Jefferson.

Office of Human Research
Division of Human Subjects Protection
Institutional Review Board

Jefferson Alumni Hall
1020 Locust Street, Suite M-34
Philadelphia, PA 19107
T 215-503-8966
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May 12, 2015

Amanda Roman-Camargo, M.D.
Obstetrics and Gynecology/Maternal Fetal Medicine

Dear Dr. Roman-Camargo:

The **Institutional Review Board (IRB)** has reviewed the involvement of humans as research subjects in your study entitled:

"Randomized Control Trial: Physical Exam Indicated Cerclage in Twin Gestations" (Departmental) Control #14D.238

In accordance with Federal-Wide Assurance #00002109 to the U.S. Department of Health and Human Services, this study was **approved** for one year by Board #2405 on **05/08/15** for up to 4 subjects/year at Thomas Jefferson University following:

NEW/FULL (X) **EXPEDITED/NEW ( )** **Board Review**

* Dr. Stuart Weiner (Co-Investigator) was not present for deliberations and vote on this protocol.

THIS APPROVAL REQUIRES THAT INFORMED CONSENT BE OBTAINED FROM ALL PERSONS PRIOR TO THEIR INVOLVEMENT IN THE STUDY BY THE USE OF THE LATEST APPROVED PATIENT CONSENT FORM.

EACH SUBJECT MUST RECEIVE A COPY OF THEIR SIGNED CONSENT FORM.

This approval expires on **05/07/16**, one year from the original approval date, unless suspended or terminated earlier by action of the IRB. At the end of the current approval, a report (Form OHR-9) must be submitted to the IRB summarizing progress on the study during that period.

If you wish to continue the study beyond the expiration of this approval, an application for continuation of your study must be submitted to the IRB at least one month prior to the expiration date.

Any injury and/or unanticipated problem involving risks to the human research subjects not included in the written consent form must be reported promptly to the IRB using Form OHR-10 OFF-SITE or OHR-10 ON-SITE. This report should describe the event, evaluate its probable relationship to the experimental treatment received by the subject, and summarize the resulting outcome of the event.

Any proposed change in the protocol or in the written consent form must be submitted with Form OHR-12 to the IRB for review and approval before the proposed change can be implemented.

This approval verifies that the IRB operates in accordance with applicable federal, local and institutional regulations that govern IRB operations.

Sincerely yours,

Kyle Conner, M.A., CIP
Associate Director
Division of Human Subjects Protection

KC/vcd

Association for the Accreditation of Human Research Protection Programs, Inc. — Full Accreditation

Thomas Jefferson University
Informed Consent Document for Human Subjects Research – OHR-8 (v.12/11/13)

Department: OB/GYN

Principal Investigator: Amanda Roman, MD **Telephone**: 215-955-9200

Co-Investigator(s): Vincenzo Berghella, MD; Jason Baxter, MD, MSCP; Meiling Hua, MD; Anju Suhag, MD; Alexis Gimovsky, MD; Corina Schoen, MD; Navathe, MD; Adeeb Khalifeh, MD.
Telephone: 215-955-9200

Medical Study Title: A Randomized Control Trial: Physical Exam Indicated Cerclage In Twin Gestations

Lay Study Title: A research study to examine the effectiveness of using cervical stitch to prevent premature delivery in women with twin pregnancy and cervical dilation prior 24 weeks of gestation

What Is Informed Consent

You are being asked to take part in a medical research study. As required by federal regulations, this research study has been reviewed and approved by an Institutional Review Board (IRB), a University committee that reviews, approves and monitors research involving humans. Before a knowledgeable decision about whether to participate in a research study can be made, the possible risks and benefits related to the study should be understood. This process of learning and thinking about a study before deciding to participate is known as *informed consent* and includes:

- Receiving detailed information about this research study;
- Being asked to read, sign and date this consent form once the nature of the study is understood and a decision is made to participate. If there is anything about the study you don't understand or if there are questions, you should ask for explanations before signing this form;
- Being given a copy of the signed and dated consent form to keep.

A patient who joins a research study has a relationship with the study doctor that is different than the relationship with a treating or personal doctor. A treating doctor treats a specific health condition with the goal of improving that condition. A study doctor treats all subjects according to a research plan to obtain information about the experimental drug, device or procedure being studied and with the understanding that there may or may not be benefit from being in the study. The study doctor and study staff can provide more information about research as opposed to treatment.

