

# **Status of Research on Uterine Fibroids (leiomyomata uteri) at the National Institutes of Health**

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## **Introduction**

Uterine fibroids (leiomyomata uteri) are the most common benign (non-cancerous) tumors that are present in the muscular wall of the uterus of women over 30 years of age and are more common in African American women (1-2). According to current textbooks of medicine, it is estimated that leiomyomas are present in 20-25 percent of reproductive age women but are 3 - 9 times more frequent in black than in white women (3). However, a recently completed epidemiological study of uterine fibroids by the National Institute of Environmental Health Sciences (NIEHS) (4) found that by age 50 the cumulative incidence of uterine fibroids was over 80 percent for African American women and about 70 percent for white women. These numbers are much higher than reported from medical records. The differences suggest that while many women have fibroids, not all have clinically symptomatic fibroids and seek medical care. Data suggests that large fibroids cause more symptoms than small fibroids, leading scientists to question what causes fibroids to grow and become clinically symptomatic.

However, fibroids are one of the leading causes for hysterectomy in the United States. Even though they are benign, fibroids may cause reproductive problems such as uterine enlargement, heavy or abnormal uterine bleeding, pelvic pressure, severe cramping, pain, infertility, and miscarriage. Research is beginning to provide information about why fibroids develop or why they grow.

Fibroids result in a substantial cost to the United States health care system. A recent study (5) has found that the disease results in 2.1 billion dollars in direct costs annually, 1.7 billion of which are a direct result of inpatient hospital costs due to hysterectomy. These expenses are disproportionately borne by African-American women due to the increased prevalence of the condition in that racial and ethnic group (6). Building upon their studies of gene regulation in uterine fibroids (7-9), National Institute of Child Health and Human Development (NICHD) intramural investigators have noted similarities between fibroids and keloids, a disorder of wound healing that is also increased disproportionately in African-Americans (10). The NICHD intramural team has noted that the shared abnormalities in formation of connective tissue between keloids and fibroids raise the possibility of a genetic predisposition that may explain the increased prevalence of the two conditions (11,12). The results of these studies build upon the Fibroid Growth Study conducted by the National Institute of Environmental Health Sciences (NIEHS), that revealed fibroid growth greater than 3 inches (5 centimeters) was largely due to deposition of connective tissue, not an increase in cell number (13).

There has been much recent attention to research on uterine fibroids, and progress is beginning to be encouraging and revealing. In a trans-NIH effort, the Office of Research on Women's Health (ORWH) served as the lead convener to a February 2005 conference entitled, *Advances in Uterine Leiomyoma Research: 2<sup>nd</sup> NIH International Congress*, held at NIH (14, 15). Primary NIH sponsors included: the National Institute of Child Health and Human Development (NICHD), the National Institute of Environmental Health Sciences (NIEHS), the National Cancer Institute (NCI), the National Center for Research Resources (NCRR) and the National Institute of Biomedical Imaging and Bioengineering (NIBIB); other collaborators were the Centers for Disease Control and Prevention (CDC), Food and Drug Administration (FDA), Agency for Healthcare Research and Quality (AHRQ), Health Resources and Services Administration (HRSA), Substance Abuse and Mental Health Services Administration (SAMHSA), and Office on Women's Health (OWH), Office of the Secretary, Department of Health and Human Services (DHHS), representing a truly comprehensive effort to assess the current state of knowledge about fibroids. This conference brought together extramural and intramural researchers from across the United States and from other countries, clinicians, patient advocates, and others to explore such timely topics as the disease burden and clinical manifestations of fibroids, and the epidemiology, genetics, and pathobiology of fibroids. There was much excitement as advances in knowledge and new research tools were described. The summary of this conference is in press (15).

One major development resulting from a recommendation during the international congress was the collaboration of the ORWH with NICHD intramural investigators to establish a fibroid tissue bank that will promote research on fibroid disease by providing access to tissue samples for NIH-funded investigators throughout the world.

