CLINICAL PROTOCOL

Study Title:	Cervix monitor for elasticity and length measurements
Study Protocol Number:	CM01A
Clinical Investigator:	Heather van Raalte, MD
Clinical Site:	Princeton Urogynecology
Targeted enrollment:	10 patients
Sponsor:	Advanced Tactile Imaging, Inc. (ATI), Eunice Kennedy Shriver National Institute of Child Health &Human Development (NIH)
Project:	Cervix monitor for risk assessment of spontaneous preterm delivery

Introduction

Preterm birth is a leading global cause of neonatal mortality despite of numerous advances and intensive research in perinatal medicine. Almost one million children die each year due to complications of preterm birth and in almost all countries with reliable data, preterm birth rates are increasing. Of the 14 million survivors per year, many face a lifetime of disability, including learning disabilities, visual and hearing impairments.

Preterm birth occurs for a variety of reasons. The majority of preterm births happen spontaneously, though some are due to early induction of labor or caesarean birth, typically due to for medical maternal or neonatal conditions. Common causes of spontaneous preterm delivery (SPTD) include multiple pregnancies, infections, chronic conditions, lifestyle, family history, cervical incompetence; however, often no one cause is identified. Although SPTD is often a multifactorial event, precocious cervical softening, shortening and dilatation are a common denominator.

The uterine cervix has to provide structural integrity and mechanical resistance to ensure normal development of the fetus as the uterus expands to accommodate the fetus' growth. Preterm delivery is closely related to a premature cervical ripening. The scientific basis for the proposed project is that the elasticity modulus of a cervix is a more sensitive parameter characterizing the stage of cervical ripening. The main component of the cervix tissue is collagen. Cervical ripening is the result of realignment of collagen, degradation of collagen cross-linking due to proteolytic enzymes. These processes affect the elasticity modulus of the cervical tissue. Therefore, assessment of cervix by a device measuring cervical elasticity (stiffness) and cervical length (effacement) appears to be an adequate approach for identifying pregnant women at high risk of SPTD.

The primary cervical elasticity assessment currently used in clinical practice is relying on the clinician's evaluation of the cervix as "hard, medium or soft" which is descriptive and subjective. Clinicians use terms such as *softening*, *shortening*, *funneling*, *effacing*, and *dilating* to describe changes in the cervical conditions that occur during pregnancy. Collectively, these changes are called *cervical remodeling* and refer to both the tissue's intrinsic material property changes and its resultant anatomical changes. These changes definitely require objective and reliable quantification.

In the scope of this project we propose to develop and clinically validate a new and cost-effective device, Cervix Monitor (CM), for detecting cervix conditions leading to SPTD and its risk assessment. The CM will be based on measuring of the applied pressure to the cervix by a tactile sensor array (stress data) and ultrasound measurement of cervix length (strain data). Tactile and ultrasound sensors will be allocated on the tip of the disposable measuring part of vaginal probe (see Figure 1). Both stress and strain data will allow cervix elasticity and effacement evaluation. The discovery of novel biomarkers that could reliably identify women who will subsequently deliver preterm, may allow for timely medical intervention and targeted therapeutic treatments aimed at improving maternal and fetal outcomes.

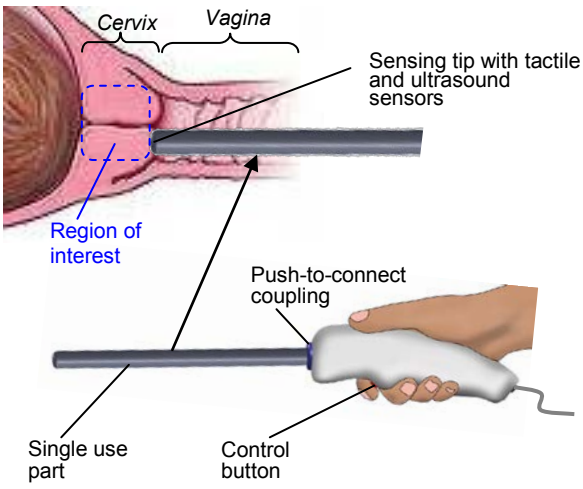

Figure 1. *Concept of proposed cervix monitor. It will allow elasticity and length measurements of the uterine cervix during gestation to explore and detect conditions leading to spontaneous preterm delivery.*

The objectives of the Phase I research, which covers the proposed protocol, are listed below.

Study Objectives

The objectives of the Phase I pilot clinical study are:

1. To assess potential risks of CM to pregnant women and fetuses in a study with non-pregnant women,
2. To verify proposed data collection and examination techniques, and
3. To assess device performance, measurement repeatability and usability.

