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 the most 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 epidemiolgical study of uterine fibroids by the National Institute of Environmental Health Sciences (NIEHS) (Baird et al, Am J Obstet Gynecol. 2003; Baird and Dunson, Epidemiology 2003) 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. NIEHS investigators are addressing this question in a clinically relevant population of women enrolled in the Fibroid Growth Study (see NIEHS section).

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. For example, scientists at the National Institute of Child Health and Human Development (NICHD) and the University of South Florida, Tampa, have identified 145 genes that are involved in the development and growth of uterine fibroids. The study also provided evidence that susceptibility to uterine fibroids is passed from father to daughter. This study and others like it will help to better understand how fibroids grow and to develop new therapies to treat women who have them. It is also possible that fibroids may grow in response to environmental factors, such as diet, smoking, exercise, or exposure to certain chemicals.
The National Institutes of Health (NIH), and specifically the Office of Research on

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[1] Robbins Pathologic Basis of Disease (6th Ed); 1999. p.1063.

[2] Blaustein's Pathology of the Female Genital Tract (5th Ed); 2002 p.564.

[3] DeCherney, A.H., Nathan L. Current Obstetric & Gynecologic Diagnosis & Treatment (9th Ed); 2003. p. 693.

Women's Health (ORWH), consider research on uterine fibroids to be among the top priorities for women's health research, and efforts are underway to address this condition through new research. Fibroid research will continue to be a priority and we will continue to encourage and fund new research on this condition that affects so many women.

The following provides examples of research on uterine fibroids being conducted by the NIH:

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. Indications are that African-American women are at higher risk, but because this supposition is based on hysterectomy statistics, it was not known if this is a true difference or is due to differences in diagnosis and treatment. The NIEHS Uterine Fibroid Study, a cross-sectional epidemiological study of uterine leiomyomas in women age 35-49, randomly selected from membership in a prepaid health plan in Washington, DC, was initiated 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 show 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. African American women are also more likely to have surgical interventions such as myomectomy and hysterectomy compared to Caucasian or Hispanic women. The following site provides a description of the NIEHS /National Center on Minority Health study on fibroids: http://www.NIEHS.

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. 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/National Center on Minority Health and Health Disparities 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 and Mouse Comparison: The Comparative Pathobiology Group has focused its research on defining the pathogenesis/carcinogenesis of disorders affecting the reproductive tract of humans and rodents, and assessing the role of environmental and endogenous factors in the induction of these disorders. Data show that transforming growth factor alpha (TGF-α) is expressed exclusively in malignant uterine smooth muscle cell tumors (leiomyosarcomas) of mice. However, in benign uterine smooth muscle cell tumors (leiomyomas) of mice and women this growth factor is not present. In mice, a positive correlation exists between TGF-α and epidermal growth factor expression, and increased cell proliferation as measured by the expression of proliferating cell nuclear antigen (PCNA) in the malignant uterine leiomyosarcomas.

In women, we have found that IGF-I is overexpressed in uterine leiomyomas compared to normal myometrium during the proliferative phase of the menstrual cycle, and it appears that the IGF-I receptor signaling pathway is important in uterine leiomyoma growth. Studies to assess the role of Bcl-2 and Bax in modulating cell survival and death in human uterine leiomyomas have been conducted. The results show that both positive and negative regulatory proteins of programmed cell death (apoptosis) are present in human uterine leiomyomas and that altered apoptosis does not appear to play a significant role in the development of these tumors. In vitro model systems for studying uterine leiomyomas are limited in that human derived leiomyoma cells grow poorly in culture and begin to senesce early. Researchers have overcome these obstacles with the creation of a hTERT immortalized uterine leiomyoma cell line. Uterine leiomyoma tumorigenesis can be studied in a prospective manner using these immortalized cells. In determining the role of environmental agents in fibroid growth and development, researchers have found that in CD-1 mice, prenatal and neonatal exposures to DES result in uterine leiomyomas similar to those observed in women.

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 Program, NCRR supported one fibroid research subproject in FY 2002. In the future, NCRR will continue to support the GCRC infrastructure for investigators conducting fibroid research.

In FY 2002, NCRR supported scientists at the University of North Carolina, Chapel Hill General Clinical Research Center. These scientists are developing strategies to prevent fibroid problems and new therapies that may reduce the need for radical surgical procedures like hysterectomy.

National Cancer Institute (NCI)

Uterine fibroids or uterine leimyomata (singular: leimyoma) 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 leimyomata 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 leimyomata are among the tumor types being studied in this grant.

National Institute of Child Health and Human Development (NICHD)

As reflected in its mission, the National Institute of Child Health and Human Development (NICHD) supports research on the human reproductive system, which includes research into the causes, treatment and prevention of uterine fibroids, benign tumors also known as leiomyomata. In fact, the Institute's support of uterine fibroid research has increased nearly fourfold since FY 2000, and it plans to continue expanding this important research area in FY 2004.

