

# **RANDOMIZED CONTROL TRIAL: PHYSICAL EXAM INDICATED CERCLAGE IN TWIN GESTATIONS**

## **Principal Investigator:**

### **Amanda Roman, MD**

Division of Maternal-Fetal Medicine  
Department of Obstetrics and Gynecology  
Thomas Jefferson University Hospital  
833 Chestnut Street, First Floor, Philadelphia, PA  
Email: [amanda.roman@jefferson.edu](mailto:amanda.roman@jefferson.edu)  
Phone: 215-955-9200  
Fax: 215-955-5041  
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## Table of Contents

<b>STUDY SUMMARY .....</b>	<b>4</b>
<b>DEFINITIONS .....</b>	<b>5</b>
<b>1 INTRODUCTION .....</b>	<b>6</b>
1.1 BACKGROUND .....	6
1.2 CLINICAL DATA TO DATE .....	7
1.3 RISK/BENEFITS .....	7
<b>2 STUDY OBJECTIVES .....</b>	<b>8</b>
2.1 PRIMARY OBJECTIVE.....	8
<b>3 STUDY DESIGN .....</b>	<b>9</b>
3.1 GENERAL DESIGN .....	9
3.2 PRIMARY STUDY ENDPOINTS .....	9
3.3 SECONDARY STUDY ENDPOINTS .....	9
<b>4 SUBJECT SELECTION AND WITHDRAWAL .....</b>	<b>9</b>
4.1 INCLUSION CRITERIA .....	9
4.2 EXCLUSION CRITERIA .....	10
4.3 SUBJECT RECRUITMENT AND SCREENING .....	10
<b>5 STUDY .....</b>	<b>13</b>
5.1 DESCRIPTION .....	13
5.2 TREATMENT REGIMEN .....	13
5.3 METHOD FOR ASSIGNING SUBJECTS TO TREATMENT GROUPS .....	13
5.4 PLACEMENT OF CERCLAGE .....	13
<b>6 STUDY PROCEDURES .....</b>	<b>13</b>
6.2 RANDOMIZATION .....	14
6.3 INTERIM CONTACTS .....	14
6.4 CERCLAGE REMOVAL .....	14
6.5 PREGNANCY OUTCOME .....	15
<b>7 STATISTICAL PLAN .....</b>	<b>15</b>
7.1 SAMPLE SIZE DETERMINATION .....	15
7.2 STATISTICAL METHODS.....	15
<b>8 SAFETY AND ADVERSE EVENTS .....</b>	<b>16</b>

<b>8.1 DEFINITIONS .....</b>	<b>16</b>
<b>8.2 RECORDING OF ADVERSE EFFECTS .....</b>	<b>17</b>
<b>8.3 REPORTING OF ADVERSE EFFECTS AND UNANTICIPATED PROBLEMS .....</b>	<b>18</b>
<b>8.4 MEDICAL MONITORING .....</b>	<b>21</b>
<b>8.4.1 Data and Safety Monitoring Board .....</b>	<b>21</b>
<b>9 DATA HANDLING AND RECORD KEEPING .....</b>	<b>21</b>
<b>9.1 CONFIDENTIALITY .....</b>	<b>21</b>
<b>9.2 SOURCE DOCUMENTS .....</b>	<b>22</b>
<b>9.3 RECORDS RETENTION .....</b>	<b>22</b>
<b>10 STUDY MONITORING, AUDITING, AND INSPECTING .....</b>	<b>22</b>
<b>10.1 STUDY MONITORING PLAN .....</b>	<b>22</b>
<b>10.2 AUDITING AND INSPECTING .....</b>	<b>23</b>
<b>11 ETHICAL CONSIDERATIONS .....</b>	<b>23</b>
<b>12 CONFLICT OF INTEREST .....</b>	<b>23</b>
<b>13 PUBLICATION PLAN .....</b>	<b>24</b>
<b>14 REFERENCES .....</b>	<b>24</b>
<b>APENDIX #1 .....</b>	<b>25</b>
<b>APENDIX #2 .....</b>	<b>26</b>

RCT PEIC Twins  
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### **List of Abbreviations**

AE: Adverse Event

CI: Confidence Interval

CL: Cervical Length

HIPAA: Health Insurance Privacy and Portability Act of 1996

IRB Institutional Review Board

PEIC: Physical exam indicated cerclage

PTB: Preterm Birth

RCT: Randomized Controlled Trial

SAE: Serious Adverse Event

### Study Summary

<b>Title</b>	Randomized control trial: physical exam indicated cerclage in twin gestations
<b>Short Title</b>	RTC: PEIC Twins
<b>Methodology</b>	Multi-center, open label, randomized trial
<b>Study Duration</b>	3 years for subject enrollment, and an additional 6 months for analysis and manuscript preparation.
<b>Study Center</b>	Thomas Jefferson University
<b>Objectives</b>	The primary objective of this study is to determine if physical exam indicated cerclage use reduces the incidence of spontaneous PTB in asymptomatic women with twin gestations with cervical dilation diagnosed on pelvic exam before 24 weeks of gestation.
<b>Number of Subjects</b>	52
<b>Diagnosis and Main Inclusion Criteria</b>	Women, age older than 18, with a twin gestation and cervical dilation on pelvic exam and/or visible membranes on speculum exam between 16 to 23 6/7 weeks gestation
<b>Study Product and Planned Use</b>	Cervical cerclage
<b>Reference therapy</b>	Standard obstetrical expectant management
<b>Statistical Methodology</b>	Statistical analysis will be based on the intention-to-treat principle. The risk of spontaneous preterm birth before 34 weeks will be quantified by use of the odds ratio and 95% CI. Multivariate analysis will be performed using logistic regression.

## **Definitions**

PPROM: Preterm premature rupture of membranes, rupture of the amniotic membranes prior to 37 weeks of gestation.

PTB: Preterm birth: Birth prior to 37 weeks.

LBW: Low birth-weight infants, birth weight less than 2500 grams

Perivable gestational age: gestational age around 23-26 weeks of gestation, associated with high neonatal morbidity and mortality and high risk of neurodevelopmental delay.

Cervical dilation: any quantifiable uterine cervical opening by speculum or digital exam, if dilation progresses, it is associated with delivery of the fetus

Amniocentesis: is a surgical procedure for obtaining a sample of amniotic fluid from the amniotic sac in the uterus of a pregnant woman by inserting a hollow needle through the abdominal wall under continuous ultrasound guidance; it is used in diagnosing certain genetic defects or intrauterine infections.

Amnioreduction: consist of the removal of variable amount of amniotic fluid by amniocentesis

Cervical cerclage is a suture/tape surgically placed around the cervix as close as possible to the high of the internal os. This suture is a non-absorbable sterile material and needs to be removed later on before delivery

## 1 Introduction

This document is a protocol for a human research study.

