Title: Role of hormonal status on vascularization and vaginal tissue in women with pelvic organ prolapse

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The University of Texas Medical Branch at Galveston
More Than Minimal Risk Consent Form

Protocol Title: **"Role of hormonal status on vascularization and vaginal tissue in women with pelvic organ prolapse"**

IRB Number: **13-114**

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Why am I being asked to take part in this research study?
You are being asked to take part in this study because you have elected to undergo surgical intervention for stage II or greater prolapse. Your participation in this study is completely voluntary. You may refuse to participate or stop your participation in this research study at any time without penalty or loss of benefits and without jeopardizing your medical care at UTMB.

Study Summary:
The pelvic organs are supported in place by muscles of the pelvic floor and layers of connective tissue. This support system may become torn or stretched and/or or may weaken with aging. Loss of pelvic floor support is often associated with pelvic organ prolapse, urinary and fecal incontinence and other problems.

The purpose of this study is to determine tissue differences, including estrogen effects and muscle and connective tissue changes, between pre- and post-menopausal women with pelvic organ prolapse. Research findings will add to clinical knowledge and help to identify new therapeutic targets, ultimately guiding better medical management and the development of safer, non-surgical and noninvasive treatment options for pelvic floor dysfunction.

The following things you should know about this research study:

- The purpose of the study is to determine tissue differences, including estrogen effects and muscle and connective tissue changes, between pre- and post-menopausal women with pelvic organ prolapse. If you chose to participate, you will be asked to come to the clinic for 2 study visits prior to your surgery. At these visits you will have a pelvic floor ultrasound, blood drawn and complete study questionnaires. You will also have optical coherence tomography imaging (OCT) which is similar to ultrasound except that it uses light, not sound waves, to look at the "skin" of the inside of the vagina. If you are post-menopausal, you will also be asked to use a vaginal cream. At the time of your surgery, vaginal fluid and tissue will be collected.
- The study visits will take approximately 1-2 hours and your study participation should take approximately 6 weeks.
- Risks or discomforts from this research include vaginal discharge, irritation, or bleeding.
- If you are pre-menopausal, you will receive no direct medical benefit from your study participation. If you are post-menopausal, there is a potential benefit of less dry, healthier vaginal tissue.
- Taking part in this research study is voluntary. You do not have to participate and you can stop at any time.

Please take your time to read this entire form and ask questions before deciding if you want to take part in this research project.

What is the purpose of this research study?
The purpose of this study is to determine tissue differences, including estrogen effects and muscle and connective tissue changes, between pre- and post-menopausal women with pelvic organ prolapse. Research findings will add to clinical knowledge and help to identify new therapeutic targets, ultimately guiding better medical management and the development of safer, nonsurgical and noninvasive treatment options for pelvic floor dysfunction.

How many people will take part in this study?
The estimated total number of subjects that may be involved in this study is 30. At least 15 subjects are anticipated to complete the study with participation evenly distributed across the 3 study arms (e.g., 5 participants each in the premenopausal group, post-menopausal on estrogen cream and post-menopausal on placebo therapy).

What procedures are involved as part of this research study?
If you agree to participate in the study, you will be asked to sign and date this written consent form before taking part in study activity.

You will participate in either the pre-menopausal or the post-menopausal study group, depending on your menopausal status. If you can get pregnant or have not gone through menopause, you will take part in the pre-menopausal study group, and you will not use the topical vaginal cream in this study. If you have gone through menopause, you will participate in the post-menopausal group, and you will be given either the topical vaginal estrogen cream or placebo (non-estrogen containing) cream for daily use prior to your scheduled surgery. Neither you nor the study doctors will know if the vaginal cream you are assigned contains estrogen or placebo.

Study Visit 1
You will come to the Pelvic Health Center at Victory Lakes 2-6 weeks prior to your scheduled surgery day. When possible, the study visit will be scheduled to coincide with a pre-op clinical visit. You will complete the following study procedures:

- Optical coherence tomography (OCT) scan
- Pelvic floor ultrasound
- Blood draw
- Study questionnaires
- Topical vaginal cream assignment (post-menopausal participants only)
- Urine Pregnancy Test (pre-menopausal participants or at the discretion of the study gynecologist).