### The National Institute of Environmental Health Sciences (NIEHS)

Despite the morbidity and high medical costs associated with fibroids, there has been little epidemiological study of this condition. African-American women have been thought to be at higher risk, but because this supposition was based on hysterectomy statistics, it was not known if this was a true difference or was due to differences in diagnosis and treatment. The NIEHS Uterine Fibroid Study, an epidemiologic study of uterine leiomyomata in women age 35-49, randomly selected from membership in a prepaid health plan in Washington, DC, was initiated in 1996 to better define the cause of this health disparity. Ultrasound screening of premenopausal women and medical record review of surgically menopausal women provided data to estimate age-specific cumulative incidence. The data showed that more than 80 percent of black women and about 70 percent of white women develop fibroids before they reach menopause. Health disparity issues for uterine fibroids are reflected in the high prevalence statistics and in the fact that African American women have larger and more numerous tumors. Data from the study have been analyzed to identify risk factors for fibroids. Earlier menopause, fewer births after age 24, alcohol intake, and a physically inactive lifestyle were factors associated with fibroid development in both African American and white women. Prenatal DES exposure and higher circulating LH levels (Luteinizing Hormone – a hormone produced by the pituitary to promote ovulation) were also linked to fibroid

development. NIEHS is currently examining vitamin D and IGF-1 (Insulin-like Growth Factor-I – a protein found in tissue and blood that stimulates the growth of cells). Participants in the study were recontacted in 2001 and 2004 to monitor symptom development and treatment choices. The following site provides a description of the NIEHS study on fibroids: <http://dir.niehs.nih.gov/direb/studies/ufs/home.htm>

**Uterine Fibroid Growth Study:** The Fibroid Growth Study is designed to investigate why some fibroids grow to become health problems while others do not. Funding is provided jointly by the NIEHS and the National Center for Research on Minority Health and Health Disparities (NCMHD). Scientific direction and oversight is provided by NIEHS. The University of North Carolina Hospitals, the General Clinical Research Center and the Integrated Laboratory Systems, Inc. are collaborators in this research. The study has four specific aims. First, fibroid growth will be evaluated over time by magnetic resonance imaging (MRI). Second, the relationship between fibroid growth and symptoms or outcome (i.e., surgery/no surgery) will be determined. Third, markers that may be related to growth will be identified. Lastly, hormone and lifestyle factors that may be related to fibroid growth will be examined. It is hoped that the findings from this study will help develop strategies to prevent fibroids in women at high risk for problems and develop new therapies that reduce the need for radical surgical procedures like hysterectomy. More information about the Fibroid Growth Study is available at: <http://www.niehs.nih.gov/fibroids/home.htm>

**Environmental Estrogens and Fibroids - a Rat Model:** The environmental components of this disease, such as exposures to estrogens, phthalates, and solvents are currently under study using exposure assessment methods in women with fibroids coupled with mechanistic studies in cell culture systems and animal models. One hypothesis derived from mechanistic studies is that uterine smooth muscle tumor cells closely resemble normal uterine smooth muscle cells during pregnancy but have escaped controls that cause these cells to regress or die. Specifically, the pregnancy-like phenotype allows these cells to proliferate in response to estrogens, estrogen-like compounds, and other environmental cues. However, the neoplastic cells fail to regress or die as do normal smooth muscle cells at the time of parturition (delivery) when supraphysiological levels of prostaglandins, oxytocin, and other parturition-related hormones trigger the contractile response of the uterus during labor and remodeling of the uterus after delivery. Studies conducted using the Eker rat as an animal model for uterine leiomyoma support the research hypothesis. For example, treatment of young rats with estrogenic compounds like diethylstilbestrol (DES) accelerates the growth of the leiomyoma, while tumor incidence in aged rats is significantly reduced with multiple pregnancies and deliveries. The NIEHS/NCMHD epidemiologic study on fibroids has confirmed these relationships in women: pregnancy is protective, and prenatal exposure to DES is associated with increased incidence of fibroids in adulthood.

**Environmental Estrogens and Fibroids - *In Vitro* Human, Potbellied Pig, and Mouse Comparisons/Model Systems:** Intramural research at the NIEHS has focused on defining the pathogenesis of fibroids in humans and model systems, and in assessing the role of environmental and endogenous factors in the induction of this disorder. *In vitro* model

systems for studying fibroids are limited in that human derived leiomyoma cells grow poorly in culture and begin to senesce early. Investigators at the NIEHS have overcome these obstacles with the creation of an hTERT immortalized uterine leiomyoma cell line. This cell line will help to advance *in vitro* research in understanding the mechanisms of fibroid development and in identifying targets for treatment intervention strategies. The NIEHS is also assessing the utility of the potbellied pig as a model for spontaneously occurring fibroids. Unlike commercially raised hogs, potbellied pigs provide an aging population, with the life span estimated to be as long as 20-25 years, with an average of 10-15 years. Intact potbellied pig females are subject to cyclic hormonal influences about every 21 days, somewhat approximating the year-round cyclic hormonal influences of the menstrual cycle in women. The potbellied pig appears to have a high incidence of spontaneous fibroids, previously unrecognized due to the low-density and scattered distribution of pet pigs. Studies are underway to understand the biological relevance of these tumors to fibroids found in women. In determining the role of environmental agents in fibroid growth and development, researchers at the NIEHS have found that in mice, prenatal and neonatal exposures to DES result in uterine leiomyomas similar to those observed in women. This model will be useful in elucidating molecular mechanisms by which environmental agents possibly induce or influence this disease.