### 1.1 Background

The incidence of preterm birth (PTB) in the United States is 12% with more than 500,000 deliveries occurring at less than 37 weeks gestation annually, however the incidence of early preterm (less than 34 weeks) remains unchanged at 3.4% being this the most vulnerable neonatal group.<sup>1</sup> Risk factors for spontaneous preterm births include a previous preterm birth, multiple pregnancies, black race, smoking, periodontal disease, low maternal body-mass index and short cervical length.<sup>2</sup>

In 2010, the twin birth rate was 33.1 twins per 1000 total births. The twin birth rate increased steadily by 76% overall from 1980 to 2009. The number of twin births has risen substantially due to the increased use of assisted reproductive technology. Twin pregnancies have 50% incidence of PTB, 10 times more at risk of low birth-weight infants (LBW) and had 5 times more risk of early neonatal death.<sup>3</sup> The increased rate of PTB in twins is associated with increased neonatal morbidity and mortality rates. Disorders related to short gestation and LBW is the second cause of infant death (17.2%).<sup>1</sup>

In singleton pregnancies with risk factors for PTB, effective medical interventions have been identified to reduce the risk of recurrent PTB. For women with prior PTB: weekly treatment with intramuscular 17-alpha hydroxyprogesterone caproate beginning at 16-20 weeks gestation until 36 weeks<sup>4</sup> and cervical length surveillance from 16 to 24 weeks and ultrasound indicated cervical cerclage for women with cervical length less than 25mm before 24 weeks of gestation.<sup>5</sup> For women with no prior PTB and incidental finding of cervical length less than 20mm before 23 weeks of gestation will benefit from vaginal progesterone<sup>6</sup> or pessary.<sup>7</sup> Similar to singleton pregnancies, short cervical length less than 25mm before 24 weeks in twins pregnancies predicts preterm birth;<sup>8,9</sup> however, treatment with 17-alpha hydroxyprogesterone caproate,<sup>10</sup> vaginal progesterone<sup>11,12</sup> or ultrasound indicated cervical cerclage<sup>13-15</sup> were not effective in reducing the rate of PTB in women with twin gestations. There are small trials, subgroup analyses, and a meta-analysis suggesting that vaginal progesterone and the Arabin cervical pessary may reduce rates of preterm birth in twins of mothers with a short cervix but this information has not been confirmed.<sup>16,17</sup>

The identification of cervical dilation during the second trimester is a rare event but represents the worst prognostic factor for PTB in both singleton and twin gestations. This finding is independent of other risk factors, especially if the amniotic membranes are exposed to the vaginal environment; this presentation is associated with a 90% rate of PTB in singletons.<sup>18-22</sup> Physical-exam indicated cerclage between 14 to 26 weeks in singleton pregnancies decreased PTB < 28 weeks by 92% and <32 weeks by 64% in prospective cohorts, it decreased neonatal morbidity and 10-fold increase in neonatal survival when compared with expectant management.<sup>19-24</sup> There are few case reports of twin pregnancies with cervical dilation where physical exam indicated cerclage outcomes were similar to those in singleton pregnancies.<sup>25-28</sup> The current management of women with twin pregnancies, dilated cervix and visible amniotic membranes is expectant management. There is no current information whether physical exam

indicated cerclage would prolong pregnancy and decrease the risk of preterm birth, especially in the very preterm birth group.

Our primary hypothesis in performing this study is that the use of a physical exam indicated cerclage in women with asymptomatic cervical dilation before 24 weeks will prolong pregnancy and will decrease the incidence of PTB less than 34 weeks gestation when compared with expectant management.

## 1.2 Clinical Data to Date

A retrospective review of 12 women with twin pregnancies who underwent a physical exam-indicated cerclage (dilated cervix on examination or membranes visible at the external cervical os on speculum examination) during the second trimester were compared with 31 singleton pregnancies undergoing the same procedure from 1997 to 2012.<sup>25</sup> Comparing twins to singletons, the median time from cerclage placement to delivery was similar (92 vs. 106 days,  $p=0.3$ ), as was the median GA at delivery (33.5 vs. 35.0 weeks,  $p=0.2$ ). The likelihood of delivery at  $>32$  weeks (75.0% vs. 71.0%,  $p>0.9$ ) and the likelihood of neonatal survival to discharge (83.3% vs. 83.9%,  $p>0.9$ ) were also similar. A case report of 4 women with twin pregnancy and cervical dilation with bulging membranes gave birth on an average of 48.5 days after cerclage placement.<sup>26</sup> A more recent publication evaluated 104 women with twin pregnancy vs. 334 singleton pregnancies with dilated cervix, median gestation at delivery was (31.9 weeks vs. 32.7 weeks) and delivery before 28 weeks (33.7% vs. 35.8%,  $P = .69$ ) respectively.<sup>28</sup> **None of these publications have had an appropriate control group: twin gestation with expectant management.** Only one small retrospective cohort study had a control group with expectant management,<sup>27</sup> 23 women were identified with twin pregnancy, cervical dilation and visible membranes between 16-24 weeks; 16 underwent physical exam indicated cerclage while 7 received expectant management (control). In the control group 50% of the women were delivered prior to 24 weeks. Interval from time at diagnosis to delivery was significantly prolonged by approximately 6.8 weeks in the cerclage group, they had significant decreased SPTB  $\leq 28$  weeks (31.2% vs. 85.7%  $p=0.02$ ) and increased neonatal survival upon discharge 71.8% vs. 42% ( $p=0.1$ ).

## 1.3 Risk/Benefits

Major risks of physical exam indicated cerclage that have been reported in previous studies involving singleton pregnancies and include intraoperative rupture of membranes between 4% and 15%, cervical laceration, bleeding, chorioamnionitis (undiagnosed at the time of cerclage or acquired posteriorly to its placement due to exposed membranes into the vaginal flora), failure to place the cerclage due to advanced cervical dilation and failure of the cerclage on prolonging pregnancy with possible pregnancy loss or delivery at a periviable gestational age around 23-26 weeks of gestation.<sup>23, 24, 29-32</sup> Other risks of cerclage are those associated with anesthesia during the surgical procedure: hypotension, allergy to medications, post spinal headache. After the cerclage placement other risks maybe present during the following weeks as preterm contractions with the cerclage in place may can cause laceration of the cervix and bleeding or preterm premature rupture of membranes in which case the cerclage needs to be removed.



Minor side effects include increased noninfectious vaginal discharge: there is a theoretical disruption the vaginal flora associated with foreign object, and minimal discomfort at the time of cerclage removal.