The OCT and pelvic floor ultrasound are imaging tests used to collect images of muscle and connective tissue; both tests involve a vaginal probe being inserted in the vagina. The OCT will be guided by a colposcope (lighted microscope with camera for magnified view of the cervix and vagina) and a magnetic positioning system. Digital images (photographs) will be taken of the cervix and vagina to record the location of the OCT images. The OCT procedure takes about 10-15 minutes and produces high resolution 3-dimensional images; the pelvic floor ultrasound takes about 30-45 minutes. If you are pre-menopausal, these tests will be scheduled around your menstrual cycle.

You may have up to 20ml (4 teaspoons) of blood drawn from a vein in your arm by a qualified phlebotomist or nurse to measure levels of hormones in your blood and the remainder of your sample will be stored for future research. If you agree to allow your tissue/blood/cells to be collected and stored for research, you are free to change your mind at any time. Information on how to withdraw consent for use of your samples is provided in the "Safe Withdrawal from the Study" section below.

You will be asked to complete the UroGynecology Clinical Intake Form (which is part of your standard of care) if not previously completed at your initial clinical care visit or if previously completed more than 3 months ago. The Clinical Intake Form includes the following standardized questionnaires for assessing pelvic floor health and well-being and should take you about 20 minutes to complete. Questions related to urinary symptoms and how it affects you will be asked using the Urinary Distress Inventory-6 (UDI-6) questionnaire. The next set of questions, Pelvic Organ Prolapse Distress Inventory (POPDI-6), will ask if you have certain bowel, bladder, or pelvic symptoms and, if you do, how much they bother you. Questions related to colorectal-anal symptoms will be asked using the Colorectal-Anal Distress Inventory 8 (CRADI-8); questions related to bladder, bowel or vaginal symptoms affect their activities, relationships and feelings will be asked using the Pelvic Floor Impact Questionnaire (PFIQ); and questions related to you and your partner's sex life will be asked using the Pelvic Organ Prolapse/Urinary Incontinence Sexual Function Questionnaire (PISQ-12). Data from these questionnaires, in addition to demographic data (such as your gender, age, ethnicity) and information related to your pelvic floor dysfunction and treatment will also be coded and analyzed for purposes of this study.

If you are post-menopausal, you will be randomized (that is assigned by chance, like a coin toss) to receive either the vaginal estrogen cream or placebo (non-estrogen) cream. The estrogen cream provided is FDA-approved for topical vaginal use; it is <u>not</u> an investigational product. Use of the topical vaginal cream will allow us to study the effect of estrogen on local blood flow. As part of standard of care, some doctors will give their patients vaginal estrogen cream prior to surgery based on the appearance of the vaginal tissue during the exam.

Neither you nor the study doctors will know if the vaginal cream you are assigned is estrogen or placebo. You will apply 0.5 gram of the vaginal cream daily for up to 6 weeks as instructed, and will be asked to stop using the cream 2 days before your surgery date. You will record your daily usage on a study diary. You will bring the completed diary and the spent or used tube of study cream with you to the next study visit.

You will inform the study doctor promptly of any discomfort and/or issues that arise while on study.

Study Visit 2
You will return to the Clinic within a week prior to your scheduled surgery day. You will bring your completed diary and tube of study cream with you to this visit. You will repeat the OCT, pelvic floor ultrasound, blood draw and study questionnaires previously done in Study Visit 1. If you are pre-menopausal, the imaging tests will be scheduled around your menstrual cycle as determined in Study Visit 1.

Additional Study Visit
It may be necessary to ask you to return to the Clinic for an additional study visit. If you experience study-related discomfort or an adverse event, a study exam may be performed at this visit.

Surgical Tissue Collection
After anesthesia and prior to surgical excision, vaginal fluid (secretions) will be collected similar to getting a pap smear and a saline solution will be used to rinse the tissue in the vagina and up to 30ml (or 2 Tablespoons) of this rinse material may be collected for research. The collection of the vaginal fluid and the rinse material (also called vaginal lavage) will take about 5-10 minutes of time in surgery.