The NICHD recognized a need for developing more conservative, non-surgical therapies for uterine fibroids. To achieve this goal, the Institute is supporting two research projects to design and test a novel treatment method that uses high intensity focused ultrasound. The first of these studies is developing and refining the treatment equipment; the second is evaluating the safety and efficacy of the treatment method. If successful, these studies will pave the way for future clinical trials. In addition, the NICHD is supporting clinical trials of other non-surgical treatment methods. These trials evaluate the use of different progesterone receptor modulators (which can have both estrogen agonist and antagonist actions) to shrink tumors in pre-menopausal women. If successful, these treatments could significantly lower treatment costs for uterine fibroids and potentially preserve a women's fertility, while improving her reproductive outcomes.

The NICHD is sponsoring several research projects to identify the basic molecular and cellular processes involved in fibroid formation, suppression, or regression; and to understand the roles and interrelationships of certain steroids (especially sex hormones) and genetics in the formation of these tumors. For example, the Institute funds research to develop a modified line of genetically-stable cells that can be used to study the basic cellular processes involved in the stimulation or suppression of fibroid formation. Another project examines the role of certain growth factors on a signaling pathway involved in reproduction that could also be involved in tumor formation. The Institute further supports clinical research that builds on new knowledge about the role of abnormal expression of genes affecting cell growth and growth regulation, and examines the medical treatment and molecular basis of fibroid diseases.

This line of research is of particular interest because African American women are more prone than other ethnic minority groups to develop the conditions of keloids and uterine fibroids. In addition, scientists in NICHD's intramural research program are working with other NIH scientists to elucidate the characteristics of families in which there is a high prevalence of both uterine fibroids and renal cancer (natural history). Intramural scientists also have recently published a number of articles in peer reviewed journals relating to their research on uterine fibroids (see articles).

The NICHD's extramural research program will be expanding very soon. Applications in response to the November 2002 Request for Applications (HD03005), "Leiomyomata Uteri -- Basic Science and Translational Research," (co-funded by OWRH and NIEHS)

were submitted and will be undergoing their second level of review at the September National Advisory Council meeting. The Institute hopes to fund seven to eight new grants in this area, allowing scientists to ascertain the mechanisms of fibroid development and growth.

Office of Research on Women's Health (ORWH)

ORWH and the Research on Women's Health Subcommittee have continued to identify uterine fibroids and other benign gynecologic disorders among the leading areas for which attention should be directed for stimulating new research. ORWH has and will continue to stress the importance of this topic to the scientific community. In addition, ORWH collaborates on research related to uterine fibroids with several NIH institutes and centers (ICs), as well as with the Agency for Healthcare Research and Quality (AHRQ), and is currently co-funding several research grants that focus on uterine fibroids, alternatives to hysterectomy and intermediate outcomes of hysterectomy.

The ORWH is co-funding with NICHD and NIEHS a new RFA that focuses on leiomyomata uteri, the biological processes that lead to their development, and their long-term sequelae. The objective of this important new RFA 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. Proposals in response to this RFA have been received and have undergone NIH scientific review. A number of these grant applications will be funded in September 2003.

The Community Prevention Study (CPS) of the Women's Health Initiative (WHI) ran from 1995 until 2001. One of the studies funded through this program was the ENDOW Study, "Ethnicity, Needs, and Decisions of Women." ENDOW involved diverse ethnic/racial groups, including African-American, Hispanic, Navajo and non-Hispanic white women. The study explored ethnic, geographic, and cultural variations in attitudes and decision-making about hysterectomy and hormone replacement therapy. Study investigators developed and pilot-tested materials appropriate to different socio-cultural groups to enhance women's decision-making, especially as related to surgical versus non-surgical treatment for uterine fibroids.

ORWH has recently or is currently co-funding several research grants with AHRQ that focus on uterine fibroids, alternatives to hysterectomy and intermediate outcomes of hysterectomy. These include:

1. Decision making (Medicine or Surgery) for Abnormal Uterine Bleeding: A randomized clinical trial was conducted to compare the effects of enhanced medical therapy versus hysterectomy on functioning and well-being in premenopausal women with abnormal uterine bleeding such as that associated with uterine fibroids, who had not responded to three months of initial medical management. A further study compared the effects of two types of hysterectomy (supracervical versus total) on the functioning and well-being of women who had

undergone abdominal hysterectomy for abnormal uterine bleeding such as that associated with fibroids. Group differences in quality-of-life, clinical, sexual function, and economic outcomes were examined in 3000 premenopausal women who suffered from abnormal uterine bleeding across four clinical centers. The data from these studies should provide useful information to assist women and their health care providers to determine their course of treatment for uterine fibroids.

2. Intermediate Outcomes of Hysterectomy and Alternatives: This project, begun 2002, 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.
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