The potential benefits include prolongation of pregnancy, decreasing very preterm delivery (< 28 weeks), very low birth weight (<1500 grams), low birth weight (<2500 grams) and decreased neonatal morbidity (admission to the intensive care unit, respiratory distress, need of intubation, necrotizing enterocolitis, intraventricular hemorrhage), neonatal mortality and long term disease or disability associated with prematurity. This potential benefits are based on results of previous retrospective cohorts of available research in singletons and case reports in twin pregnancies. These benefits significantly outweigh the risk of having a complication related to cerclage placement.

Measurement to decreased risks associated to the cerclage: All of the investigators have received formal training on physical exam indicated cerclage placement. The training and experience of the investigators will minimize the risks associated with cerclage placement.

Our protocol specifically states that the cerclage will be removed if the patient has persistent preterm contractions associated labor, has premature preterm rupture of membranes (PPROM), presents with active cervical bleeding or if she remains asymptomatic and reaches 36 weeks of gestation.

## **2 Study Objectives**

The overall objective of this study is to assess the efficacy of the use of a physical exam indicated cerclage for prevention of PTB in a population of women with twin gestations, dilated cervix and visible membranes at the time of speculum exam between 16 0/7 to 23 6/7 weeks.

### **2.1 Primary Objective**

The primary objective of this study is to determine if physical exam indicated cerclage reduces the incidence of spontaneous PTB before 34 weeks in asymptomatic women with twin gestations, dilated cervix and visible membranes diagnosed on pelvic exam between 16 0/7 to 23 6/7 weeks of gestation.

### **2.2 Secondary Objective**

To determine if cerclage reduces the incidence of spontaneous PTB <28 weeks and <32 weeks in asymptomatic women with twin gestations and dilated cervix diagnosed on pelvic exam between 16 to 23 6/7 weeks of gestation

To determine if cervical cerclage reduces the incidence of neonatal admission to the neonatal intensive care unit, decrease length of stay in the neonatal intensive care unit, decrease neonatal disease or death associated with prematurity in asymptomatic women with twin gestations, dilated cervix and visible membranes diagnosed on pelvic exam between 16 to 23 6/7 weeks of gestation

### 3 Study Design

#### 3.1 General Design

This is a multi-center, open-label, randomized study. Women with twin gestations that have dilated cervix (1-5cm) with visible membranes during ultrasound, pelvic exam and/or speculum exam will be invited to participate in the trial.

#### 3.2 Primary Study Endpoints

Spontaneous preterm delivery at less than 34 weeks gestation

#### 3.3 Secondary Study Endpoints

Secondary effectiveness endpoints:

- Gestational age at delivery
- Interval between diagnosis and delivery
- Birth weight of each neonate
- Spontaneous preterm birth rates at less than 24, 28, 32 and 37 weeks gestation
- Spontaneous rupture of membranes before 34 weeks gestation

Secondary safety endpoints:

- Admission to the NICU and length of stay
- Neonatal death before discharge
- Composite adverse neonatal outcome (includes necrotizing enterocolitis, Intraventricular hemorrhage (grade 2 or higher), respiratory distress syndrome, retinopathy, treatment for sepsis and neonatal death)
- Chorioamnionitis (clinical or histological)
- Significant adverse maternal effects including intraoperative rupture of membranes, bleeding and cervical laceration (tear).

### 4 Subject Selection and Withdrawal

#### 4.1 Inclusion Criteria

1. Pregnant women more than 18 years of age
2. Diamniotic twin pregnancy (limits the participants to female gender)
3. Asymptomatic
4. Cervical dilation 1- 5 cm and/or visible membranes by pelvic exam or speculum exam on second trimester ultrasound between 16-23 6/7 weeks gestation

## 4.2 Exclusion Criteria

1. Singleton or higher order than twins multiple gestation
2. Cervical dilation more than 5 cm
3. Amniotic membranes prolapsed into the vagina, unable to visualize cervix
4. Fetal reduction after 14 weeks from higher order
5. Monoamniotic twins
6. Twin-twin transfusion syndrome
7. Ruptured membranes prior to randomization
8. Major fetal structural anomaly
9. Fetal chromosomal abnormality
10. Cerclage already in place for other indication
11. Active vaginal bleeding
12. Suspicion of chorioamnionitis
13. Placenta previa
14. Painful regular uterine contractions
15. Labor

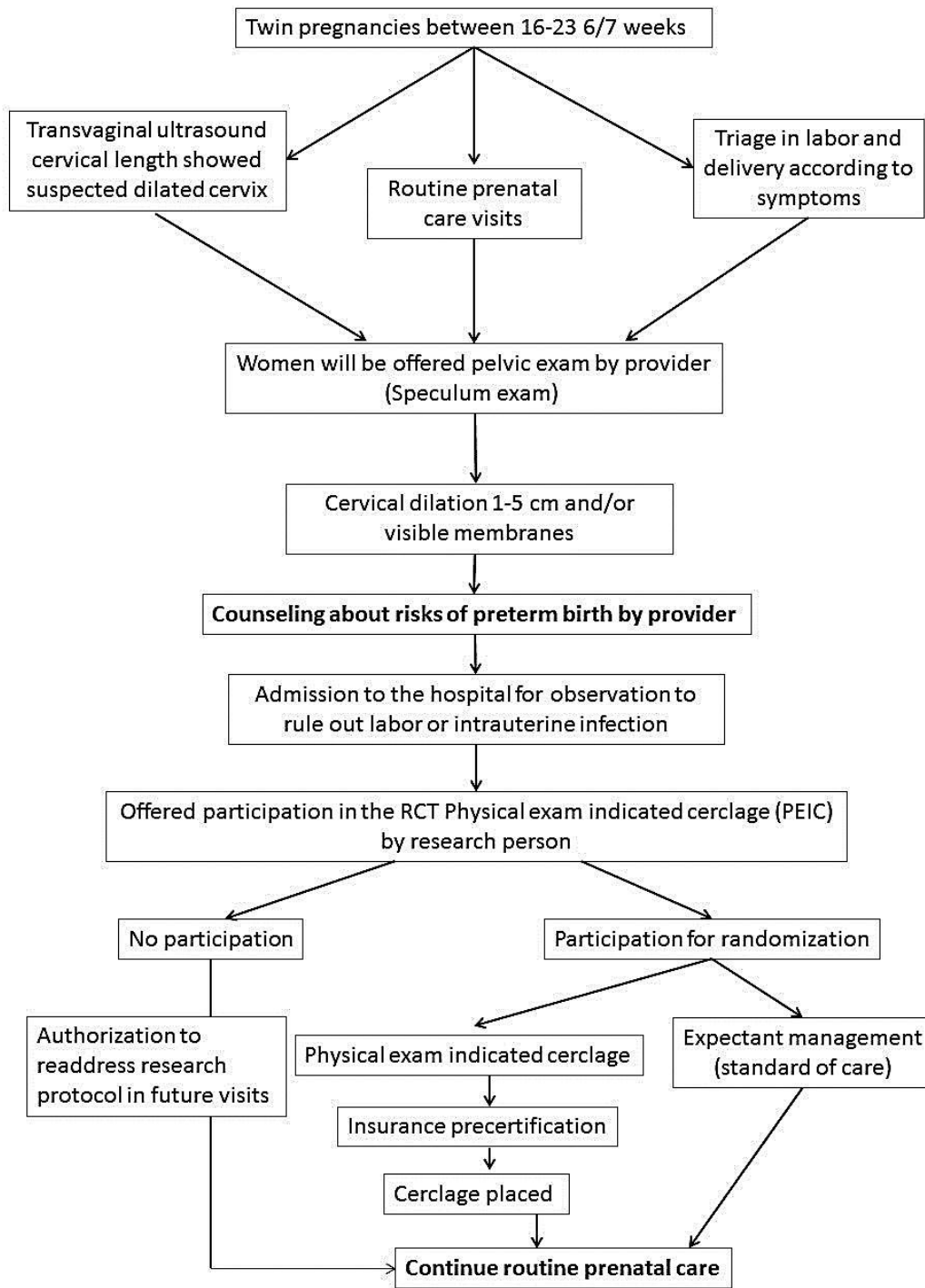
## 4.3 Subject Recruitment and Screening

