was selected as being clinically meaningful. It is assumed that pessary and micronized progesterone are more likely to be effective for preventing spontaneous rather than indicated preterm birth. If 20% of the preterm births at this gestation are indicated (lower than that typically expected since these women will all have a short cervix) and if there is a 40% reduction in spontaneous preterm birth and no reduction in indicated preterm birth, then the overall effect size would be slightly less than a one-third reduction in all preterm births.

Table 3 below shows the sample sizes required to detect 30-33% reduction in PTB < 35 weeks if the rate in the placebo group is 50-60%, with type I error 2.5% 2-sided and power of 90%. Type I error was chosen to be 2.5% 2-sided since there will be two primary comparisons (between pessary and placebo and between progesterone and placebo).

Table 3. Sample Sizes per Group for Different Primary Outcome Rates, Power and Effect Sizes[2]

Reduction in Primary Outcome Rate	% Power	Primary Outcome Rate in Placebo Group		
		50%	55%	60%
30%	80	210	180	150
	85	240	200	170
	90	270	230	190
33.3%	80	170	140	120
	85	190	160	140
	90	220	190	160

[2]Rounding up to next 10

In STTARS, women were given a test injection of progesterone (17-α hydroxyprogesterone caproate) and asked to return for randomization in three days or more. A total of 2.7% of women did not return or withdrew consent. Since a compliance run-in such as this is not feasible for PROSPECT, it is assumed conservatively that as many as 5% of the women drop out and effectively become crossovers. This would require an adjustment in the sample size of approximately 10.8%. Thus, adjusting for 5% crossover, a sample size of 630 patients is sufficient to detect a one-third reduction in the primary outcome rate of 55% in the placebo group with 90% power for either the pessary or the progesterone arm, and at least 80% power if the effect size is as low as 30%.

5.3 Feasibility

The feasibility of answering the primary research question will be addressed after the first 100 patients have been randomized and delivered. These data would be presented to the Data and Safety Monitoring Committee (DSMC) before any comparison by group. The DSMC would be charged with making a recommendation regarding potential revision of the sample size.

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.[36] This method is flexible with regard to the timing of the interim analyses. 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 .0125 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. If recruitment proceeds as planned and annual analyses are conducted, it is expected that two interim analyses will be conducted at approximately 35% and 65% of the final sample size of 630.

If a maternal death occurs after randomization and before discharge following delivery recruitment to the trial will be paused until the DSMC has been convened to determine whether the study should proceed.

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.[37]

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 risks and confidence intervals 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.[38] 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*."[39] 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 mm; < 20 mm and ≥ 20 mm)
- Screening to randomization interval
- Debris/funneling on randomization ultrasound
- Chorionicity
- Obesity by BMI category
- Parity
- Bacterial vaginosis/Nugent score at enrollment—Nugent ≥ 7 with pH > 4.4
- Fetal fibronectin positive
- Type of conception/use of ART
- Prior cervical surgery including LOOP/ LEEP

Loss to follow-up will be defined as no information regarding pregnancy prior to 35 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 will be used to compare time-to-event variables, such as time to delivery or fetal demise and gestational age at delivery or fetal demise.

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 20% African-American and 15% Hispanic, similar to the STTARS trial there is limited power (50% or less) 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:

- PR01 Screening Log.
- PR01A Eligibility Checklist
- PR02 Eligibility and Randomization Form is completed for all patients eligible for the study.
- PR03 Study Drug Randomization Log: lists patients randomized to progesterone or placebo, and provides the drug code number.
- PR03A Pessary Accountability Log lists the specific pessary(ies) given to each patient.
- PR04 Baseline Form is completed for all randomized patients. This form includes detailed demographic and social data, medical and obstetrical history, and current pregnancy complications.
- PR04A Previous Pregnancy Outcome Form.
- PR05 Study Visit Form documents monthly study visits, possible side effects and compliance
- PR06 Study Drug Dispensing and Compliance Log documents the dispensing of study medication and the return of any unused study medication.
- PR06A Study Drug Final Use Form documents the reason for stopping study drug.
- PR07 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.
- PR08 Maternal Delivery and Outcome Form documents specific pregnancy complications since randomization, in addition to labor, delivery and postpartum information.
- PR09 Neonatal Baseline Form records date and time of birth, delivery data and status at delivery, for each fetus/infant.
- PR10 Neonatal Outcome Form records outcome data for all infants admitted to the NICU or special care nursery.
- PR11 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.
- PR12 Adverse Event Form records serious and non-serious adverse events.
- PR13A Women's Views on the Arabin Pessary, a patient questionnaire.
- PR13B Women's Views on the Study Medication, a patient questionnaire.
- PR14 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 PROSPECT 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 PROSPECT 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 PROSPECT 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 fourteen 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 Program Scientist convenes and attends the meetings.