An NIEHS grantee at the University of Texas MD Anderson Cancer Center is working to understand the etiology of uterine leiomyoma at the molecular level and to elucidate the molecular mechanisms by which exposure to endocrine disruptors may impact the development of these tumors. One of the aims of this project is to determine if loss a tumor suppressor gene function is an alternative pathway for development of leiomyoma. In addition this researcher is attempting to determine if the prepubertal period is a window of susceptibility for exposure to environmental exposures and determine at the molecular level whether this exposure impacts the expression of genes that may contribute to the development of leiomyoma. These experiments will yield new insights into the molecular mechanisms responsible for the altered responsiveness of uterine leiomyomas to endogenous and exogenous hormones and increase our understanding of the potential mechanisms by which exposure to endocrine disruptors could contribute to the development of this disease.

Another NIEHS funded study at Vanderbilt University proposes to significantly increase our understanding of environmental toxins and uterine gene expression. Specifically, the investigators describe a series of experiments to elucidate the mechanisms underlying the early and late estrogenic responses. They propose to test the hypothesis that the early responses are estrogen receptor independent, but that they initiate a cascade of events to prepare targets for the later estrogenic dependent events. Determination of this early and late response cross talk may provide information translatable to other estrogenic target tissues and may provide a better understanding of how fibroids develop. Finally, these studies may provide essential mechanistic data to evaluate how environmental toxins influence uterine disease.

## National Cancer Institute (NCI)

Uterine fibroids or uterine leiomyomata (singular: leiomyoma) are the most common gynecologic tumors in women. Although they are usually non-cancerous, they are often associated with infertility and account for about 200,000 hysterectomies and 18,000 myomectomies performed annually in the U.S. The following are summaries of NCI-funded projects related to uterine fibroids research:

A project directed at resolving the controversy concerning the relative contributions of progesterone and estrogen in the development of leiomyomas will use normal and neoplastic myometrium (muscular wall of the uterus) to examine the hormonal mechanisms that regulate the process. The study uses a progesterone receptor (PR) knockout mouse to study the role of PR in myometrial proliferation and tumorigenesis. Results from this study will provide insight into factors affecting leiomyomata development and could help in designing better therapy. The availability of DNA microarray technology has resulted in gene expression data for many types of tumors, and the researchers of one study are developing data mining tools and computer programs for analysis of this data with the long-term goal of applying these methods to cancer discovery and classification. Uterine leiomyomata are among the tumor types being studied in this grant.

## National Center for Research Resources (NCRR)

The National Center for Research Resources develops and supports critical research technologies and resources which underpin and advance health-related research supported by the NIH and other research organizations. Through the General Clinical Research Center (GCRC) and the Research Centers in Minority Institutions (RCMI) Programs, NCRR supported four fibroid research subprojects in FY 2005. In the future, NCRR will continue to support the clinical research infrastructure for investigators conducting fibroid research.

Scientists at the University of North Carolina, Chapel Hill General Clinical Research Center are developing strategies to prevent fibroid problems and new therapies that may reduce the need for radical surgical procedures like hysterectomy.

At the GCRC at Pennsylvania State University Hershey Medical Center, scientists are using serial ultrasound to determine if oral contraceptives accelerate fibroid growth and accelerate the development of new fibroids in women with existing fibroids.

Scientists at Meharry Medical College utilize the RCMI-supported Clinical Research Center to collaborate with investigators at Penn State. They are determining the role of oral contraceptives in the development and growth of uterine fibroids using serial ultrasound evaluations in African American and Hispanic women. In addition, scientists are also evaluating serum and urine levels of sex steroids to determine if African

American women produce higher levels of these hormones than their Caucasian and Hispanic counterparts. These studies are of particular interest because of the increased prevalence of uterine fibroids in African American women as compared to other racial and ethnic groups in the United States.

### National Institute of Child Health and Human Development (NICHD)

Uterine fibroids constitute a significant public health concern. While uterine fibroids represent the most common gynecologic tumor in women, the mechanisms that initiate uterine fibroids growth and pathogenesis are not completely understood. This disorder is clinically important because it is a significant source of abnormal uterine bleeding, anemia, and pelvic pain and pressure. These symptoms frequently lead to various medical and/or surgical interventions. Surgical procedures are of primary concern because uterine fibroids remain the leading indication for a hysterectomy in the United States. Thus, both the economic costs and effect on quality of life can be substantial. Increased emphasis on a condition that poses a serious reproductive threat for many women and represents a disproportionate burden for African American women would enhance our ability to preserve the fertility and reproductive health of all women.