### 1. Potential study subjects will be identified from 2 different sources:

- 1.1. Transvaginal ultrasound cervical length will be offered at the time of a routine second trimester fetal anatomy ultrasound exam. Patients with twin gestations between 18 and 23 6/7 weeks will be asked to give consent to have their cervical length measured using transvaginal ultrasound, prior to the routine ultrasound. This ultrasound is already performed as part of the PREVENTION OF PRETERM BIRTH WITH A PESSARY IN TWIN GESTATIONS "POPPT TRIAL" (IRB Control # 14D.216) which has been approved by IRB. We will use the recommended guidelines published by the Pregnancy Foundation ([www.pregnancyfoundation.org/CLEAR](http://www.pregnancyfoundation.org/CLEAR)), called CLEAR. Sonographers who will be performing screening TV ultrasounds at all sites will be certified through CLEAR or equivalent before the start of the study. After discussing the ultrasound findings, a woman with suspected cervical dilation at time of the ultrasound evaluation will have a pelvic exam with speculum in a private room. This exam would be standard care for a woman found to have a dilated cervix, preterm.
  - 1.2. Patients presenting to the Emergency Room or Labor and Delivery (TJUH 7th floor) between 16-23 6/7 weeks gestation, which may require a pelvic evaluation as part of their triage assessment.
2. If the patient meets inclusion criteria (dilated cervix 1-5 cm and/or visible membranes during the speculum exam), she will be admitted to labor and delivery for observation and counseling by an obstetrician regarding the risks of preterm birth as per standard of care. Standard of care at TJUH includes observation for 24 hours to rule out active labor and/or intrauterine infection (persistent uterine contractions with progression of cervical dilation).

3. If the patient remains asymptomatic with no signs of labor, intrauterine infection or preterm rupture of membranes, she will be approached by research personnel, in a private room, to review the research protocol, risks, benefits and alternatives and implications of randomization. The patient will be given ample time to have all questions addressed and consider participation.
4. **Randomization:** If the patient agrees to participate in the study, the informed consent form will be signed and a copy will be given to the patient. Subjects with dilated cervix 1-5 cm and visible membranes who are eligible and consent to participate in the study will be randomly assigned to one of two groups: Cervical cerclage or standard obstetric management. Subjects will be randomized using blocks of randomly varying size (e.g., 2, 4 and 6).
5. **Insurance precertification:** for those patients assigned to cerclage, an insurance precertification process will be requested. If the patient doesn't have insurance, a medical necessity letter will be provided, coverage will be requested and financial office will be consulted. The patient will be notified of the precertification outcome. At this time, insurance companies are routinely covering the procedure and the costs associated with it.
6. **Cervical cerclage:** After insurance approval, cerclage will be scheduled in the operating room under anesthesia. Amniocentesis prior to the cerclage to rule out chorioamnionitis, surgical technique, type of suture, medications and maternal physical activity after surgery will be at the discretion of the surgeon.
7. After randomization, subjects will continue with their usual clinical prenatal visits, and will participate in the study until delivery. The study investigator will communicate with the subject's primary obstetrician and cerclage placement will be done by the study investigator. The primary obstetrician will be responsible for all prenatal care. Subjects will be given a phone number to call if they have any questions or concerns about the cerclage or the study. A physician who is knowledgeable about the study will be available at all times.
8. **Interim Contacts:** Subjects in both groups will be contacted by the research assistants monthly either by phone or in person at the time of their prenatal visit. The research assistants will ask the subjects if they have had any complications with their pregnancy including any evaluations and/or admissions for preterm labor, preterm contractions, vaginal discharge, vaginal bleeding or discomfort. (see appendix #1 and #2 for questionnaire)
9. **Cervical cerclage removal:** cerclage will be removed during the 36th week of pregnancy if the subject remains asymptomatic, but it may be removed earlier if indicated. Cervical cerclage can be removed by her primary physician in the office. Some reasons for early removal include active vaginal bleeding, preterm labor with persistent contractions and advanced cervical dilatation despite tocolysis, severe subject discomfort or subject request. Cervical cerclage removal involves: 1) sterile speculum exam, 2) identification of the knot of the suture or tape at the anterior lip of the cervix, 3) gentle traction of the suture and cut with scissors one side of the tape and pulling the tape out of the cervix, 4) expected discomfort associated with the speculum exam, pressure when pulling the suture/tape and minimal bleeding (one tablespoon).
10. **Pregnancy Outcome:** After subjects have completed the study and delivered, information regarding labor and delivery, and the outcome of the pregnancy, will be abstracted from the subjects' medical records. Medical release form will be signed at time of enrollment to obtain information about pregnancy outcome from medical records including prenatal care visits, ultrasound reports, labor and delivery and outcome of the newborns. In case the woman transfers her care or delivers at a different institution, the medical form release will be used to collect data from outside institution.
11. **If patient declines participation** and she is stable, she will be discharged home and continue weekly outpatient prenatal care visits. If patient elects to have expectant management (standard obstetric

management) and declines participation in the study, she may choose to participate at a later time (up to 23 6/7 weeks), if she still meets inclusion criteria. A contact number of the research personnel will be provided.