The surgical tissue that is excised and removed is standard for the surgery performed, and typically this tissue is discarded after surgery. The tissue collected for this research is discarded surgical tissue, about 2-4 postage stamps in size, depending on whether anterior and/or posterior surgical repair is performed.

If you sign this consent form, you will be giving the study team access to your UTMB medical record for purposes of this study. Data to be collected includes demographics, medical/surgical history, hormonal status, medications, body mass index (BMI), and tobacco status.

USE OF RESEARCH TESTS AND SPECIMENS
Data and specimens collected in this study are being used to investigate contributing factors to pelvic floor dysfunction. When you join this study, a unique study code is assigned to your person and to data and specimens collected for this study. Study codes do not contain any personal identifiers and are assigned to protect your identity. Only the study team can directly access or link to your personally identifiable information which is kept separate from research data and specimens.

OCT and pelvic floor ultrasound are being done to learn more about blood flow and thickness of pelvic floor muscle and connective tissue.

Your blood sample will be used to measure levels of hormones in your blood, and a portion may be stored for future use.

You will not be given individual study results as these investigations are preliminary; the results of what these tests might mean are not yet understood. However, if any abnormality is found during ultrasound, you will be informed and referred for further evaluation and testing.

Some of the vaginal fluid, vaginal rinse material (or lavage), and discarded surgical specimen will be used in laboratory testing related to infection, inflammatory markers, structural elements and hormone receptors. Some of your tissue may be used to grow cell cultures. A portion of your blood sample and surgical specimen may be stored or banked for future analysis for purposes of this study. Specimen storage or banking involves transferring specimens into several smaller coded sample tubes for freezing and storage in the research Biorepository on the UTMB campus.

Laboratory testing for this study will be performed at UTMB and at the Oak Crest Institute of Science in Pasadena, California. Your specimens and data may also be used in ongoing collaborative research with Oak Crest in studies further examining the characteristics of vaginal tissues and/or secretions in pelvic floor dysfunction. The collaborative studies being done with Oak Crest are sponsored by the National Institutes of Health (NIH).

Samples not used as part of this study will be stored in the Biorepository indefinitely or lifetime of the Biorepository and used by the pelvic health team and other UTMB researchers for approved research in the future.

Only coded samples and data may be shared with researchers; your personal identity remains protected and anonymous. If you do not want your samples to be shared, you should not sign this consent form.

Your stored samples may not be used in future genetic studies unless you give your permission below. Genetic studies isolate DNA for analysis. DNA is the substance in our cells that contains the information or "genes" we inherit from our parents or other family members. Your DNA contains genes which predict physical characteristics (eye color, height, etc.) and may also be a factor in the development of certain disorders or illnesses and/or prediction of response to drug therapies. It is your choice whether to allow genetic testing of your samples.

Permission for Future Sample Use

Genetic Research: ☐ Yes, my samples may be used in genetic research in the future.
☐ No, my samples may not be used in genetic research.

Permission for Future Contact

The study team may need to contact you in the future to request additional information or to inform you about another study which you may be eligible. Should you agree to give permission, you are under no obligation to respond to a future contact or agree to any request.

☐ Yes, I give permission for future contact outside of this study.
☐ No, I do not give permission for future contact outside of this study.

What extra tests and procedures will I have if I take part in this study?

There are some extra tests that you will need to have if you take part in this study.

You will have the following extra tests:

- Optical coherence tomography (OCT) scan
- Pelvic floor ultrasound
- Blood draw
- Study questionnaires
- Topical vaginal cream assignment (post-menopausal participants only)
- Urine Pregnancy Test (pre-menopausal participants or at the discretion of the study gynecologist).

The research study will pay for all the extra tests.

What are the possible risks for choosing to participate in this research study?

Some common risks and/or discomforts of study participation are listed below. The study-related procedures may also involve risks that cannot be predicted at this time.

Topical vaginal cream: Allergic reaction; irritation or other discomfort; vaginal burning, bleeding, infection and/or increased discharge; trauma from applicator, headache and/or breast tenderness.

