The second National Institutes of Health International Congress on advances in uterine leiomyoma research: conference summary and future recommendations

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Objective: To summarize the proceedings of the Advances in Uterine Leiomyoma Research: 2nd NIH International Congress, which was convened on February 24–25, 2005 by the Department of Health and Human Services (DHHS), National Institutes of Health (NIH) in Bethesda, Maryland.

Design: Scientific information was presented at a 2-day conference, which was a collaborative effort of agencies across the DHHS and members of the academic, clinical, and medical communities involved in uterine leiomyoma research.

Conclusion(s): The conference brought together scientists in biomedicine, epidemiology, basic research, therapeutics, and translational medicine and fostered an exchange of scientific information among members of the uterine leiomyoma research and health care communities. This document summarizes this exchange and outlines research needs and recommendations for future research directions. (Fertil Steril® 2006;86:800–6. ©2006 by American Society for Reproductive Medicine.)

Key Words: NIH conference summary, uterine leiomyoma, fibroid, clinical treatment, clinical/basic studies, research recommendations

Uterine leiomyomas (i.e., fibroids, myomas) are the most common gynecologic tumors in women of reproductive age (1–3). As the number one cause of hysterectomy in the United States, with an estimated 200,000 hysterectomies performed annually in women, leiomyomas have a profound effect on women's health (4). Uterine leiomyomas clinically affect 25%–30% of American women; however, an incidence of upward of 77% has been reported (5). They represent an increased burden for African American women, with some studies indicating they are diagnosed three times more frequently than in White women (6, 7). Although uterine leiomyomas are benign tumors of smooth muscle origin that rarely progress to malignancy, they are often associated with reproductive and gynecologic disorders ranging from infertility and pregnancy loss, to pelvic pain, and excessive uterine bleeding (8–12).

Numerous studies have evaluated the hormonal dependency, epidemiology, molecular biology, pathology, and genetics of fibroids (1, 2, 13); yet, many unanswered questions remain related to their etiology and the role of genetic or environmental influences on their pathogenesis. At present, limited noninvasive therapies for fibroids and no early intervention strategies are available (14, 15). This report summarizes emerging advances in the areas of basic, applied, and translational research on uterine leiomyomas, as well as current approaches and therapies for clinical management as presented by scientists at the Advances in Uterine Leiomyoma Research: 2nd NIH International Congress. Future research recommendations as proposed by meeting attendees and participants are also discussed.

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SESSION I. DISEASE BURDEN AND MANIFESTATIONS

Clinical Manifestations and Outcomes of Uterine Leiomyoma

The existing quality of rigorously conducted clinical trials upon which current management of uterine leiomyoma is based is poor (14). Lee Learman, M.D., Ph.D., University of California—San Francisco, approached the topic by criti-

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cally evaluating the strength of evidence supporting a cause-and-effect relationship between common symptoms and development of leiomyomas. Learman emphasized that in many studies of leiomyoma, successful treatment is often incorrectly equated with causality.

In his approach to the literature, Learman used the Hill criteria for causality (16). He emphasized the paucity of natural history studies examining leiomyoma and the relative absence of controlled, prospective cohort studies comparing women with and without disease. Problems with diagnostic accuracy for the presence of leiomyomas were noted, as was the problem that procedures to assess symptoms, such as uterine bleeding (17, 18) or pelvic pain (9, 19), lacked precision or were poorly controlled. Most of the existent reports are cross-sectional, not encompassing prospective cohort studies.

Leiomyomas have been associated with infertility and for this symptom, Learman pointed out that the strength of association was strongest in studies done in women undergoing assisted reproduction techniques (ARTs), as reviewed by Pritts (11).

Although the evidence of association between leiomyomas and many symptoms is weak, Learman cited several retrospective studies relating adverse outcomes of pregnancy to leiomyomas (8, 12). Collectively, these studies point to a strong association of adverse obstetrical outcomes associated with leiomyomas. Learman concluded the presentation by suggesting that additional translational research is needed to improve understanding between the association of leiomyomas and symptoms.

Molecular Characterization of Leiomyomas

Carl Barrett, Ph.D., National Cancer Institute (NCI), NIH in collaboration with Duke University, Walter Reed Army Medical Center, and the National Institute of Environmental Health Sciences (NIEHS), has used DNA microarrays to examine the molecular features of leiomyomas using gene ontology and curated gene sets. Several imprinted genes were found to be up-regulated and statistically significant. Hypoxia-induced genes, which were differentially expressed, were inconsistently up-regulated or down-regulated. Leiomyomas exhibited no clear pattern of dysregulation of insulin-like growth factor (IGF)-I-related genes, but there was an overwhelming up-regulation of IGF-II-regulated genes and collagen genes. Barrett suggested that future molecular characterization studies of expressed genes might focus on pathway analysis and gene expression as a function of growth rate, multiplicity, and chromosomal location. He called for validation of findings in other surgical specimens so that important functional studies might be conducted. In particular, he envisions functional studies to overcome the paucity of relevant animal and cell culture models.