## **5 Study**

### **5.1 Description**

Cervical cerclage is a surgical procedure done under anesthesia. It consist of a suture/tape surgically placed around the cervix as close as possible to the high of the internal os. The surgery is performed through the vagina. This suture is a non-absorbable sterile material and needs to be removed later during pregnancy on before delivery

### **5.2 Treatment Regimens**

Subjects will be randomized in a 1:1 fashion to either receive the physical exam indicated cerclage, or expectant management. Women will still be able to withdrawal from the study after randomization if they feel that either expectant management or cerclage have an unacceptable risk of extreme premature delivery with increased risk of severely handicap children.

#### **5.2.1 Physical exam indicated cerclage**

For those randomized to physical exam indicated cerclage placement, the surgical procedure will be scheduled in the operating room under anesthesia prior to insurance precertification.

#### **5.2.2 Expectant management**

For those randomized to expectant management, they will continue routine pregnancy care.

### **5.3 Method for Assigning Subjects to Treatment Groups**

A computer system will be used to communicate the randomization assignments to the trial staff. Subjects will be randomized centrally using blocks of randomly varying size (e.g, 2, 4 and 6).

### **5.4 Placement of Cerclage**

Physical exam indicated cerclage is placed by trained physician in the operating room under anesthesia (regional or general at the discretion of the anesthesiologist). Antibiotics prior to the procedure and tocolysis with indomethacin, amniocentesis to rule out chorioamnionitis, amnioreduction, surgical technique, election of sutures, and admission to the hospital for observation or maternal physical activity after randomization will be at the discretion of the attending physician performing the cerclage.

## **6 Study Procedures**

### **6.1 Cervical evaluation**

Potential study subjects will be identified from 2 different sources:

- 1.1. Transvaginal ultrasound cervical length will be offered at the time of a routine second trimester fetal anatomy ultrasound exam between 16-23 6/7 weeks gestation as part of the PoPPTs study (IRB approved), verbal consent will be requested prior to transvaginal ultrasound.

- 1.2. Patients presenting at emergency room in labor and delivery (triage, TJU 7<sup>th</sup> floor) between 16-23 6/7 weeks gestation, which may require a pelvic evaluation as part of their triage assessment (verbal consent will be requested as per standard of care)

## **6.2 Randomization**

Patients with dilated cervix and visible membranes who are eligible and consent to participate in the study will be randomly assigned to one of two groups: Physical exam indicated cerclage or standard expectant obstetric management. Subjects will be randomized using random block sizes of four. Patients allocated to the physical exam indicated cerclage group will have the cerclage surgically placed.

## **6.3 Interim Contacts**

Patients in both groups will be contacted by the research assistants monthly either by phone or in person at the time of their prenatal visit. The research assistants will ask the patients if they have had any complications with their pregnancy including any evaluations and/or admissions for preterm labor, vaginal bleeding, leaking of amniotic fluid, vaginal discharge and/or discomfort or if they received medications like antenatal steroids for fetal lung maturity, tocolysis or magnesium sulfate infusion. Consents for release of medical information will be signed at the time of randomization to gather medical information pertinent to the study in case of admissions to other institutions.

Patients will be instructed to report any adverse symptoms including pain, vaginal bleeding, contractions, decreased fetal movements and leakage of fluid immediately. They will be given a phone number to call if they have any questions or concerns about the study. A physician who is knowledgeable about the study will be available at all times. The study investigator will communicate with the patient's primary obstetrician; physical exam indicated cerclage placement will be done by one of the study investigators, but removal at any time can be done by the primary obstetrician. The primary obstetrician will be responsible for all prenatal care and delivery.

## **6.4 Cerclage Removal**

1. The cerclage will be removed by the primary obstetrician during the 36th week of gestation. Removal of cerclage can be performed in the office or triage room, there is no need of anesthesia or admission to the hospital. Some reasons for early removal may include: active vaginal bleeding, preterm labor with persistent contractions despite tocolysis, cervical dilatation, prolapsed amniotic membranes through the cerclage, severe subject discomfort or subject request. Cervical cerclage removal involves: 1) sterile speculum exam, 2) identification of the knot of the suture or tape at the anterior lip of the cervix, 3) gentle traction of the suture and cut with scissors one side of the tape and pulling the tape out of the cervix, 4) expected discomfort associated with the speculum exam, pressure when pulling the suture/tape and minimal bleeding (one tablespoon).

## **6.5 Pregnancy Outcome**

After subjects have delivered, information regarding outcome of the pregnancy and neonatal outcome until mother and neonate are discharge home. The information will be abstracted from the subjects'

medical records. A release of medical records consent will be signed at the time of randomization, in case the patient delivers at an outside institution.

## 7 Statistical Plan

1. This is a multi-center, open-label, randomized study
2. Subjects will be randomized in a 1:1 fashion to either receive the cervical cerclage, or standard obstetric management
3. Method for assigning subjects to treatment groups: A computer-based system will be used for the randomization assignments. Subjects will be randomized using blocks of randomly varying size (e.g., 2, 4 and 6).

### 7.1 Sample Size Determination

Calculation of sample size was based on a reduction in the incidence of spontaneous delivery before 34 weeks from 80% in the expectant management group to 40% in the cerclage group, with a power of 80%. To detect this difference at a significance level of 5%, we will need to enroll a total of 46 subjects with 23 subjects in each arm, plus 10% for loss of follow up. Total 52 subjects with 26 subjects in each arm

### 7.2 Statistical Methods

The primary outcome is spontaneous preterm birth before 34 weeks of gestation. Secondary outcomes include gestational age at delivery, interval between diagnosis and delivery, birth weight, spontaneous preterm birth rates at less than 24, 28, 32 and 37 weeks gestation, clinical chorioamnionitis and spontaneous rupture of membranes at less than 34 weeks gestation. Secondary safety outcomes include admission to NICU, neonatal death, length of stay in the NICU until discharge home, composite adverse neonatal outcome that includes necrotizing enterocolitis, intraventricular hemorrhage (grade 2 or higher), respiratory distress syndrome, retinopathy of prematurity and treatment for sepsis), and significant adverse maternal effects will include: intraoperative rupture of membranes, chorioamnionitis, postpartum hemorrhage (estimated blood loss and requirement of blood transfusion, cervical tear and uterine rupture).

Statistical analysis will be based on the intention-to-treat principle.

Comparisons between the two groups will be made with the Mann-Whitney U test. Univariate comparisons of dichotomous data will be performed with Fishers exact test. The p values for all hypotheses will be two sided, and p values of less than 0.05 will be considered to be significant. The risk of spontaneous preterm birth before 34 weeks will be quantified by use of the relative ratio and 95% CI. Multivariate analysis will be performed using logistic regression. The risk of spontaneous preterm birth from randomization until 34 weeks will be assessed with Kaplan-Meier analysis, in which gestational age



is the timescale, spontaneous delivery is the event, and elective deliveries are censored. SPSS software package (version 16.0) will be used for all statistical analyses.