OCT: Possible discomfort with the probe in connection with the evaluation. Some women have reported minor irritation, redness and vaginal bleeding.

Pelvic floor (endovaginal) ultrasound: The test is usually painless although some women have reported mild discomfort from the pressure of the probe. There are no known harmful effects on humans.

Blood draw: The discomfort associated with drawing blood from a vein is a light pinch or pinprick at the puncture site. The risks include possible bruising and swelling around the puncture site; less commonly, infection, small blood clot or bleeding at the puncture site and faintness from the procedure.

Genetic research: If you agree to allow your samples to be used in genetic studies, you should be aware of some of the general concerns that could affect you and your relatives. Genetic studies have raised concern as to whether study participants would be placed at risk for discrimination based on genetics. The federal Genetic Information Nondiscrimination Act (GINA) was passed to address this concern. GINA makes it illegal for medical insurance companies and most employers to discriminate based on genetic information. The protections of GINA do not apply to life, disability or long-term care insurance.

The study team strives to protect participants from placing them in a position where sensitive information could be disclosed that could lead to discrimination or the misuse of information. Identifying information is removed from study data and samples. Information for genetic research studies is kept separate from hospital medical records. Although protections are in place, you should be aware of the general concerns for risks of discrimination and psychological or social harms.

For example:

	Frequent 30% of subjects	Occasional 15% of subjects	Rare Less than 1% of subjects
Serious			Blood clot, stroke, breast, endometrial, or ovarian cancer
Less Serious		Allergic reaction, irritation, vaginal discomfort/burning	Vaginal bleeding, infection, Headache, breast tenderness
Minor	Increased vaginal discharge	Trauma from applicator	

Psychological Stress

Some of the questions we will ask you as part of this study may make you feel uncomfortable. You may refuse to answer any of the questions, take a break or stop your participation in this study at any time.

Loss of Confidentiality

Any time information is collected; there is a potential risk for loss of confidentiality. Every effort will be made to keep your information confidential; however, this cannot be guaranteed.

Risks to Embryo, Fetus or Breast-fed Infant

If you are part of this study while pregnant or breast-feeding an infant, it is possible that you may expose the unborn child or infant to risks. For that reason, pregnant and breast-feeding females

cannot participate in the study. If you can become pregnant, a blood pregnancy test will be done (using 1 teaspoon of blood drawn from a vein by needle-stick), and it must be negative before you participate in this study. If you do become pregnant during this study, you must tell the researchers immediately.

What are the potential benefits for participating in this research study?
If you are pre-menopausal, you will receive no direct medical benefit from your study participation. If you are post-menopausal, there is a potential benefit of less dry, healthier vaginal tissue.

Will I be paid for participating in this research study?
For your time and effort, you will receive a $50 Target gift card when you complete Study Visit 1 and Study Visit 2, for a total of $100. If an additional study visit is necessary, you will receive an additional $50 gift card upon completion of that visit. If needed, some assistance with gasoline or alternate transportation may be provided as determined and available on a case-by-case basis.

Is there an alternative treatment/procedure?
You do not have to participate in this research to receive care for your medical problem.

If I agree to take part in this research study, can I be removed from the study without my consent?
Yes. The researchers may decide to take you off this study if:

- You become pregnant during the course of the study
- Your medical problem remains unchanged or becomes worse.
- The researchers believe that participation in the research is no longer safe for you.
- The researchers believe that other treatment may be more helpful.
- The sponsor or the FDA stops the research for the safety of the participants.
- The sponsor cancels the research.
- You are unable to keep appointments or to follow the researcher's instructions.

Your data will be retained even if you are withdrawn from the study before completion.

Will my insurance provider or I be charged for the costs of any part of this research study?
No. Neither you, nor your insurance provider, will be charged for anything done only for this research study (i.e., the Screening Procedures, Experimental Procedures, or Monitoring/Follow-up Procedures described above).

However, the standard medical care for your condition (care you would have received whether or not you were in this study) is your responsibility (or the responsibility of your insurance provider or governmental program). You will be charged, in the standard manner, for any procedures performed for your standard medical care.