What is the purpose of this study?

Women with twin pregnancy who have a dilated (open) cervix detected on physical exam before 24 weeks are at increased risk for delivering their babies preterm (before 37 weeks gestation). Prematurity is associated with many complications for the babies including respiratory (breathing) problems, bleeding inside of the brain (a form of stroke), increased risk of infection, kidney, temperature and feeding problems. These complications occur more often at earlier gestational ages. The cervical cerclage is a suture (a wide flat string) placed around the cervix (the opening to the womb), that may help to prevent preterm birth. Cervical cerclages have been used for many years to prevent preterm birth in women carrying one baby, and found to have a dilated cervix. While some case reports have found that cervical cerclage may prevent preterm birth in twin pregnancies, the use of cervical cerclage to prevent preterm birth in this study is experimental.

The purpose of this research is to determine whether the use of cervical cerclage in women with twin pregnancy and cervical dilation before 24 weeks will prevent, or reduce the occurrence of preterm birth.

How many individuals will participate in the study and how long will the study last?
We hope to enroll 52 patients nationally or internationally and 12 patients here at Jefferson. Each participant will be in the study from the time of enrollment to the end of your pregnancy and the discharge of the infants from the hospital after delivery.

What will happen during the study?

Women with twin pregnancy who are found to have cervical dilation (an open cervix) at pelvic exam before 24 weeks will be invited to participate in the study.

Before any research activities can happen, you will be given time to read this consent form and discuss the research protocol with your family or your significant other. The information in the form will be reviewed with you, and all of your questions will be answered. One of the physicians involved in this research project will explain to you all the risks, benefits and alternatives to the surgical procedures involved in the cerclage placement before you decide whether you would like to participate in this study. If you agree to participate in the study, you will be asked to sign this form.

You will have a vaginal exam done so the research clinician can examine your cervix.

You will then be randomly assigned (flipping a coin) to one of two management strategies for your dilated cervix:

Arm 1: You will have a surgical procedure under anesthesia called cervical cerclage at the Thomas Jefferson Hospital main operating room; this involves placing a suture or tape around your cervix (opening to the womb) to close it again. The procedure will be performed by an Ob/Gyn doctor with special training in this kind of procedure. The doctor placing the cervical cerclage must be a study investigator; this cannot be placed by your regular Ob/Gyn. If you agree with the procedure, a precertification request will be sent to your insurance to assure coverage of your surgery. Your surgery will be scheduled as soon as possible after insurance approval, usually for the same day or the following day. You will receive antibiotics during the surgery and pain medication after the procedure. You maybe kept under observation in the hospital for up to 24 hours and be discharged when you are considered to be safe to go home.

After the cervical cerclage has been placed, you will receive routine prenatal care from your Ob care provider. The study coordinator will notify your Ob care provider that you are participating in the study and that you have a cervical cerclage placed. The study coordinator will contact you monthly to ask how your pregnancy is progressing. Your care provider will remove the cerclage during your 36th week of pregnancy (approximately 4 weeks before your due date), or earlier if needed. The cerclage can removed in the office during a speculum exam, you will not be required to return to the operating room for removal of the cerclage. The provider removing the cerclage does not have to be a study investigator.

Arm 2: You will receive routine prenatal care. No cerclage will be placed. The study coordinator will notify your Ob care provider about the findings during your physical exam and that you are participating in the study and that you did not receive a cerclage. The study coordinator will contact you monthly to ask how your pregnancy is progressing.

You have a 50% chance of being assigned to Arm 1 and 50% chance of being assigned to Arm 2.

After randomization to either Arm 1 or 2, you will continue routine prenatal care that may include admissions to the hospital for preterm contractions or labor, tocolysis, antenatal steroids to improve fetal lung maturity, magnesium sulfate to protect fetal brain, antibiotics and fetal monitoring as needed per standard of care.

After you are assigned to your study group, all of your care will be managed by the regular clinical team, not the research team. While Dr. Roman-Camargo is the director of the study, she will not be your treating physician. Clinical questions about treatment should be addressed to your clinical team.