## **8 Safety and Adverse Events**

### **8.1. Policies to decrease adverse events**

1. Transvaginal cervical length: Sonographers who will be performing screening transvaginal ultrasounds at all sites will be certified through CLEAR or equivalent before the start of the study.
2. Pelvic exam: Pelvic exam will be performed by trained obstetrician & gynecologist or nurse practitioner.
3. Cervical cerclage placements: Surgical procedure will be performed by trained obstetrician & gynecologist in this surgical technique
4. Anesthesia: will be provided by trained anesthesiologist in the operating room

### **8.2 Definitions**

#### **Unanticipated Problems Involving Risk to Subjects or Others**

Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc)
- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

#### **Unanticipated Adverse Surgical procedure Effect**

An Unanticipated Surgical procedure Effect is any serious adverse effect on health or safety, or any life-threatening problem or death caused by, or associated with a surgical procedure, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a that relates to the rights, safety, or welfare of subjects.

#### **Serious injury**

Any injury or illness that is any one of the following:

- Life-threatening

- Results in permanent impairment of a body function or permanent damage to body structure
- Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure

### **Adverse Event**

An adverse event (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

1. Results in study withdrawal
2. Is associated with a serious adverse effect related to the surgical procedure
3. Is associated with clinical signs or symptoms
4. Leads to additional treatment or to further diagnostic tests
5. Is considered by the investigator to be of clinical significance

### **What will be monitored:**

**Stopping rules:** Any unanticipated effects and all adverse effects resulting in research subject death or injury will be reported to the PI immediately, no later than 10 days after the event and will include:

1. Maternal sepsis with admission to ICU attributable to the cerclage placement
2. Maternal death attributable to the cerclage placement
3. Maternal bleeding requiring blood transfusion attributable to cerclage placement
4. Fetal and/or neonatal death or injury attributable to the cerclage placement

Frequency of monitoring reports: after approximately 50% of the subjects have delivered

### **8.3 Recording of Adverse Effects**

At each contact with the subject, the investigator must seek information on adverse effects by specific questioning and, as appropriate, by examination. Information on all adverse surgical procedure effects should be recorded immediately in the source document, and also in the appropriate adverse effect module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should be recorded in the source document, though should be grouped under one diagnosis.

All adverse effects occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse effects that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse effects that occur after the study period should be recorded and reported promptly (see section 8.3 below).

The minimum initial information to be captured in the subject's source document concerning the adverse effect includes:

- Study identifier
- Subject number
- A description of the event
- Date of onset
- Investigator assessment of the association between the event and study treatment
- Current status
- Whether study treatment was discontinued
- Whether the event is serious and reason for classification as serious

## **8.4 Reporting of Adverse Effects and Unanticipated Problems**

### **8.4.1 Investigator reporting: Notifying the principal investigator**

Principal investigator contact information for reporting purposes

Report adverse effects by phone and facsimile to:

Amanda Roman-Camargo, MD

Email: amanda.roman@jefferson.edu

Phone: 215-955-9200

Fax 215-955-5041

### **Adverse Effects**

Any adverse effect that results in serious injury or death, and any type of unanticipated adverse effect, regardless of seriousness or severity, must be reported to the principal investigator by telephone within 24 hours of the event.

Within the following 48 hours, the principal investigator shall provide further information, as applicable, on the unanticipated adverse event or the unanticipated problem in the form of a written narrative. This should include a copy of the completed Unanticipated Problem form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing unanticipated adverse effects shall be provided promptly to the principal investigator.

### **Deviations from the study protocol**

Deviations from the protocol must receive both principal investigator and the investigator's IRB approval before they are initiated. Any protocol deviations initiated without principal investigator and the investigator's IRB approval that may affect the scientific soundness of the study, or affect the rights,

safety, or welfare of study subjects, must be reported to the Principal investigator and to the investigator's IRB as soon as a possible, but no later than 5 working days of the protocol deviation.

#### **Withdrawal of IRB approval**

An investigator shall report to the principal investigator a withdrawal of approval by the investigator's reviewing IRB as soon as a possible, but no later than 5 working days of the IRB notification of withdrawal of approval.

#### **8.4.2 Investigator reporting: Notifying the IRB**

##### **Adverse Effects**

All unanticipated effects and all adverse effects resulting in research subject death or injury reported by the investigator to the study Principal investigator must also be reported to the investigator's local IRB in accordance with their reporting requirements, though no later than 10 working days.

##### **Protocol Deviations**

Any protocol deviations initiated without principal investigator and/or the investigator's IRB approval that may affect the scientific soundness of the study, or affect the rights, safety, or welfare of study subjects, must be reported to the Principal investigator and to the investigator's IRB as soon as a possible, but no later than 5 working days of the protocol deviation.

Any adverse event that occurs any time during or after the research study, which in the opinion of the principal investigator is:

- Unexpected (An event is "unexpected" when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document

AND

- Related to the research procedures (An event is "related to the research procedures" if in the opinion of the principal investigator, the event was more likely than not to be caused by the research procedures.)

The above is required regardless of whether the event is serious or non-serious, on-site or off-site

##### **Adverse Effects**

All unanticipated effects and all adverse effects resulting in research subject death or injury must be reported to the investigator's local IRB in accordance with their reporting requirements, though no later than 10 working days.

## **Protocol Deviations**

Any protocol deviations initiated without principal investigator and/or IRB approval that may affect the scientific soundness of the study, or affect the rights, safety, or welfare of study subjects, must be reported to the investigator's IRB as soon as a possible, but no later than 5 working days of the protocol deviation.

## **Reporting Process**

Report unanticipated problems as defined above to the IRB office as a written report of the event (including a description of the event with information regarding its fulfillment of the above criteria, follow-up/resolution and need for revision to consent form and/or other study documentation).

Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's study file.

## **Other Reportable events:**

For clinical trials, the following events are also reportable to the IRB:

- Any adverse event that would cause the principal investigator to modify the protocol or informed consent form, or would prompt other action by the IRB to assure protection of human subjects.
- Information that indicates a change to the risks or potential benefits of the research, in terms of severity or frequency. For example:
  - An interim analysis indicates that participants have a lower rate of response to treatment than initially expected.
  - Safety monitoring indicates that a particular side effect is more severe, or more frequent than initially expected.
  - A paper is published from another study that shows that an arm of your research study is of no therapeutic value.
- Breach of confidentiality
- Change to the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research participant.
- Incarceration of a participant when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study.
- Complaint of a participant when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
- Protocol violation (meaning an accidental or unintentional deviation from the IRB approved protocol) that in the opinion of the investigator placed one or more participants at increased risk, or affects the rights or welfare of subjects.