7.2 Committees

7.2.1 Steering Committee

This committee consists of seventeen members. The Principal Investigator from each of the fourteen clinical centers, the BCC, and the NICHD MFMU Network Program 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 Program 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

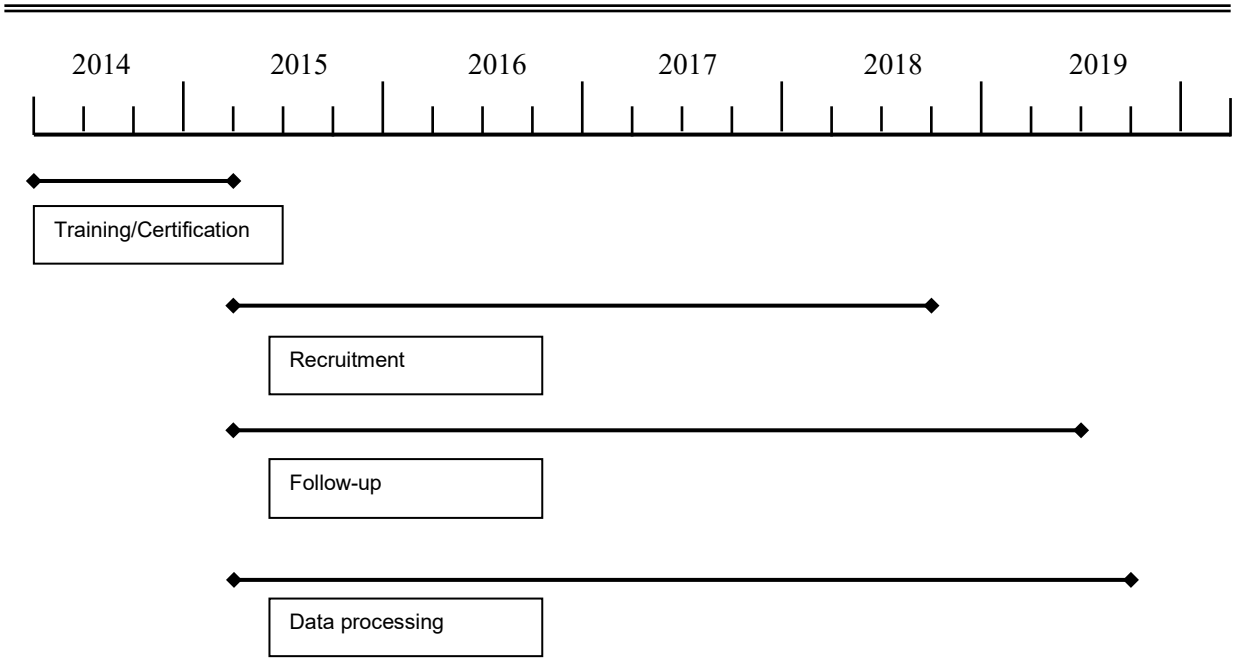
The Publications Committee is a standing committee of the Steering Committee. The functions of this committee are to develop publication policies and to review all manuscripts and abstracts prior to submission. The goals of this committee are fair and appropriate authorship credit and high quality publications.

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 3. Timetable



8.1 Training and Certification

A preliminary workshop was held with the nurse coordinators in April 2013. Final training will be conducted for research staff in January 2015, 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 April 2015.

