Characterisation of Tissue Stiffness to Improve the Diagnosis and Management of Uterine Fibroids

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Background:

Uterine fibroids are the most common gynecological tumors, with a prevalence up to 70% in premenopausal women [1,2]. Although these tumors are benign, 20% – 50% of women with uterine fibroids are symptomatic [1] and morbidities are significant, including menstrual abnormalities (e.g. heavy and prolonged bleeding leading to iron deficiency anemia), bulk symptoms (e.g. pelvic pain, bowel and bladder obstructions, abdominal protrusion), and infertility [1–5]. Symptomatic fibroids can negatively impact women's quality of life and results in loss of productivity [6,7]. The management of uterine fibroids is estimated to cost the healthcare system between $2200 and $15,952 per patient, per year [8].

Uterine fibroids are globular masses composed of disordered myometrial cells contained within abundant extracellular matrix [9,10]. Fibroids degenerate as they outgrow their blood supply [11], and can take on a range of characteristics while presenting on a spectrum of very soft to extremely hard masses [4,11–13]. Fibroid degeneration state is currently not considered in diagnosis, management or surgical planning. Instead, fibroids are classified based only on their location [14] and are described by their size and shape.

While medical management is advancing [5,10,12,15] surgical removal through myomectomy or hysterectomy is the current standard of care for uterine fibroids [5]. Myomectomy can spare the uterus to preserve fertility, yet complications occur in 2-35% of cases [16–18]. Fibroid mechanical properties appear to be relevant to surgical outcome: our surgeons at TOH report *very hard* or

very soft fibroids increase surgical time and injury risk as respective morcellation or identification of the dissection plane can be difficult. Surgeons who are given information of fibroid stiffness prior to surgery may be able to alter their approach in order to mitigate these reported risks. These properties cannot be determined through MRI or US. Pre-operative fibroid characterization through SWE would be an extremely welcomed innovation in uterine fibroid diagnosis, monitoring and intervention planning.

Research goal: to create a sensitive and specific classification scheme to differentiate uterine fibroids based on their stiffness characteristics determined through SWE and to use this classification to guide medical and surgical management decisions

Main purpose: to determine if transvaginal shear wave elastography can be used as a clinical tool to measure stiffness properties of uterine fibroids.

Primary objectives:

(1) To validate stiffness measured through SWE from healthy and uterine fibroid tissue against mechanical tissue properties of the same tissues obtained through mechanical testing ex-vivo,
(2) Test the reliability of fibroid and healthy uterine tissue stiffness obtained through SWE,
(3) To use SWE stiffness measures to differentiate between healthy tissues and the varying states of uterine fibroids.

Secondary objective:

(1) To compare 2D and 3D ultrasound volume estimates of uterine fibroids and compare measurement error using MRI as a gold standard.

Methodology

Study Design: This prospective observational cohort study. Two populations will be recruited for this study: Patients with fibroids (FIB) and healthy controls (CON).

Participants: Thirty women, aged ≥18 years, and consented for hysterectomy (due to uterine fibroids) or myomectomy at The Ottawa Hospital – General Campus will be recruited for the

FIB group. Potential FIB participants will be excluded if they are suspected to have adenomyosis or leiosarcomas prior to surgery. Potential FIB participants will be screened for eligibility and consented for the study by the research coordinator or research assistant. The CON group will include women, aged ≥18 years, with no history of gynecological pathologies, have regular menstrual cycles, and not be pregnant at the time of data collection.

Based on findings by [19,20], a sample size of 30 in each group was deemed appropriate to detect effect size of at least 12kPa with 90% power at a significance level of α=0.05. Due to the prospective design, we will not know the distribution of fibroid types a priori. A power analysis to confirm final sample size will be conducted with preliminary data collected from our first 15 participants in each group FIB participants and 15 CON participants.

Recruitment: Prospective FIB participants will be recruited from a list of patients consented for myomectomy or hysterectomy due to uterine fibroids at The Ottawa Hospital – General Campus. Potential participants that have provided "permission to contact" by research as indicated on the institution's electronic medical record (EMR) or the OBIEE dashboard will be contacted by the study's research coordinator or research assistant. If "permission to contact" is not specified then only patients of our participating gynecologists will be recruited. In these cases, the participating gynecologist will contact the patient to introduce the study themselves, and if agreed, the study's research coordinator or research assistant will contact them to discuss the study further. Initial contact will be made through telephone (see attached telephone script). If they agree to participate, then ultrasound imaging session(s) will be booked within one week of their surgery.

CON participants will be recruited from the community. Advertisement posters will be placed around The Ottawa Hospital and the University of Ottawa. Individuals interested in participating will contact the research coordinator by phone or email. Potential CON participants will be screened for eligibility and if they agree to participate then experimental session(s) will be booked at their convenience.

At the time of the ultrasound imaging session, a consent form containing further information about the purpose of the study, risks and benefits will be provided. Participants will be allotted as much time as they would like to review the form and ask the researchers any questions/concerns they may have. At time of study introduction, we will offer to send a full consent form prior to ultrasound imaging session so they can review the form at their

convenience. Signed consent will be obtained onsite by the research coordinator or research assistant before data collection commences.