## **Unanticipated Adverse Effects**

### **Evaluation**

The principal investigator shall immediately evaluate each Unanticipated Adverse Effect. Such evaluations shall be reported to the IRB office, and participating investigators, within 10 working days after the principal investigator first receives notice of the effect.

### **Unreasonable risk to subjects**

After evaluating an Unanticipated Adverse Effect, if the principal investigator determines the effect presents an unreasonable risk to subjects, the principal investigator shall terminate the study or parts of the study presenting that risk as soon as possible. Study termination shall occur no later than 5 working days after the principal investigator makes this determination and not later than 15 working days after the principal investigator first received notice of the effect.

### **Withdrawal of IRB approval**

The Principal investigator shall notify the IRB office and participating investigators of any withdrawal of approval of the study by a reviewing IRB within 5 working days after receipt of the withdrawal of approval.

## **8.5 Medical Monitoring**

It is the responsibility of the principal Investigator to oversee the safety of the study. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see section 9 Auditing, Monitoring and Inspecting). Medical monitoring will include a regular assessment of the number and type of adverse events.

### **8.5.1 Data and Safety Monitoring Board**

An independent Data and Safety Monitoring Board (DSMB) will review data relevant to safety (not efficacy) after approximately 50% of the subjects have delivered. The DSMB will provide a recommendation as to whether the study should continue without modification of the protocol or informed consent. All unanticipated problems involving risks to participants or others will be reported by Dr. Amanda Roman-Camargo to the head of the DSMB for this study

## **9 Data Handling and Record Keeping**

### **9.1 Confidentiality**

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

## **9.2 Source Documents**

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

## **9.3 Records Retention**

It is the principal investigator's responsibility to retain study essential documents for at least 2 years after the last approval of a marketing application in their country and until there are no pending or contemplated marketing applications in their country or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by an agreement with the sponsor. In such an instance, it is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

## **10. Study Monitoring, Auditing, and Inspecting**

### **10.1 Study Monitoring Plan**

Research data will be reviewed by the study coordinator for correctness. Research charts will undergo periodic random audits to ensure the integrity of the data. The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or

quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

## **10.2 Auditing and Inspecting**

The investigator will permit study-related monitoring, audits, and inspections by the EC/IRB, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

## **11. Ethical Considerations**

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study. The investigator should provide a list of EC/IRB members and their affiliate to the sponsor.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the EC/IRB for the study. The formal consent of a subject, using the EC/IRB-approved consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

## **12. Conflict of Interest**

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study.



### 13. Publication Plan

Neither the complete nor any part of the results of the study carried out under this protocol will be published or passed on to any third party without the consent of the principal investigator. Any investigator involved with this study is obligated to provide the principal investigator with complete test results and all data derived from the study.

### 14. REFERENCES

1. Hamilton BE, Hoyert DL, Martin JA, Strobino DM, Guyer B. Annual summary of vital statistics: 2010-2011. *Pediatrics* 2013; **131**(3): 548-58.
2. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. *Lancet* 2008; **371**(9606): 75-84.
3. Martin JA, Hamilton BE, Sutton PD, Ventura SJ, Mathews TJ, Osterman MJ. Births: final data for 2008. *National vital statistics reports : from the Centers for Disease Control and Prevention, National Center for Health Statistics, National Vital Statistics System* 2010; **59**(1): 1, 3-71.
4. Meis PJ, Klebanoff M, Thom E, et al. Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. *N Engl J Med* 2003; **348**(24): 2379-85.
5. Owen J, Hankins G, Iams JD, et al. Multicenter randomized trial of cerclage for preterm birth prevention in high-risk women with shortened midtrimester cervical length. *Am J Obstet Gynecol* 2009; **201**(4): 375 e1-8.
6. Hassan SS, Romero R, Vidyadhari D, et al. Vaginal progesterone reduces the rate of preterm birth in women with a sonographic short cervix: a multicenter, randomized, double-blind, placebo-controlled trial. *Ultrasound Obstet Gynecol* 2011; **38**(1): 18-31.
7. Goya M, Pratcorona L, Merced C, et al. Cervical pessary in pregnant women with a short cervix (PECEP): an open-label randomised controlled trial. *Lancet* 2012; **379**(9828): 1800-6.
8. Makrydimas G, Sotiriadis A. Prediction of preterm birth in twins. *Best practice & research Clinical obstetrics & gynaecology* 2014; **28**(2): 265-72.
9. Conde-Agudelo A, Romero R, Hassan SS, Yeo L. Transvaginal sonographic cervical length for the prediction of spontaneous preterm birth in twin pregnancies: a systematic review and metaanalysis. *Am J Obstet Gynecol* 2010; **203**(2): 128 e1-12.
10. Rouse DJ, Caritis SN, Peaceman AM, et al. A trial of 17 alpha-hydroxyprogesterone caproate to prevent prematurity in twins. *N Engl J Med* 2007; **357**(5): 454-61.
11. Norman JE, Mackenzie F, Owen P, et al. Progesterone for the prevention of preterm birth in twin pregnancy (STOPPIT): a randomised, double-blind, placebo-controlled study and meta-analysis. *Lancet* 2009; **373**(9680): 2034-40.
12. Rode L, Klein K, Nicolaides KH, Krampfl-Bettelheim E, Tabor A, Group P. Prevention of preterm delivery in twin gestations (PREDICT): a multicenter, randomized, placebo-controlled trial on the effect of vaginal micronized progesterone. *Ultrasound Obstet Gynecol* 2011; **38**(3): 272-80.
13. Roman AS, Rebarber A, Pereira L, Sfakianaki AK, Mulholland J, Berghella V. The efficacy of sonographically indicated cerclage in multiple gestations. *J Ultrasound Med* 2005; **24**(6): 763-8; quiz 70-1.
14. Roman A, Berghella V, Calluzzo I, Fleischer A, Rochelson B. 94: Ultrasound indicated cerclage in twin pregnancy. *American Journal of Obstetrics and Gynecology* 2014; **210**(1, Supplement): S61.