What will happen if I am harmed as a result of taking part in this study?
It is important that you report any illness or injury to the research team listed at the top of this form immediately. Compensation for an injury resulting from your participation in this research is not available from the University of Texas Medical Branch at Galveston.

You or your insurance company or health care plan, will be billed and you will be responsible for any charges.

You will be responsible for paying any costs related to illnesses and medical events not associated with being in the study. There are no plans to provide other forms of compensation. However you are not waiving any of your legal rights by participating in this study.

If I agree to take part in this research study, will I be told of any new risks that may be found during the course of the study?
Yes. You will be told if any new information becomes available during the study that could cause you to change your mind about continuing to participate or that is important to your health or safety.

How will my information be protected?
All results obtained in this study will be kept confidential and only available to the research study team. Your individual information will not be reported, only the results of all participants as a group. Information you provide on the health history questionnaire will be stored separately from data for the exercise tests; the exercise test data will contain no personal information about you.

Data or specimens collected in this research might be deidentified and used for future research or distributed to another investigator for future research without your consent.

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

How will my privacy be protected?
We have rules to protect information about you. Federal and state laws and the federal medical Privacy Rule also protect your privacy. By signing this form you provide your permission, called your "authorization," for the use and disclosure of information protected by the Privacy Rule.

The research team working on the study will collect information about you. This includes things learned from the procedures described in this consent form. They may also collect other information including your name, address, date of birth, and information from your medical records. This could include information about HIV and genetic testing, or treatment for drug or alcohol abuse or mental health problems.

The research team will know your identity and that you are in the research study. Other people at UTMB, particularly your doctors, may also see or give out your information. We make this information available to your doctors for your safety. If you think this study might affect your clinical care, please inform your doctor.

People outside of UTMB may need to see or receive your information for this study. Examples include government agencies (such as the Food and Drug Administration), safety monitors, other sites in the study and companies that sponsor the study.

We cannot do this study without your authorization to use and give out your information. You do not have to give us this authorization. If you do not, then you may not join this study.

We will use and disclose your information only as described in this form; however, people outside UTMB who receive your information may not be covered by this promise or by the federal Privacy Rule. We try to make sure that everyone who needs to see your information keeps it confidential – but we cannot guarantee that your information will not be re-disclosed.

The use and disclosure of your information has no time limit. You may revoke (cancel) your permission to use and disclose your information at any time by notifying the Principal Investigator of this study by phone or in writing. If you contact the Principal Investigator by phone, you must follow-up with a written request that includes the study number and your contact information. The Principal Investigator's name, address, phone and information are on page one of this consent form.

If you do cancel your authorization to use and disclose your information, your part in this study will end and no further information about you will be collected. Your revocation (cancellation) would not affect information already collected in the study, or information we disclosed before you wrote to the Principal Investigator to cancel your authorization.

Finally, please specifically authorize the use of your private health information relating substance abuse, psychiatric information, or HIV/AIDS, if applicable, for the above-described purposes. Initial: _____

Who can I contact with questions about this Research study?
If you have any questions, concerns or complaints before, during or after the research study, or if you need to report a research related injury or bad side effect, you should immediately contact Dr. Vincent at 409-772-2610 or, if after normal office hours, at 409-772-2222 or toll free 800-917-8906 or Lauren Dawson at 409-354-9792.

This study has been approved by the Institutional Review Board. If you have any complaints, concerns, input or questions regarding your rights as a subject participating in this research study or you would like more information about the protection of human subjects in research, you may contact the Institutional Review Board Office by email at irb@utmb.edu.

CONSENT TO PARTICIPATE:
The purpose of this research study, procedures to be followed, risks and benefits have been explained to you. You have been given the opportunity to ask questions, and your questions have been answered to your satisfaction. You have been told who to contact if you have additional questions. By signing this form, you are confirming that you have read this consent form and voluntarily agree to participate as a subject in this study.

_____	_____
Signature of Subject	Date and time

Using language that is understandable and appropriate, I have discussed this project and the items listed above with the subject

_____	_____
Signature of Person Obtaining Consent	Date and Time Consent Obtained

_____
Printed name of Person Obtaining Consent