The Fibroid Growth Study (FGS): General Overview

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Abstract

Objectives: The objective of the FGS is to investigate the growth dynamics of uterine leiomyomas in a clinically relevant population of women. The underlying hypothesis is that uterine leiomyomas are heterogeneous in terms of their growth characteristics and in their clinical symptoms or outcomes, and that differences in leiomyoma growth dynamics can be discriminated by molecular markers and cellular phenotypes. The purpose of this poster is to present the overall study design and a basic description of the participant population, as well as the status of data analysis.

Methods: Participants included 120 premenopausal women with at least one uterine leiomyoma equal to or greater than 2 cm in diameter and/or at least an 8-wk gestational uterus size due to multiple leiomyomas. Magnetic resonance image (MRI) scans were conducted at the first visit and then at about 3, 6, and 12 months. Every participant had a physical exam and provided urine and blood samples at the time of each scheduled MRI. Every participant responded to an initial extensive telephone-administered questionnaire followed by abbreviated monthly questionnaires. When surgery was required as standard care, MRI was conducted before surgery and the surgical pathologist mapped uterine leiomyomas for comparison to MRI.

Results/Conclusion: The participant population provides a reasonable sample from which to conduct our analysis. Preliminary analyses of growth and histopathology have been conducted.

Background and Significance

- Uterine leiomyomas are the most common type of reproductive tract tumor in women. They are **the leading cause for hysterectomy**, with symptoms and complications accounting for one-third of all hysterectomies in the United States. Symptoms include heavy bleeding, pelvic pressure, severe cramping, pain, infertility, and miscarriage. However, in most cases, leiomyomas are not symptomatic.
- **Health Disparities:** Uterine leiomyomas are most prevalent in black women. It is estimated that >80% of African American women have leiomyomas by the time they reach menopause, compared to about 70% among whites. Prevalence in other racial and ethnic groups is not known. Black women also have more and larger tumors than white women. Black women have significantly more hysterectomies and myomectomies for treatment, and are typically younger when they undergo these procedures. The cause for this disparity is not known. ***In order to evaluate leiomyomas in the population most at risk for leiomyoma-related symptoms and treatment, recruitment procedures were designed so that about half of our study population were black women. Women of all racial and ethnic backgrounds were encouraged to participate.***
- **The cause of leiomyoma development and growth is not known.** Within the same woman, some leiomyomas grow, others shrink or change very little. There are no previous studies that allow us to predict the expected pattern of growth for clinically identified fibroids.

Study Purpose and Hypotheses

Study Purpose:

- To learn more about why some leiomyomas grow to cause symptoms and complications while others do not.
- It is hoped that the findings from this study may help researchers develop strategies to prevent leiomyomas in women at high risk for problems, or new therapies that may reduce the need for radical surgical procedures like hysterectomy.

Hypotheses:

1. Uterine leiomyomas are heterogeneous in terms of their growth characteristics and clinical symptoms and/or outcomes.
2. Differences in leiomyoma growth dynamics can be discriminated by molecular markers and cellular phenotypes. The development of such markers for growing and/or clinically relevant leiomyomas will be important in future studies of the etiology, therapy, and prevention of these leiomyomas.

Experimental Design

- 120 women with large and/or multiple leiomyomas participated in this study. Participants were premenopausal, had one or more leiomyomas, and spoke English. In addition, they had one or both of the following characteristics, as confirmed by ultrasound imaging:
  - At least one leiomyoma that was 5 centimeters or more in diameter, and/or
  - A uterus enlarged to the size typical during the 12th week of pregnancy due to multiple tumors.
  - Criteria were changed to at least one leiomyoma that was 2 cm or more in diameter and a uterus enlarged to the 8th week of pregnancy for the last 16 women enrolled in order to increase data for small tumors.
- These women had up to four study-related visits to a clinic at University of North Carolina (UNC) Hospitals over a one-year period. Visits included a physical exam, blood/urine collection, and Magnetic Resonance Image (MRI) scans.
- Participants also completed an initial comprehensive telephone questionnaire, followed by monthly telephone updates. Questions relating to medical, menstrual, pregnancy, and sexual histories and lifestyle were asked.
- There are various treatment options available for leiomyomas, including surgery. If a woman chose surgery for treatment, we asked her permission to collect and examine post-operative tissues; if the woman had a myomectomy, we asked permission to remove a small piece of normal uterine tissue for comparison to the leiomyoma tissue.
- This study has four specific aims.
  1. Compare leiomyoma growth as a function of leiomyoma multiplicity and location by MRI analysis in women with high risk for surgical intervention (i.e., hysterectomy/myomectomy)
  2. Examine the relationship between leiomyoma growth and clinical symptoms or outcome.
  3. Identify molecular, cellular, and pathological characteristics of the leiomyomas with differing growth dynamics.
  4. Examine endocrinological parameters and lifestyle factors related to differential growth dynamics of uterine leiomyomas.

Recruitment Techniques

- **52%** recruited through the physician network within the UNC hospital system.
  - PRIMARY METHOD: Clinicians in the OB/GYN ultrasound clinic described the study to women who met requirements and forwarded their name to the study nurse for follow-up
  - SECONDARY METHODS:
    - Distribution of brochures to OB/GYN and family practices within the hospital network
    - Grand Rounds presentation
- **13%** recruited from bookmarks placed in area libraries
- **13%** recruited from the study website
- **11%** recruited by word of mouth (through family & friends)
- **11%** recruited by other methods, including press releases and public service announcements on the radio

Specific Aim 1: Compare leiomyoma growth as a function of leiomyoma multiplicity and location by MRI analysis in women with high risk for surgical intervention (hysterectomy/myomectomy)

Image Capture: MR sequences were conducted in the transverse and saggital planes and included pre-contrast T1-weighted spoiled gradient echo (SGE)and T2-weighted, fast spin echo (FSE) sequences.