Study Description

Study Timeframe

December 1, 2016 – February 28, 2017.

Sample Size

The study will involve 10 remunerated subjects.

Clinical Site

The study will be conducted at Princeton Urogynecology, Princeton, NJ.

Subjects

The study will involve 10 non-pregnant, 2 CM measurements per subject. Adult non-pregnant pre-menopausal women scheduled for a regular gynecological examination at Princeton Urogynecology (Princeton, NJ) will be considered eligible for enrollment into the study. Each patient will first be studied with the existing clinical means and then with the CM. A clinical research assistant will maintain a log as to any concerns/complications with the CM.

Enrollment

Conditions precluding patients from participation are listed in the study exclusion criteria below. In addition, cognitively impaired patients will not be asked to participate. No patients will be excluded on the basis of race. Adult women in reproductive age (21-44 years) will be included.

Inclusion criteria

1. Adult women age 21-44 years
2. Non-pregnant women

Exclusion criteria

1. Active cancer of the colon, rectum wall, cervix, vaginal, uterus or bladder
2. Ongoing or prior radiation therapy for abdominal or pelvic cancer
3. Recent (less than four months) pelvic surgery
4. Surgically absent uterus, rectum or bladder
5. Significant circulatory or cardiac conditions that could cause excessive risk from the examination as determined by attending physician
6. Severe abdominal or pelvic adhesions preventing access to pertinent anatomy
7. Known or suspected bleeding disorder
8. HIV or hepatitis B positive serology
9. Warty lesions on the vulva
10. Extensive varicose veins on the vulva
11. Active skin infection or ulceration within the vagina/vulva (Herpes infection)
12. Presence of a vaginal septum
13. Severe hemorrhoids

Data Collection

Cervix tissue elasticity and length measurement data as well as patient age, weight, height and parity, patient questionnaire (CM scan comfort, pain).

Device

Cervix Monitor (CM)

Assignments

Informed Consent Form (ICF) and authorization to release privacy data (HIPAA) Form will be obtained from the subject prior to surgery. Clinical investigator will follow the IRB approved informed consent process to answer all questions and provide explanations during enrollment to about the study.

Methods and Procedures

The examination procedure will comprise the steps of:

1. Inserting the speculum into the vagina to provide appropriate visualization and access to the cervix.
2. Performing CM measurements at 3, 6, 9, and 12 o'clock specifying the probe tip location on cervix on the touch screen display.
3. Review the measurement results (elasticity and length values) and repeat two measurements, one at the location with the lowest elasticity and one at the location with highest value.
4. Removing the probe and speculum from the vagina.

This CM examination procedure will be explored and further optimized based on the practical experience.

Data Analysis

Measurement repeatability between two measurements will be assessed with a reliability parameter, which is also known as an intraclass correlation (ICC), as it equals the correlation between any two measurements made on the same subject. The difference between pairs of measurements will be plotted against their mean in a Bland-Altman plot. The average difference between measurements will be calculated as well as the 95% limits of agreement (LOA).

Study End Points

Study end points (measures that will be considered as success):

1. The examination using CM is safe, does not cause significant discomfort and is capable of production of expected measurement results.
2. The CM elasticity measurements have intraoperator ICC of 0.90 or above; 95% LOA is within ±15%.
3. The CM cervix length measurements have intraoperator ICC of 0.93 or above; 95%LOA is within ±10%.

Protection of Human Subjects

Human Subjects Involvement, Characteristics and Design

Adult non-pregnant women scheduled for a regular gynecological examination at Princeton Urogynecology (Princeton, NJ) will be considered eligible for enrollment into the study with Cervix Monitor (CM). Conditions precluding patients from participation are listed in the study exclusion criteria below. This study with non-pregnant women is conducted to assess potential risks to pregnant women and fetuses as required by Code of Federal Regulations, Title 45, §46.204(a). This study with non-pregnant women will be conducted before initiation the study with pregnant women.

The highest priority will be given to consideration of examination safety with CM probe, disturbing the cervix tissue during pregnancy and potential risk of premature delivery, infection or miscarriage. Clinical study coordinators will maintain a log as to any concerns, complications, or suggested improvements in using the CM probe. After the CM examination a questionnaire will be presented to patients to assess their comfort and pain concerns relative to the procedure. All clinical investigators will have their CV on file with the local IRB and complete training and certification in Protecting Human Research Participant. Explanation of how data from the sites will be obtained, managed, and protected is presented in Data and Safety Monitoring Plan section (see below).