You will be ask to sign a release of medical information in case you delivered at a different institution than Thomas Jefferson University Hospital or if your babies are transferred to a different institution prior to being discharged home.

Soon after your babies have been delivered, you will be asked to answer some questions about your pregnancy and your baby's health. The research team will also review your medical records for information about the outcome of your pregnancy or will use the medical release form to obtain records from a different institution than Thomas Jefferson University Hospital.

What are the side effects and other risks or discomforts involved?

- Minimal discomforts are expected during the pelvic exam (like when you have your pap smear done) and possible anxiety caused by the evaluation of your cervix.
- The likelihood of cerclage placement's side effects are based on previous use in singleton pregnancies.
    - Additional risks are related to the surgical procedure and risks of anesthesia (usually regional anesthesia: spinal or epidural).
    - Breaking the bag of water (rupture of amniotic membranes) during surgery that could mean the possible loss of your pregnancy, cervical tearing and scaring, bleeding (usually around 2 tablespoons), intrauterine infection, inability of cerclage placement due to advanced cervical opening, preterm labor and preterm delivery.
    - Although many women experience vaginal discharge during pregnancy, you are very likely to experience vaginal discharge if you have a cerclage placed. It is possible that the cerclage may not prevent preterm birth or prolong pregnancy more than routine care (Arm 2).
    - In case of contractions you may experience vaginal bleeding secondary to cervical tearing, if you have the cerclage in place. You should call your obstetrician in case of any vaginal bleeding
    - All attempts will be made to rule out intrauterine infection prior to presenting to the study. However, intrauterine infection may be present, but unknown at the time of the cerclage placement, or it may develop afterword.
    - The present research protocol may involve risks that are currently unforeseeable.

Things you should know about side effects:

- Who will or will not have side effects is not predictable
- Some side effects are mild while others may be severe
- There may be treatments available that could reduce the severity of side effects
- The study doctor/research staff will discuss the risks listed below in greater detail with you

Tell the study doctor or research team as soon as possible if any of the side effects, risks or discomforts listed below occur or if you think a side effect that is not listed may be happening.

If your condition worsens, if side effects become very severe, or if it turns out that being in this study is not in your best interest, you will be taken out of the study.

If questions come up about side effects, ask the study doctor or staff at any time during or after the study.

The likelihood of side effects of cerclage placement is based on previous experience in singleton pregnancies.

- Common, some may be serious, could happen in 20% or more of subjects:
    - Vaginal discharge
    - Spontaneous rupture of membranes (water breaking)

- Possible side effects, some may be serious
    - Accidental rupture of membranes during cerclage placement (5-20%)-A change in the type of bacteria that naturally live in the vagina
    - Erosion or abrasion of vaginal or cervical tissue
    - Damage to the cervix (tearing, scarring)
    - Contractions
    - Vaginal bleeding

Are there benefits from being in this study?

In singleton pregnancies with dilated cervix, some studies have shown that cerclage may prevent preterm birth or prolonged pregnancy and decrease newborn complications. Most women with twin pregnancies and dilated cervix will deliver before 28 weeks. If you have a cerclage placed, it is possible that the cerclage may prolong pregnancy and decrease the chance of delivering your babies earlier than 28 weeks.

There may be no benefit to you from being in this research, but we hope that what we learn may be helpful to future patients or society in general. If the cerclage is found to prevent preterm birth, this knowledge could be helpful to many women and babies in the future.

Are there alternatives to being in the study?

Routine care of women with twin pregnancy and preterm cervical dilation varies in the United States, and at this time there are very few interventions to offer women, that have been proven to prolong pregnancy. Participation in this study is entirely voluntary. There may be other alternatives that could be considered. These alternatives may include: ending the pregnancy or expectant management (waiting and watching). The study doctor will provide information about the study and any alternative treatments available.

How will privacy and confidentiality (identity) be protected?

Federal regulations require that certain information about individuals be kept confidential. This information is called "protected health information" (PHI). PHI includes information that

identifies an individual personally such as name, address and social security number, or any medical or mental health record, or test result, that may have this sort of information on it. The laws state that people may see and review their medical records at any time. However, in a research study, people may not see the study results or other data about the study until after the research is completed unless the study doctor decides otherwise.