NICHD Initiatives: Several recent NICHD-sponsored research initiatives have been announced. The objectives of these initiatives are to strengthen research in this critical area of women's health, contribute to reducing the burden of this disease, and improve the quality of life for women affected with this disorder. The Leiomyomata Uteri: Basic Science and Translational Research Program, in collaboration with ORWH, supports eight projects funded in 2003. The Cooperative Reproductive Science Research Centers at Minority Institutions Program, in collaboration with ORWH and NCCR, supports a clinical research project on uterine fibroids at Meharry Medical College. The Women's Reproductive Health Research (WRHR) Career Development Program, in collaboration with ORWH, is an ongoing training and career development program for junior ob/gyn physician scientists. The WRHR Program is located at 20 medical schools and universities nationwide.

Overview of NICHD Research: To address the need for increased attention in this area, the NICHD in collaboration with ORWH sponsored the Leiomyomata Uteri: Basic Science and Translational Research Program. The long-term goals of this initiative include strengthening the science base, improving our understanding of how uterine fibroids develop and grow, and providing clues to more effective conservative management that would go a long way to preserve the fertility and reproductive health of all women.

The eight NICHD extramural projects that were funded in the fall of 2003 highlight major areas of basic science and translational research. In one study, the investigators are examining how female sex hormones activate specific proteins that may promote uterine cell proliferation and tumor growth through the creation of a microarray that is suitable for profiling the expression of selected genes in women of different ages and racial

groups. Another research project is initiating a genome-wide screen to characterize the genetic pathways and genetic liability for developing uterine fibroids, with particular emphasis on racial overexpression in African American women. One other project is investigating the pathophysiology of uterine fibroids from the point of view of gene interactions. Understanding cell death and cell survival pathways active in uterine fibroids may help explain long-term tumor regression. To increase our understanding of the molecular mechanisms of estrogen-dependence in uterine fibroids, scientists are investigating the relationship with the immune response and treatment associated with a selective estrogen receptor modulator in animal and human cell lines.

In another study, the focus is on selected enzymes responsible for estrogen biosynthesis that are produced locally in uterine fibroids and the critical roles they play in the growth and development of fibroids. One line of research is targeting the role that growth factors and hormones play in the pathogenesis of uterine fibroids. The investigators are reviewing gene interactions and their relationships to hormones and connective tissue that may contribute to fibroid growth. To advance our current knowledge about the molecular regulation of uterine fibroids, scientists are identifying the mechanisms responsible for cell cycle regulation in uterine fibroids that may explain the differences among tumors. Animal models and human cell lines are being used to assess whether fibroid tumors develop as a response to injury. This type of insult can promote cell proliferation that is stimulated by growth factors and hormones.

Other NICHD-supported extramural scientists are approaching this area of research from several fronts. One research project is exploring how defective cell cycle regulation and estrogen receptor signaling pathways contribute to our understanding the regulatory mechanisms involved in growth and regression of uterine fibroids in women who have received gonadotropin releasing hormone analogues. Another study is investigating the use of high intensity focused ultrasound treatment for uterine fibroids as a new therapeutic modality. To find an effective alternative medical treatment for symptomatic fibroids, investigators are studying an antiprogestin in a clinical trial to determine if there is improvement in the quality of life when compared to a placebo. Since many women with fibroids use oral contraceptives and hormones are thought to stimulate fibroid growth, a clinical trial is enrolling women on oral contraceptives to determine if there is acceleration in the growth rate of their uterine fibroids. Another research project is concentrating on the natural history of fibroids during and after pregnancy. These investigators are also exploring the association of fibroids with specific adverse pregnancy outcomes in a diverse cohort of over 3,000 women from 13 counties in North Carolina.

NICHD intramural investigators have continued to explore the mechanisms responsible for fibroid development and growth through basic and translational research studies conducted on campus, and in collaboration with the NCI, NIEHS, the Department of Obstetrics and Gynecology at the Uniformed Services University of the Health Sciences, and the University of South Florida in Tampa. In the past 3 years the group has conducted and published several research papers on uterine fibroids (6-12, 16, 17). The advances in understanding of disease development arose of genetic studies, which

indicated that uterine fibroids have many features in common with a disorder of pathologic wound healing, keloids. The connective tissue generated by the cells comprising uterine fibroids is markedly abnormal and this fact may contribute to fibroid growth, as abnormally-formed connective tissue can not be remodeled and absorbed as would normally-formed connective tissue. Collectively, the results of the studies suggested that the abnormal secretion of this connective tissue may contribute the persistence and growth of uterine fibroids (12). These findings may explain why some therapies (such as GnRH agonist) provide only temporary reduction in size, and do not result in long-term benefit.