Source of Materials

Upon patient's consent, relevant clinical and demographical data will be collected. Specifically, obstetrical history, course of the previous current pregnancy(s), history of prior surgery and a connective tissue disorders (i.e. Ehlers-Danlos Syndrome, Benign Joint Hypermobility Disorder, etc.), race, age, height, weight, and parity will be documented.

Prior to taking the CM scan, standard obstetric external and internal vaginal examination will be performed by a clinical investigator. Attention to cervix softness, elasticity and any abnormalities

will be made and the results recorded to map the cervix surface. A 4-point grading system for cervix elasticity would be giving soft (0), or moderately soft (1), or moderately stiff (2), or stiff (3) elasticity scores to cervix. These subjective measurements would then be correlated with the CM data for agreement or discordance.

The CM examination will be performed as described above in Methods and Procedures section. The process is quick, non-invasive and should cause no additional discomfort to the patient as compared to a standard pelvic examination. All results will be recorded using an examination chart, which will be a part of the Case Report Form (CRF) specifically designed for the study. The chart will summarize all findings by all mean to characterize the cervix in terms of appearance and elasticity.

All necessary clinical and demographic data will be derived from existing records and de-identified. No additional clinical tests will be ordered to support this research. A specific clinical study number will be generated for each examination case so the link between the data and the patient will be created without revealing patient identity.

Potential Risks

Investigators do not expect any additional risks or side effects from the use of CM beyond those normally associated with standard manual palpation and transvaginal ultrasound, such as extremely rare possibility of physical damage of the vagina, cervix tissue and infection. Other risks include software/hardware malfunction, toxicity, allergic reaction, electrical shock and breach of confidentiality.

Recruitment and Informed Consent

Patients scheduled for vaginal examination will undergo a standard study admission protocol. This includes: completion of administrative and clinical forms, procedure informed consent, and a history and physical examination. Prior to enrollment, each patient will be assessed against the study inclusion criteria, usually during their initial clinical screening evaluation. Once a patient has been found to be acceptable for participation in the study, the consent interview will be conducted in private in the pre-procedure facility by the clinical research coordinator or clinical investigator performing the procedure. All informed consents will be reviewed and approved by the institution IRB prior to the initiation of the study. Subjects will be informed of the potential risks and benefits of the research and of their right to withdraw from the study at any time without penalty. A statement that the particular CM examination procedure may involve risks to the subject and to the fetus which are currently unforeseeable will be included into the informed consent as required by Code of Federal Regulations (CFR) Title 45, §46.116(b)(1). The subject will be free to ask any questions pertaining to the study. Informed consents will be signed and dated by the subject, investigator and research assistant.

According to the requirements of CFR Title 45, §46.204 (a), the study with pregnant women will follow after assessment of the risks of CM examination procedure with non-pregnant.

We will comply with all applied requirements of CFR Title 45, Part 46, Protection of Human Subjects, in Subpart B – Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research.

Protection Against Risks

All investigators performing the CM examination will receive appropriate training in order to negate the lack of familiarity with the device. The risk of physical damage to the vagina and cervix will be minimized by utilization of standard procedure to assess the cervix using a speculum. A physical contact of the probe tip with the cervix surface will be detectable by a tactual feedback from the CM probe. The risk of cross-contamination and infection will be

eliminated by the use of disposable (single use) probe shaft which be sterilized and stored in a sterile sheath before the clinical use. It is highly unlikely that the use of the CM probe can produce any toxicity since the probe shaft is made of certified biocompatible.

Software and hardware malfunction risks are minimized by completion of full component and system testing cycle prior to the initiation of the clinical study. The devices will go through performance bench testing on simulator models to verify proper CM functionality. Standard software verification and validation procedures mitigate the risk of incorrect characterization being presented to the user during the patient examination. All participating clinical investigators will be trained to recognize inappropriate software and hardware behavior and to react on it.

Possible risks to the patient caused by electrical shock are negligible due to absence of supplied voltage to the probe, to protective features of electronics and isolated medical-grade power supply to electronics and computer. The device will go through a full cycle of EMC and electrical safety testing at an independent certified test facility. If ordered by local IRB, the device will be also tested by appropriate hospital personnel responsible for biomedical safety.

To protect against the risk of breach of confidentiality, patient confidentiality will be maintained at all times. The record of patient's progress while on this study will be kept in locked file cabinets to which only limited research staff will have access. The confidentiality of any central computer record will be carefully guarded, and no information by which patient can be identified will be released or published. All information on the case report forms or any information communicated from clinics to the company will be de-identified. The psychological risk will be minimized by the fact that no change in clinical diagnosis and patient management will result from this study.