8.2 Recruitment and Data Collection Period

Approximately 160,000 women deliver at MFMU Network centers annually. Based on the 2009 twin birth rate of 33.2 per 1,000 live births,[1] at least 5312 twins per year are born within the Network sites (2656 pregnancies). If only 50% consent to undergo screening, this provides 1328 twin gestations per year. Assuming 20% have a short cervix, this provides 266 patients eligible for randomization per year. If 67% of those eligible for randomization consented, 177 twin gestations could be enrolled per year. The sample size of 630 needed could therefore be achieved in approximately 42 months with 15 patients recruited per month. These are reasonably conservative estimates since the proportion of twin births in MFMU is likely higher than the U.S. average even without including maternal transports. Given the

high-risk nature of this population and the lack of any proven interventions, it is also reasonable to anticipate that the consent rate would be higher than most MFMU studies.

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 and Progesterone for Preterm Prevention in Twin Gestation with a Short Cervix

OBJECTIVE: To determine whether the Arabin Pessary or vaginal progesterone reduces the risk of preterm birth in women with a twin gestation and a short cervix.

ORGANIZATION

Clinical Centers:	Magee, UAB, Ohio State, UTSW, Utah, Brown, Columbia, Case Western, UT-Houston, UNC, Northwestern, UTMB-Galveston, Colorado, Duke, Stanford, UPenn, UCSF, Baylor
Subcommittee:	Joseph Biggio, MD (Chair)

DESIGN

Major Eligibility Criteria:	❖ Twin gestation ❖ Gestational age 16^0 to 23^6 wks ❖ Cervical length < 30.0 mm
Groups:	❖ Progesterone ❖ Matching placebo ❖ Arabin Pessary
Random Allocation:	Standard urn design; 1:1:1 allocation
Level of Masking:	Unmasked/Double-masked
Stratification:	❖ Clinical site
Sample Size:	❖ 630
Assumptions:	❖ Outcome event=delivery < 35^0 weeks gestation or fetal loss ❖ Placebo group event rate =55% ❖ Progesterone group event rate =36.7% (33% reduction) ❖ Pessary group event rate=36.7% (33% reduction) ❖ Type I error = 2.5% (two sided with two primary comparisons) ❖ Power =90% ❖ Adjustment for 5% crossover
Interim Analysis:	❖ Lan-DeMets group sequential method

SCHEDULED EVALUATIONS / DATA COLLECTION

Pre-Randomization:	❖ Cervical length measurement by trained sonographer
Randomization:	❖ Pregnancy, exposure and medical history ❖ 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) ❖ Patient questionnaire 8 weeks after randomization and again at 36 wks gestation. ❖ Study medication groups: one-month supply of study meds < 35 wks
Delivery:	❖ Pessary group: assessed for fit or replacement, as needed ❖ Delivery and neonatal data

MANAGEMENT PROTOCOL

Study Medication Groups:	❖ 200mg micronized vaginal progesterone softgel capsule or placebo, daily from randomization to < 35 wks
Pessary Group:	❖ Placement management from randomization to < 35 wks

OUTCOME MEASURES

Primary:	❖ Delivery prior to 35 wks or fetal loss
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	❖ April 2015 to September 2018
Data Collection	❖ April 2015 to June 2019
Closeout/Analysis	❖ June 2019 to May 2020

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 and Progesterone for Preterm Prevention in Twin Gestation with a Short Cervix (PROSPECT)

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

Studies have shown that women pregnant with twins are more likely to deliver their babies preterm (before 37 weeks of pregnancy) compared with women pregnant with one baby. Babies born preterm have a greater chance of having serious, long-term health problems or dying.

A short cervix (which is the lower, narrow part of the womb) is more common in women carrying twins. Women who have a short cervix are more likely to deliver their babies preterm.

The purpose of this research study is to find out whether a pessary or vaginal progesterone lowers the risk of babies being born preterm to women who are carrying twins and have a short cervix. A pessary is a round, soft silicone device that goes around the cervix. Progesterone is a hormone naturally produced by the placenta.

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 less than 30 mm (about 1 inch), a member of the research staff may contact you to talk about taking part in a study in which you will be randomized (like choosing one of three numbers out of a hat) into one of three treatment groups: 1) the pessary group will have a pessary placed around the cervix, 2) the progesterone group will be given vaginal progesterone capsules, and 3) the placebo group will be given vaginal placebo capsules (the capsules look like the progesterone capsules but contain no medicine). If the length of your cervix measures between 30 mm and 35 mm (about 1 to 1½ inches), a member of the research staff may ask you to have another vaginal ultrasound within one to four weeks to see if your cervix measures less than 30 mm at that time. You and your doctor 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 babies. 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.