The NICHD intramural team has also initiated clinical trials of new medical therapies for uterine fibroids that do not induce a ‘medical menopause.’ A current trial should be concluded within a few years. A second trial using a medication designed to interfere with formation of the connective tissue is being launched, based upon the translational studies conducted by NICHD investigators. A third line of clinical research pursued by NICHD investigators involves genetic conditions where uterine fibroids are associated with renal cancers in collaboration with other investigators at the NIH.

Studies have shown that African-American women pursuing advanced treatment for infertility, such as in vitro fertilization, do not achieve the same rates of success as Caucasian women for reasons that were unclear but access to medical care was suspected to be a factor. In the past two years, NICHD intramural investigators examined this issue in a setting where access to medical care was not a barrier to care. The team observed that, in fact, the presence of uterine fibroids in African-American women was largely, if not entirely, responsible for the reduction in success of advanced infertility treatment (18).

#### Office of Research on Women’s Health (ORWH)

ORWH considers research related to uterine leiomyoma (fibroids) and other benign gynecologic disorders as important priorities for women’s health research. Given the prevalence of these conditions in all women, and the health disparities found for this disorder among women of color, ORWH has actively collaborated across the NIH, with other Federal partners, the extramural scientific community and advocacy groups to expand research in this area.

ORWH served as the lead convener to a February 2005 conference entitled, *Advances in Uterine Leiomyoma Research: 2<sup>nd</sup> NIH International Congress*, held at NIH (14, 15). Primary NIH sponsors included: NICHD, NIEHS, NCI, NCCR, and NIBIB; other collaborators were CDC, FDA, AHRQ, HRSA, OWH, and SAMHSA. This conference brought together extramural and intramural researchers, clinicians, patient advocates, and others to explore such timely topics as the disease burden and clinical manifestations of fibroids, the epidemiology, genetics, and pathobiology of fibroids. The conference also included extensive discussions of recent advances in the clinical management, translational research frontiers, including clinical trials and new therapeutic targets that are being evaluated for the treatment of fibroids.



ORWH has maintained and expanded its collaborations to co-fund of research related to uterine fibroids with several NIH institutes and centers, as well as with AHRQ. During fiscal year 2005, ORWH co-funded a number of research grants that focus on the basic science related to uterine fibroids, the study of the alternatives to hysterectomy and intermediate outcomes of hysterectomy.

The ORWH is co-funding with NICHD a basic science initiative that focuses on leiomyomata uteri, with a special emphasis on the biological processes that lead to their development, and their long-term sequelae. The objective of this important program is to strengthen research in this critical area of women's health, contribute to reducing the burden of this condition, and improve the quality of life for women affected with this disorder. Some of these grants focus on identifying genes that predispose women to develop fibroids and the genetic contributions to the etiology, growth and natural history of these tumors, and possible gene-environment interactions. Factors related to the immune response that may permit the use of targeted therapies are being evaluated in another project and may eventually serve as a non-surgical alternative. Numerous studies are focusing on the molecular mechanisms of estrogen-dependence in certain fibroid tumors, and the molecular regulation of uterine leiomyoma. Additional projects focus on elucidating the cellular, molecular and biochemical mechanisms regulating the proliferation and motility of human uterine smooth muscle cells.

ORWH is currently co-funding a major research study with AHRQ that focuses on uterine fibroids, alternatives to hysterectomy and intermediate outcomes of hysterectomy. This project expands on a prospective longitudinal study of 811 women with non-cancerous uterine conditions of which uterine fibroids are the most common and for which hysterectomy is considered a reasonable treatment option. These conditions also include abnormal bleeding, symptomatic uterine leiomyomata, and pelvic pain or endometriosis. This study addresses the differences in clinical and quality of life outcomes at 4 to 8 years among women who have participated in three different treatment options (hysterectomy, uterus-preserving surgery, or non-surgical treatments) for their uterine conditions. This study will also develop predictive models of treatment choice and satisfaction from a broad array of domains.

New in fiscal year 2005, ORWH funded with NICHD the establishment of the first ever *Leiomyoma Tissue Bank* to address the problem of tissue availability for research. This tissue bank will provide samples to NIH-funded investigators and Department of Defense investigators on an on-going basis, thereby facilitating expanded research activities focusing on fibroids.

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