Data Collection:

Ultrasound Imaging: All participants will attend two ultrasound imaging sessions at the Motor Function and Movement Laboratory at the University of Ottawa. The sessions for the FIB participants will occur within 1 month of their planned surgery. Each session will take approximately 1 hour to complete. After providing signed informed consent, participants will complete a set of validated questionnaires about their gynecological and medical history, symptoms, and quality of life as it relates to uterine fibroids. The questionnaires include the Medical Outcomes Study 36 Item Short Form Survey[21], the Uterine Fibroids Symptoms Quality of Life questionnaire[22], and the Menstrual Bleeding Questionnaire[23].

All participants will then undergo 2D and 3D ultrasound scans with a GE ultrasound system (Voluson S6, General Electric, Boston, MA) as well as a SWE transvaginal ultrasound scan using an Aixplorer ultrasound system (Supersonic Ultrafast™ Aixplorer®, Apexium Medical, Canada). SWE and volume measurements of their uterus as a whole, at 10 healthy sites and at all relevant fibroid sites deemed will be recorded. Morphologic measurements of the selected fibroids will be made and fibroids will be given identification numbers. SWE will be used to determine tissue stiffness (kPa) at 10 healthy sites and at each fibroid. Three repetitions of each measurement will be performed to satisfy Primary Objective 2. The second ultrasound imaging session will occur within one week where the imaging protocol will be repeated. This second data collection will be to evaluate reliability (Primary Objective 2).

The rest of the data collection protocol applies to FIB participants only.
Surgical Intervention: The surgical approach (myomectomy or hysterectomy + abdominal or laparoscopic) will be recorded as well as secondary outcomes including operating time, blood loss, surgical technique conversions, failed/incomplete excisions, and additional procedures performed. These data will be used for descriptive purposes.

Tissue Sampling: Consistent with TOH protocol, all uterine tissue will be sent to pathology for evaluation. For patients who receive a hysterectomy, a pathologist will surgically excise five >=1 cm^3 samples of healthy uterine tissue from the sites identified using US and each fibroid will be dissected out. All fibroids will be labelled with their respective identification number, measured, weighed, and then transported to Dr. Labrosse's laboratory at the Ottawa Heart Institute for mechanical testing.

Mechanical Testing: The healthy tissue samples will be cut to size while the fibroids will be tested intact. All samples will be loaded into a set of 3D printed clamps attached to a biaxial tissue testing device (Biotester, CellScale, Waterloo, Canada) and tested at body temperature, cyclically in compression (1 Hz, 6% pre-compression). Relevant material properties will be calculated, including the complex modulus of elasticity, loss factor, and stiffness contrast ratio. All samples will be returned to pathology. Pathology charts will be retrospectively reviewed to extract descriptive fibroid characteristics.

Statistical Analysis Plan: All data will be tested for normality and non-parametric equivalent tests will be used as appropriate. Validation of stiffness measures derived from SWE will be done through linear regressions (Primary Objective 1) which will be performed for the healthy and fibroid tissues separately and combined to map the relationship between SWE outcomes and the results of ex-vivo mechanical testing.

For the reliability analysis (Primary Objective 2), ANOVA's will test for differences between measures taken across multiple sessions and visits to investigate site-specific differences in stiffness measures. Intra-class correlation coefficients (ICCs) will be determined for measurements within session, between-session, and between-site.

Factorial ANOVAs will evaluate site- and group (CON vs FIB) differences in uterine tissue stiffness measured with SWE. ANOVAs will also investigate differences in SWE stiffness measures between healthy tissue, normal fibroids and degenerative fibroids (Primary Objective 3). Appropriate post-hoc comparisons will be performed, and post-hoc power analyses will evaluate the effect sizes for non-significant differences.

Significant differences in 2D, 3D ultrasound, and ex-vivo volume estimates will be determined with dependent T-tests at the $p<0.05$ level (Secondary Objective 1). The standard error of measurement (SEM) will also be computed for 2D and 3D ultrasound volume measures, using ex-vivo morphology and volume measurements as a reference.

Clinical significance of project: Establishing SWE methods for uterine fibroid characterization would result in a ground-breaking advance for directing medical and surgical decision-making in this highly prevalent gynaecological condition. Magnetic resonance (MRI) and ultrasound (US) imaging are the current standards of care for evaluating uterine fibroids. They inform about number, size and location of fibroids, but are not capable of characterising the degeneration state of a given fibroid. Fibroid degeneration state has huge implications for determining the potential for and progress of medical management, and for selecting the best surgical approach. The degeneration state of a fibroid can drastically alter its material properties including stiffness, a characteristic that can be measured using SWE. Thus, SWE could provide the missing and necessary information on fibroid degeneration state to inform treatment decisions. Findings from this study has the potential to revolutionize the management of uterine fibroids, leading to more timely diagnoses, reduced surgical time and complications, better inform decisions for medical therapies and, ultimately, safer, more effective, and less costly care.

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