The progesterone product contains peanut oil and should not be used if you are allergic to peanuts. Please inform the study staff immediately if you are allergic to peanuts, because this allergy will exclude you from participating in this study.

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.2 Sample Informed Consent Form for Screening (with Common Rule 2018 changes)

Research Study Title: A Randomized Trial of Pessary and Progesterone for Preterm Prevention in Twin Gestation with a Short Cervix (PROSPECT)

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 weeks 0 days and 23 weeks 6 days 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

Studies have shown that women pregnant with twins are more likely to deliver their babies preterm (before 37 weeks of pregnancy) compared with women pregnant with one baby. Babies born preterm have a greater chance of having serious, long-term health problems or dying.

A short cervix (which is the lower, narrow part of the womb) is more common in women carrying twins. Women who have a short cervix are more likely to deliver their babies preterm.

The purpose of this research study is to find out whether a pessary or vaginal progesterone lowers the risk of babies being born preterm to women who are carrying twins and have a short cervix. A pessary is a round, soft silicone device that goes around the cervix. Progesterone is a hormone naturally produced by the placenta.

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 less than 30 mm (about 1 inch), a member of the research staff may contact you to talk about taking part in a study in which you will be randomized (like choosing one of three numbers out of a hat) into one of three treatment groups: 1) the pessary group will have a pessary placed around the cervix, 2) the progesterone group will be given vaginal progesterone capsules, and 3) the placebo group will be given vaginal placebo capsules (the capsules look like the progesterone capsules but contain no medicine). If the length of your cervix measures between 30 mm and 35 mm (about 1 to 1½ inches), a member of the research staff may ask you to have another vaginal ultrasound within one to four weeks to see if your cervix measures less than 30 mm at that time. You and your doctor 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 babies. 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.

The progesterone product contains peanut oil and should not be used if you are allergic to peanuts. Please inform the study staff immediately if you are allergic to peanuts, because this allergy will exclude you from participating in this study.

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

Research Study Title: A Randomized Trial of Pessary and Progesterone for Preterm Prevention in Twin Gestation with a Short Cervix (PROSPECT)

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 carrying twins and you are between 16 weeks 0 days and 23 weeks 6 days pregnant and a vaginal ultrasound showed that your cervix is shorter than usual (less than 30 mm, which is about 1 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

Studies have shown that women pregnant with twins are more likely to deliver their babies preterm (before 37 weeks of pregnancy) compared with women pregnant with one baby. Babies born preterm have a greater chance of having serious, long-term health problems or dying.

A short cervix is more common in women carrying twins. Women who have a short cervix are more likely to deliver their babies preterm. The best treatment for pregnant women with twins who have a short cervix is not known. Some studies have shown that placing a pessary around the cervix or using vaginal progesterone may help to prolong the pregnancy.

The purpose of this research study is to find out whether pessary or vaginal progesterone lowers the risk of babies being born preterm to women who are carrying twins and have a short cervix. A pessary is a round, soft silicone device that goes around the cervix. Progesterone is a hormone naturally produced by the placenta.

This research study is funded by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD). Fourteen medical centers across the country are part of this research study, and in all, 630 women with twin 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 choosing one of three numbers out of a hat) into one of three treatment groups: 1) the pessary group will have a pessary placed around the cervix, 2) the progesterone group will be given vaginal progesterone capsules to use daily, and 3) the placebo group will be given

vaginal placebo capsules to use daily (capsules that look like the progesterone capsules but contain no medicine).

Just before being randomized into one of the three treatment groups, a speculum exam will be done to look at your cervix to find out if it is opening or if you have an infection. Opening of the cervix may allow the membranes (your bag of waters) to be exposed to the vagina increasing 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 prior to 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.

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.

If you are randomized to either the progesterone group or the placebo group, you will place the study medication into your vagina at the first study visit. A research nurse will be there to help you. You will be given a one month supply of the study medication along with directions for daily use. You, your doctor, or research study nurse will not know which study medication group you are in. This is to make sure everyone is treated the same. In case of an emergency, your doctor can find out which treatment you are receiving.