15. Berghella V, Odibo AO, To MS, Rust OA, Althuisius SM. Cerclage for short cervix on ultrasonography: meta-analysis of trials using individual patient-level data. *Obstet Gynecol* 2005; **106**(1): 181-9.
16. Liem S, Schuit E, Hegeman M, et al. Cervical pessaries for prevention of preterm birth in women with a multiple pregnancy (ProTWIN): a multicentre, open-label randomised controlled trial. *Lancet* 2013; **382**(9901): 1341-9.
17. Zork N, Biggio J, Tita A, Rouse D, Gyamfi-Bannerman C. Decreasing prematurity in twin gestations: predicaments and possibilities. *Obstet Gynecol* 2013; **122**(2 Pt 1): 375-9.
18. Harrison V, Fawcus S, Jordaan E. Magnesium supplementation and perinatal hypoxia: outcome of a parallel group randomised trial in pregnancy. *BJOG* 2007; **114**(8): 994-1002.
19. Novy MJ, Gupta A, Wothe DD, Gupta S, Kennedy KA, Gravett MG. Cervical cerclage in the second trimester of pregnancy: a historical cohort study. *Am J Obstet Gynecol* 2001; **184**(7): 1447-54; discussion 54-6.
20. Olatunbosun OA, al-Nuaim L, Turnell RW. Emergency cerclage compared with bed rest for advanced cervical dilatation in pregnancy. *International surgery* 1995; **80**(2): 170-4.
21. Daskalakis G, Papantoniou N, Mesogitis S, Antsaklis A. Management of cervical insufficiency and bulging fetal membranes. *Obstet Gynecol* 2006; **107**(2 Pt 1): 221-6.
22. Althuisius SM, Dekker GA, Hummel P, van Geijn HP. Cervical incompetence prevention randomized cerclage t. Cervical incompetence prevention randomized cerclage trial: emergency cerclage with bed rest versus bed rest alone. *Am J Obstet Gynecol* 2003; **189**(4): 907-10.
23. Pereira L, Cotter A, Gomez R, et al. Expectant management compared with physical examination-indicated cerclage (EM-PEC) in selected women with a dilated cervix at 14(0/7)-25(6/7) weeks: results from the EM-PEC international cohort study. *Am J Obstet Gynecol* 2007; **197**(5): 483 e1-8.
24. Ventolini G, Genrich TJ, Roth J, Neiger R. Pregnancy outcome after placement of 'rescue' Shirodkar cerclage. *J Perinatol* 2009; **29**(4): 276-9.
25. Rebarber A, Bender S, Silverstein M, Saltzman DH, Klauser CK, Fox NS. Outcomes of emergency or physical examination-indicated cerclage in twin pregnancies compared to singleton pregnancies. *Eur J Obstet Gynecol Reprod Biol* 2013.
26. Levin I, Salzer L, Maslovitz S, et al. Outcomes of mid-trimester emergency cerclage in twin pregnancies. *Fetal diagnosis and therapy* 2012; **32**(4): 246-50.
27. Roman A, Calluzzo I, Fleischer A, Rochelson B. 804: Physical exam indicated cerclage in twin pregnancy. *American Journal of Obstetrics and Gynecology* 2014; **210**(1, Supplement): S391-S2.
28. Miller ES, Rajan PV, Grobman WA. Outcomes after physical exam-indicated cerclage in twin gestations. *American Journal of Obstetrics and Gynecology*; (0).
29. Higuchi M, Hirano H, Maki M. Emergency cervical cerclage using a metreurynter in patients with bulging membranes. *Acta obstetrica et gynecologica Scandinavica* 1992; **71**(1): 34-8.
30. Wong GP, Farquharson DF, Dansereau J. Emergency cervical cerclage: a retrospective review of 51 cases. *Am J Perinatol* 1993; **10**(5): 341-7.
31. Barth WH, Jr., Yeomans ER, Hankins GD. Emergent cerclage. *Surgery, gynecology & obstetrics* 1990; **170**(4): 323-6.
32. Airoidi J, Pereira L, Cotter A, et al. Amniocentesis prior to physical exam-indicated cerclage in women with midtrimester cervical dilation: results from the expectant management compared to Physical Exam-indicated Cerclage international cohort study. *Am J Perinatol* 2009; **26**(1): 63-8.

### Appendix #1: Initial Follow up

Record ID \_\_\_\_\_

Date of contact: \_\_\_\_\_

Method of contact:

- ☐ Email
- ☐ Phone call
- ☐ RedCap Survey
- ☐ Text Message
- ☐ Other: \_\_\_\_\_

Name of person contacting participant: \_\_\_\_\_

Have you experienced any complications with your pregnancy? [ ] Yes [ ] No

If yes, please describe: \_\_\_\_\_

Have you been seen for a problem outside of a regularly scheduled prenatal visit? [ ] Yes [ ] No

Was this visit for: \_\_\_\_\_

Have you been seen on labor and delivery, the labor and delivery triage unit, or the emergency room?  
[ ] Yes [ ] No; if yes please describe: \_\_\_\_\_

Have you experienced vaginal bleeding? [ ] Yes [ ] No

Have you experienced vaginal discharge? [ ] Yes [ ] No

Have you experienced contractions? [ ] Yes [ ] No

Have you experienced leaking of fluid? [ ] Yes [ ] No

Were you admitted to the hospital? [ ] Yes [ ] No

What dates were you admitted? \_\_\_\_\_

For how many days? \_\_\_\_\_

Why were you admitted to the hospital? \_\_\_\_\_

Were you treated with steroid shots for fetal lung maturity? [ ] Yes [ ] No

Were you treated with medication to stop preterm contractions or labor? [ ] Yes [ ] No

Was the cerclage removed? Why \_\_\_\_\_

Have you had sexual intercourse since you were enrolled in this study? [ ] Yes [ ] No

Additional notes/comments: \_\_\_\_\_

**Appendix #2 Monthly Follow-Up**

Since our last contact with you, have you experienced any complications with your pregnancy?

☐ Yes ☐ No. If yes, please describe: \_\_\_\_\_

Since our last contact with you, have you been seen for a problem outside of a regularly scheduled prenatal visit? ☐ Yes ☐ No

Since our last contact with you, have you been seen on labor and delivery, the labor and delivery triage unit, or the emergency room? ☐ Yes ☐ No . If yes please describe: \_\_\_\_\_

Since our last contact with you, have you experienced vaginal bleeding? ☐ Yes ☐ No

Since our last contact with you, have you experienced vaginal discharge? ☐ Yes ☐ No

Since our last contact with you, have you experienced contractions? ☐ Yes ☐ No

Since our last contact with you, have you experienced leaking of fluid? ☐ Yes ☐ No

Were you admitted to the hospital? ☐ Yes ☐ No

Why were you admitted to the hospital? \_\_\_\_\_

What dates were you admitted? \_\_\_\_\_

If yes, for how many days? \_\_\_\_\_

Were you treated with steroid shots for fetal lung maturity? \_\_\_\_\_

Were you treated with medication to stop preterm contractions or labor? ☐ Yes ☐ No

Was the cerclage removed? Why \_\_\_\_\_

Since our last contact with you, have you had sexual intercourse? ☐ Yes ☐ No

Additional notes/comments: \_\_\_\_\_