- The following individuals or entities may have access to your PHI and by law must protect it. These include investigators listed on this consent form and other personnel of Thomas Jefferson University, Jefferson University Physicians, and Thomas Jefferson University Hospitals, Inc. involved in this specific study, the University's Division of Human Subjects Protection and the Institutional Review Board (IRB), and your health insurance company (if necessary for billing for standard medical care).

PHI collected during this study may also be shared with the following entities that, while not obligated by law to protect PHI, will protect it to the best of their ability:

- The Food and Drug Administration (FDA)
- A Data and Safety Monitoring Committee (DSMC),
- With any person or agency required by law.

The following information will be provided to the entities noted above:

Study data for analysis:
Results of ultrasounds performed during your pregnancy (but not pictures)
In case of cerclage: surgical information data: surgical technique, type of suture.
Admissions to the hospital: medications during admissions while still pregnant
Delivery information

Demographic data:
Maternal age (years)
Ethnicity (self-reported)
Number of placentas (one or two)
Gestational age at the time of cervical dilation diagnosis (weeks)
Gestational age at randomization (weeks)
Gestational age at cerclage placement (weeks)
Gestational age at delivery (weeks)
Information about your babies: birth weight, Apgar scores, admission to neonatal unit and complications during their stay in the hospital until discharge home.

If you develop an illness or injury during the course of participation in this study, other PHI about treating and following the condition may be generated and disclosed as it relates to this study.

PHI collected as part of this research may be used/disclosed indefinitely. For the purpose of the study, your PHI will be removed and all the data regarding your pregnancy and babies' information will receive a research number (de-identified information). Only authorized personal will have access to your PHI data. Accidental disclosure of your "protected health information" (PHI) may put you at risk of identity theft.

You may quit the study and revoke permission to use and share PHI at any time by contacting the principal investigator, in writing, at: **Dr. Amanda Roman-Camargo, 833 Chestnut St., First floor, Philadelphia, PA 19107.** Further collection of PHI will be stopped on those who quit the study, but PHI that has already been collected may still be used.

The results of clinical tests and procedures performed as part of this research may be included in your medical records. The information from this study may be published in scientific journals or presented at scientific meetings but no one will be personally identified in these publications and presentations.

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, this Web site will include a summary of the results. You can search this Web site at any time.

What happens in case of injury as a result of being in this study?

In the event of a research-related injury, necessary and available medical care (including hospitalization) will be provided. A research-related injury is a physical injury or illness that is directly caused by any procedure or treatment used in this study that is different from the treatment you would receive if not participating in a research study. If physical injury occurs due to any drug/substance or procedure properly given under the plan for this study, medical expenses for treating the injury will be billed to your insurance carrier. You should be aware that some costs may not be covered by insurance and may become your responsibility) Costs not covered by your insurance, a government program or by another 3rd party may be paid for by the sponsor of this study. There is no plan to provide compensation for loss of wages, lost time from work, personal discomfort, or for injuries or problems related to your underlying medical condition(s).

If a bill related to a research-related injury is received that seems wrong, please discuss it with the study doctor or research coordinator.

Is there payment for being in this study?

There is no payment for participating in this research study.

Are there costs related to being in this study?

If you are assigned to receive a cervical cerclage we will request an insurance precertification from your insurance prior to the procedure to ensure that your insurance will cover the cost

associated with the procedure. If you don't have insurance at the moment of randomization, a medical necessity letter will be provided, coverage will be requested and financial office at Thomas Jefferson Hospital will be consulted. You will be notified of the precertification outcome. At this time, insurance companies are routinely covering the procedure and the costs associated with it.

Research Procedures

The use of a cervical cerclage in twin pregnancies with cervical dilation to prevent preterm birth is experimental as the effectiveness is unknown but it is the standard of care in women with singleton pregnancies. The cervical cerclage technique is not experimental.

Standard Testing Procedures

Other testing procedures and doctors' appointments constitute standard of care during pregnancy; they will be billed to your health insurance carrier as usual. These are charges that would be billed to insurance whether in a research study or not. The study doctor will explain which procedures, tests and doctor visits are considered standard of care.

If a bill is received that you think is wrong, please discuss it with the study doctor or research coordinator.

What if the research results in new findings?