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 group 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 35th or 36th 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 are on study medication, you will be asked to bring all unused study medication to in-person visits or to have the bottle available to count pills over the phone or video. You will be given a supply of study medication each month.

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.

At 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 (if you were randomized to pessary) or on the study medication (if you are randomized to study medication). You may be asked to answer these questions again around the 36th week of your pregnancy.

If you were randomized to pessary, an in-person study visit will take place between the 35th and 36th week of your pregnancy to remove the pessary. If you were randomized to study medication and you have an in-person study visit between the 35th and 36th week of your pregnancy, all unused study medication is to be returned at this visit and no more study medication will be given. If the study visit is done over the

phone or video, you will be asked to return the bottles in a prepaid envelope or to bring them with you when you deliver your baby.

You will continue to receive standard care from your doctor while you are in this research trial. About one month after you deliver your babies or at the time your babies are discharged from the hospital, whichever is the longest, we will collect information about your pregnancy, labor, deliveries, and the health of your babies. We will review your and your babies 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 babies.

Possible Risks

The progesterone product contains peanut oil and should not be used if you are allergic to peanuts. Please inform the study staff immediately if you are allergic to peanuts, because this allergy will exclude you from participating in this study.

If you are randomized to the pessary group, 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.

In a study of women pregnant with one baby, no serious side effects were associated with the pessary, including infection or rupture of membranes, or need for removal of the pessary because of discomfort. Women did report an increase in vaginal discharge. Another study of women pregnant with twins also found no increased risk of serious side effects for women who had the pessary compared with women who did not although some women had the pessary removed early for discomfort. No risks from the pessary to the baby were found in either study.

There have been several studies of the use of vaginal progesterone in pregnancy. These studies have shown that vaginal progesterone does not increase the risk of serious side effects in the mother or the newborn.

You may have vaginal itching, vaginal irritation, vaginal odor or vaginal burning, no matter which treatment 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 babies 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 babies may or may not directly benefit from your participation. If the study shows that treatment is successful, you and your babies may benefit if you are assigned to receive the progesterone medication or a pessary. In addition, if the study shows benefit, ultrasound testing, progesterone medication, 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 or study medication and at a later study visit between 26 and 30 weeks of pregnancy. These samples may be

used to find out if you have 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 your babies preterm.

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 medications and 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

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 follow-up 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 follow-up 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 babies are born, data will be collected on your labor (such as when it starts) and deliveries. Information will also be collected on your babies at delivery and on each 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 one or both of your baby's medical charts 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.

This is a clinical trial and it is critical to the interpretation of the results that you not know which treatment group you are in if you are randomized to receive study medication. 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_____ 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_____ 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_____ I **give** permission to be contacted in the future for follow-up research.

NO_____ 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 and Progesterone for Preterm Prevention in Twin Gestation with a Short Cervix (PROSPECT)

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 pessary or vaginal progesterone lowers the risk of babies being born preterm to women who are carrying twins and have a short cervix. The cervix is the lower, narrow part of your womb. A pessary is a soft, round, silicone device that is placed into the vagina to support the cervix.

If you consent, you will be in the study from randomization (between 16 weeks 0 days and 23 weeks 6 days 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 to one of three treatments (like choosing a number out of a hat): 1) pessary - a pessary will be placed around your cervix, or 2) progesterone - progesterone capsules to be inserted into the vagina daily, or 3) placebo - placebo capsules (capsules that look like the progesterone capsules but do not contain medicine) to be inserted into the vagina daily.

You will have monthly study visits (in-person or by video or phone) until the 35th week of pregnancy or delivery, whichever comes first. After delivery, the research staff will collect medical information about you and your babies 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 carrying twins and you are between 16 weeks 0 days and 23 weeks 6 days pregnant and a vaginal ultrasound showed that your cervix is shorter than usual (less than 30 mm, which is about 1 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

Studies have shown that women pregnant with twins are more likely to deliver their babies preterm (before 37 weeks of pregnancy) compared with women pregnant with one baby. Babies born preterm have a greater chance of having serious, long-term health problems or dying.