Image Analysis: Developed a computer-aided image analysis system, Volume Estimation and Tracking Over Time (VETOT) to accurately assess growth using MRI. ***See the Guyon et al. poster for details on this software.***

Growth Analysis: Preliminary findings determined by grouping tumors into specific size categories indicate that there are significant differences in growth rates between some of the size categories (i.e., medium and large tumors appear to have a faster growth rate than small tumors). A leiomyoma growth model is currently under development. ***Preliminary findings are being presented at 1:30 on Thursday by Dr. Barbara Davis.***

Specific Aim 2: Examine the relationship between leiomyoma growth and clinical symptoms or outcome.

A preliminary analysis of clinical symptoms (pain, discomfort, and bleeding) compared with outcome (surgery, no surgery) has been initiated. We have developed the following scores:

- **Perceived bleeding score**, which was developed based on the extent to which the participant feels that menstrual bleeding is interfering with her work and personal activities.
- **Combined bleeding score**, which took into account number of days of menstrual cycle bleeding, whether heavy or gushing-type bleeding occurred, the number of pads/tampons used during the days of heaviest bleeding, and whether high absorbency pads/tampons were used.
- **Pelvic pain and discomfort scores**, which is based on the participant's reporting of the amount of pain and discomfort she experienced.

Each score is on a scale of 0 to 100, with 100 representing the highest symptom score. Preliminary findings indicate that all four of these scores are higher for the surgical category than for the non-surgical category. The analysis of growth compared to symptoms will be completed in the future using these scores.

Specific Aim 3: Identify molecular, cellular, and pathological characteristics of the leiomyomas with differing growth dynamics.

Microarray analysis: Leiomyoma and normal tissue have been microarrayed. Leiomyoma samples will be analyzed for histopathologic and molecular changes correlated with growth when the growth analysis is complete. ***See the Clarke et al. poster for preliminary general findings.***

Special stain analysis: Preliminary analysis of Ki67 (cell proliferation), Trichrome (%fibrous connective tissue), and Factor VIII (vascularity) slides were conducted. ***See the Davis et al. poster for details.***

Specific Aim 4: Examine endocrinological parameters and lifestyle factors related to differential growth dynamics of uterine leiomyomas.

Endocrinological parameters: Changes in serum and urine hormones such as increases in estrogen, progesterone, and luteinizing hormone (LH) will be measured and correlated with growth. Hormone (estrogen, progesterone, human chorionic gonadotropin hCG, LH) receptor expression will be examined in both normal and tumor tissue. Metabolic factors (obesity, alterations in energy, insulin, and glucose) will also be examined.

Lifestyle factors: Data on diet, smoking, alcohol use, and exercise were collected monthly from telephone interviews and will be analyzed with growth.

Description of Participant Population

Number of MRI Time Points Completed by Treatment Group

	0 MRIs	1 MRI	2 MRIs	3 MRIs	4 MRIs	Total	Percent
Myomectomy	0	6	5	4	12	27	22%
Hysterectomy	0	9	3	1	4	17	14%
Embolization	0	0	2	0	0	2	2%
No Treatment	2	8	13	15	36	74	62%
Total	2	23	23	20	52	120	
Percent	2%	19%	19%	17%	43%		

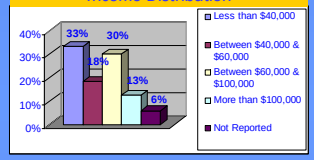
Race

Black	48%
White	41%
American Indian/Alaskan Native	1%
Asian or Pacific Islander	1%
Other	8%
Not Reported	1%

Ethnicity

Hispanic	4%
Not Hispanic	95%
Not Reported	1%

Income Distribution

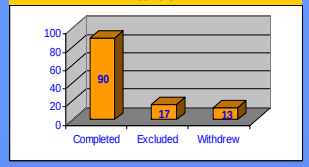


Body Mass Index (BMI)

Average BMI: **28.12** (16.5-52.2)

BMI Range	Category	Percent
<18.5	Underweight	1%
18.5 to 24.9	Normal	36%
25 to 29.9	Overweight	32%
>30	Obese	31%

Attrition



**Reasons for exclusion/withdrawal included:
- Started taking Lupron
- Planning pregnancy
- Non-compliance
- Study-related concerns (claustrophobic, blood draws, reimbursement schedule)

Age

Average Age (all participants): **39.1** (24-54)
Average Age (participants that did not undergo surgery): **40.0** (24-54)
Average Age (participants that elected surgery): **37.8** (26-49)

Reason for Surgical Intervention

Heavy Bleeding	8 (40%)
Attempting Pregnancy	4 (20%)
Pelvic Pain or Discomfort	2 (10%)
Sexual Pain or Discomfort	1 (5%)
Frequent Urination	1 (5%)
Other	5 (25%)
Total	**20**

Tissue Collection from Surgery Patients

Surgery Type	Tissue Collected	No Tissue Collected	Total
Hysterectomy	12	5	**17**
Hysteroscopic Myomectomy	2	1	**3**
Myomectomy	17	7	**24**
Embolization	0	2	**2**
Total	**31**	**15**	**46**

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This study is approved under the annual review of IRB 01-E-N209 at the DHHS NIH NIEHS and GCRC-1762 at UNC.

Visit the study website at http://www.niehs.nih.gov/fibroids.