We will complete full Risk Analysis for CM, as required by our internal Quality Management System under ISO 13485, according to American National Standard ANSI/AAMI/ISO 14971: Medical Devices – Application of Risk Management to Medical Devices.

Potential Benefits of the Proposed Research to Human Subjects and Others

There are no direct benefits to the patients in the study. However, there may be a benefit to society, in general, from the knowledge gained in connection with participation in the study.

Importance of the Knowledge to be Gained

The proposed clinical studies in the first exploratory stage of the project will allow to assess potential risks of CM to pregnant women in studies with non-pregnant women, to develop and test the data collection technique and establish possible limitations in the CM use, to assess CM measurement reproducibility, evaluate the probe ergonomic design and ease of use, and to assess the clinical suitability of the interface software to facilitate the data collection process and to get *in vivo* test data for off-line development of analysis routines. After meeting the basic research milestones in the exploratory stage, we plan extensive clinical studies on pregnant patients to obtain quantitative data on changes of cervix elasticity for the months of pregnancy, on estimating the level of the cervix softening which may qualify the patent for a medical treatment and on the range of variability of cervix stiffness which need to be taken into account while making decisions on clinical intervention.

Data and Safety Monitoring Plan

The Principal Investigator will be responsible for proper monitoring of the investigation and compliance with written monitoring procedures (§§ 812.46 and 812.25(e)); ensure that IRB approval is obtained (§812.42) and any reviewing IRB and FDA are promptly informed of significant new information about an investigation (§812.150); control distribution and disposition of investigational products (§812.43).

Clinical investigators perform the data safety monitoring function and are responsible for concurrent reporting of any adverse events that occur as a result of this study to the local approving IRB and to the Principal Investigator. All events will be categorized as to their degree of seriousness and relation to the use of the PTI. Principal Investigator will collect and analyze adverse effects, highlight its course and propose means to negate such effects.

ATI staff will monitor the study by auditing CRFs, verifying the consistency of raw CM data, and checking clinical protocol compliance. Communication with clinical investigators will be primarily in a form of phone and e-mail. In addition, ATI's representative will visit all participating clinical sites. Establishment Inspection Report (EIR), a detailed record of the inspection and findings, will be prepared after the visit. Also, such interactions will result in a clinical database that will be set to store all information obtained during the course of the study.

To protect patient data, confidentiality will be maintained at all times. All records will be identified by a study specific code and personal identifiers and linkage to study identification numbers will be maintained separately in locked file cabinets to which only designated research staff will have access. Each patient will be identified with a unique patient identification number (xxxxxxxxxxx) that consists of the patient number (001xxxxxx) and the date (xxx020102) in day-month-year format. Data for that study are all placed in a study specific patient folder. A file that matches patient identifier to a patient name and hospital ID number are kept on a password protected computer. No individual subject will be identified by name in any reports from the study. Patient's records, with regard to participation in this study, may be subject to review by the appropriate officers of the hospital conducting the clinical study and its Institutional Review Board, and patient's insurance carrier. In addition, the National Institutes of Health and Food and Drug Administration (FDA) may request and will be given access to records of participants in this study. This clinical study will be registered in ClinicalTrials.gov as required by Public Law 110-85, Title VIII and Certification of Compliance under 42 U.S.C. § 282(j).

Inclusion of Women and Minorities

Every effort will be made to increase enrollment of the minorities and the study group is expended to correspond to the patient population of the clinic as generally representative of the overall populations of Mercer County of NJ.

Minorities will be included in this research project. There is no evidence that minority status may affect CM performance. Therefore, there are no inclusion or exclusion criteria based on ethnic background, religion, or other division of the population (other than those stated above). Racial/ethnic composition of the population is expected to mirror the broad mix of individuals within the patient population serviced by corresponding clinical site (please see Targeted/Planned Enrollment Table).

The expected racial distribution of the study population at Princeton Urogynecology (Princeton, NJ) is 78% White, 15% African American, 0% American Indian/Alaska Native, 7% Asian, and 0% Native Hawaiian or Other Pacific Islander. Ethnic distribution is: 16% Hispanic or Latino; 84% - not Hispanic or Latino.

Men will not be included in the study.

Inclusion of Children

Participating gynecology departments serve only adult patients; therefore our cross section of the population will not include individuals under 21 years of age. Additionally, children are not likely to benefit from the LTI technology, given no available supporting evidence of incidence of pelvic organ prolapse in children.