Anything learned during the study period, beneficial or not, that may affect your health or willingness to continue in the study, will be discussed with you.

Can I be removed from the study or quit the study?

Your decision to participate in this research study is entirely voluntary. You have been told what being in this study will involve, including the possible risks and benefits.

Your participation in this research project may be stopped by the study doctor without your consent for any reason that he/she feels is appropriate. Examples of these reasons are: the study doctor feels it is necessary for your health or safety, you have not followed study instructions, or the Food and Drug Administration (FDA) has decided to stop the study.

You may decline to participate in this investigation or withdraw consent and quit this study without penalty and without affecting the ability to receive medical care at Thomas Jefferson University.

If you withdraw from this study, you may continue treatment with your Jefferson doctor, or you may seek treatment from another doctor of your choice.

Should you decide to withdraw from the study, please be sure to inform the study doctor. Additional tests or procedures may be needed to ensure your safety. The study doctor will explain why these tests or procedures are necessary.

CONTACT INFORMATION

Telephone number for questions about your rights as a research participant	The Jefferson Institutional Review Board	215-503-8966
For questions, concerns or complaints about the research, or if you suspect a research-related injury	The Principal Investigator, Dr. Amanda Roman-Camargo or any co-investigator listed at the beginning of this form	215-955-9200
If you have difficulty contacting the study staff	Call the Jefferson Office of Human Research	215-503-0203

If you want more information about the Jefferson Institutional Review Board or Jefferson's Human Research Protection Program, please visit our website at http://www.jefferson.edu/human_research/irb/index.cfm.

Subject Communications

Do you wish to communicate with the study staff by e-mail? YES _____ NO _____

If you checked yes, please print your e-mail address on the line below.

_____

RISKS: E-mail correspondence is not always secure and there is a risk of loss of confidentiality. To help protect against loss of confidentiality, all e-mail that originates from Jefferson University or Jefferson Hospital employees using Jefferson University or Jefferson Hospital e-mail addresses is encrypted. That means, unless you have allowed others to have access to your e-mail, only you will see the e-mail.

YOU SHOULD **NEVER** USE E-MAIL TO REPORT A SUSPECTED ADVERSE EVENT OR ANY OTHER MEDICAL PROBLEM. THESE SHOULD BE REPORTED BY TELEPHONE.

Non-Waiver of Legal Rights Statement

- ✓ **By your agreement to participate in this study, and by signing this consent form, you are not waiving any of your legal rights.**
- ✓ **In order to be in this research study, you must sign this consent form.**
- ✓ **You affirm that you have read this consent form. You have been told that you will receive a copy.**

SIGNATURES

_____
Your Name

_____
Your Signature Date

_____
Name of Person Conducting Consent Interview

_____
Signature of Person Conducting Consent Interview Date

_____
Witness Signature *(only required if subject understands and speaks English but cannot read English or if subject is blind or cannot physically sign the consent form)* *Date*

_____
Signature of Principal Investigator or Co-Investigator Date

****

_____
Copy of Signed and Dated Consent given to Subject by (*Signature above*) Date

As per University Counsel - Do not sign this consent form after 03-11-16

OPTIONAL TEACH-BACK FOR INFORMED CONSENT (GREATER THAN MINIMAL RISK STUDIES)

Is the surgical procedure (cerclage) used in this study FDA approved?

YES _____ NO _____ DON'T REMEMBER _____

Do you have to be in this research in order to be able to receive your usual care?

YES _____ NO _____ DON'T REMEMBER _____

Do you understand the risks of being in this study?

YES _____ NO _____

Is there a risk(s) you would like to know more about?

YES _____ NO _____

If yes, what risk(s)

Is there a benefit to you from being in this study?

YES _____ NO _____ DON'T REMEMBER _____

Are there other treatments you can get for your condition without being in this research study?

YES _____ NO _____ DON'T REMEMBER _____

Will you be paid for being in this study?

YES _____ NO _____ DON'T REMEMBER _____

Can you drop out of this study at any time for any reason and still receive care from the study doctor or your regular Jefferson doctor?

YES _____ NO _____ DON'T REMEMBER _____

Do you need to tell the study doctor or study staff if you are going to quit the study?

YES _____ NO _____ DON'T REMEMBER _____

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: _____