A short cervix is more common in women carrying twins. Women who have a short cervix are more likely to deliver their babies preterm. The best treatment for pregnant women with twins who have a short cervix is not known. Some studies have shown that placing a pessary around the cervix or using vaginal progesterone may help to prolong the pregnancy.

The purpose of this research study is to find out whether pessary or vaginal progesterone lowers the risk of babies being born preterm to women who are carrying twins and have a short cervix. A pessary is a round, soft silicone device that goes around the cervix. Progesterone is a hormone naturally produced by the placenta.

This research study is funded by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD). Fourteen medical centers across the country are part of this research study, and in all, 630 women with twin 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 choosing one of three numbers out of a hat) into one of three treatment groups: 1) the pessary group will have a pessary placed around the cervix, 2) the progesterone group will be given vaginal progesterone capsules to use daily, and 3) the placebo group will be given vaginal placebo capsules to use daily (capsules that look like the progesterone capsules but contain no medicine).

Just before being randomized into one of the three treatment groups, a speculum exam will be done to look at your cervix to find out if it is opening or if you have an infection. Opening of the cervix may allow the membranes (your bag of waters) to be exposed to the vagina increasing 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 prior to 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.

If you are randomized to either the progesterone group or the placebo group, you will place the study medication into your vagina at the first study visit. A research nurse will be there to help you. You will be given a one month supply of the study medication along with directions for daily use. You, your doctor, or research study nurse will not know which study medication group you are in. This is to make sure everyone is treated the same. In case of an emergency, your doctor can find out which treatment you are receiving.

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 group 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 35th or 36th 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 are on study medication, you will be asked to bring all unused study medication to in-person visits or to have the bottle available to count pills over the phone or video. You will be given a supply of study medication each month.

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.

At 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 (if you were randomized to pessary) or on the study medication (if you are randomized to study medication). You may be asked to answer these questions again around the 36th week of your pregnancy.

If you were randomized to pessary, an in-person study visit will take place between the 35th and 36th week of your pregnancy to remove the pessary. If you were randomized to study medication and you have an in-person study visit between the 35th and 36th week of your pregnancy, all unused study medication is to be returned at this visit and no more study medication will be given. If the study visit is done over the phone or video, you will be asked to return the bottles in a prepaid envelope or to bring them with you when you deliver your baby.

You will continue to receive standard care from your doctor while you are in this research trial. About one month after you deliver your babies or at the time your babies are discharged from the hospital, whichever is the longest, we will collect information about your pregnancy, labor, deliveries, and the health of your babies. We will review your and your babies 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 babies.

Possible Risks

The progesterone product contains peanut oil and should not be used if you are allergic to peanuts. Please inform the study staff immediately if you are allergic to peanuts, because this allergy will exclude you from participating in this study.

If you are randomized to the pessary group, 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.

In a study of women pregnant with one baby, no serious side effects were associated with the pessary, including infection or rupture of membranes, or need for removal of the pessary because of discomfort. Women did report an increase in vaginal discharge. Another study of women pregnant with twins also found no increased risk of serious side effects for women who had the pessary compared with women who did not although some women had the pessary removed early for discomfort. No risks from the pessary to the baby were found in either study.

There have been several studies of the use of vaginal progesterone in pregnancy. These studies have shown that vaginal progesterone does not increase the risk of serious side effects in the mother or the newborn.

You may have vaginal itching, vaginal irritation, vaginal odor or vaginal burning, no matter which treatment 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 babies 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 babies may or may not directly benefit from your participation. If the study shows that treatment is successful, you and your babies may benefit if you are assigned to receive the progesterone medication or a pessary. In addition, if the study shows benefit, ultrasound testing, progesterone medication, 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 or study medication and at a later study visit between 26 and 30 weeks of pregnancy. These samples may be used to find out if you have 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 your babies preterm.

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 medications and 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

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 follow-up 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 follow-up 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 babies are born, data will be collected on your labor (such as when it starts) and deliveries. Information will also be collected on your babies at delivery and on each 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 one or both of your baby's medical charts 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.

This is a clinical trial and it is critical to the interpretation of the results that you not know which treatment group you are in if you are randomized to receive study medication. 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_____ 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_____ 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_____ I **give** permission to be contacted in the future for follow-up research.

NO_____ 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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