SESSION II. EPIDEMIOLOGY AND GENETICS

The NIEHS Uterine Fibroid Study

Donna Baird, Ph.D., NIEHS, NIH described the NIEHS-Uterine Fibroid Study (UFS), which consisted of a random sample of premenopausal and postmenopausal women. Baird and collaborators found that African American ethnicity and age were important risk factors, and estimated that 80% of African American women and almost 70% of White women will develop uterine leiomyomas by the time they reach menopause (20). In the NIEHS-UFS, Baird found that hormonal and reproductive-related risk factors indicated no significant association between leiomyomas and infertility, shorter menstrual cycles, oral contraceptive use, or breast-feeding. Menarche at an older age appeared protective in both African American and White women, and age at first pregnancy indicated a tendency for higher risk at younger ages and lower risk at older ages.

With respect to infectious and inflammatory factors, no apparent association existed between viral or chlamydial infections and leiomyomas, and little evidence supported an inflammatory etiology. Among environmental factors, alcohol use and exposure to insect repellent showed increased risk, whereas occupational exposure to radiation or chemotherapy drugs was protective in both African American and White women. Other factors evaluated but indicating no association were smoking, caffeine intake, shift work, and exposure to solvents. Baird concluded that after adjusting for all the risk factors she had examined, an unresolved difference exists in the prevalence between African American and White women, and that the risk for African American women is equivalent to a 10-year increase in fibroid development than in comparable White women.

Genetic Links

Cynthia Morton, Ph.D., Brigham and Women's Hospital, Boston, Massachusetts, offered several lines of evidence of a genetic etiology for uterine leiomyomas. She noted that uterine leiomyomas occur three times more frequently in African American than in White women (6, 7), studies of familial aggregation indicate a 2.5-fold increased risk for uterine leiomyomas among first-degree relatives of women with leiomyomas compared to relatives of unaffected women (21), and twin-pair correlations for hysterectomy in monozygotic twins are about twice that observed in dizygotic twins (22). To further address genetic predisposition in the etiology of uterine leiomyomas, an effort is under way in Morton's laboratory, the "Finding Genes for Fibroids" project (http://www.fibroids.net), which is sponsored by the Brigham and Women's Hospital. One goal of the study is to determine whether a mutation in the *fumarate hydratase* (*FH*) gene contributes to uterine leiomyoma predisposition in women that do not have inherited syndromes. Preliminary results indicate that this mutation may predict a predisposition in White women, but does not appear to have a large effect in African American women. Another goal is the establishment of a severity classification scheme that

would subdivide the affected population into more homogeneous groups of severely versus nonseverely affected families, as determined by factors such as age at diagnosis of less than 40 years, two or more fibroid surgeries, and other measurements of leiomyoma disease severity.

Hereditary Leiomyomatosis Renal Cell Carcinoma (HLRCC): A Hereditary Form of Uterine Leiomyoma

Marston Linehan, M.D., NCI, NIH, described a hereditary form of uterine leiomyoma known as hereditary leiomyomatosis renal cell carcinoma (HLRCC), a cancer syndrome with an autosomal dominant hereditary pattern. Many HLRCC patients are at risk for developing uterine and cutaneous leiomyomas in addition to renal cell carcinoma. As part of The NCI Familial Kidney Tumor Program, 55 families were studied for HLRCC by Linehan and colleagues. Of the HLRCC families having several members affected with kidney tumors, nearly 100% of female germ-line carriers had uterine leiomyomas. Approximately 75% of the women studied were diagnosed with uterine leiomyomas before the age of 30 years, and 73% of the affected women had undergone myomectomy or hysterectomy. Fifty percent of the surgical cases had a myomectomy or hysterectomy before the age of 30 years.

Linehan, discussed the *FH*gene that codes for fumarate hydratase, the enzyme that catalyzes the conversion of fumarate to malate in the tricarboxylic acid (Krebs) cycle. Interestingly, *FH*mutations have been observed in about 90% of the HLRCC families (23). He also described the importance of hypoxia inducible factors (HIF) in stimulating increased glucose and vascular endothelial growth factor (VEGF) expression, which is associated with blood vessel development, and stated that HIF-1 and HIF-2 expression levels are high in HLRCC patients.

SESSION III. THE PATHOBIOLOGY OF UTERINE LEIOMYOMA

The Fibroid Growth Study

Barbara Davis, V.M.D., Ph.D., AstraZeneca (formerly NIEHS, NIH), presented data on the Fibroid Growth Study (FGS), sponsored by the NIEHS and the National Center on Minority Health and Health Disparities (NCMHD). In the FGS, women with fibroids as determined by ultrasound were recruited with a balanced population of race and ethnicity. Fibroid growth was measured over a 1-year period using magnetic resonance imaging (MRI). The investigators found that size and location were significant in influencing the change in volume of fibroids. They noted the rate of tumor growth was similar among women of different races or ethnicity, and did not differ among women that elected surgery. Scores for bleeding, pain, and discomfort were higher in presurgical patients than nonsurgical and postsurgical patients, and Davis surmised that these data indicate a difference between the groups that is not necessarily related to leiomyoma growth.

In tissue samples collected from surgical patients, significant amounts of fibrous tissue were identified in leiomyoma samples compared with smooth muscle tissue. Davis suggested this was indicative of fibrous tissue contributing to the growth instead of the regression of leiomyomas.

New Insights into Signaling Pathways That Regulate Uterine Leiomyoma Growth

The role of reactive oxygen species (ROS) as second messenger-molecules in the activation of signaling pathways of growth factors in primary cultures of leiomyoma and myometrial smooth muscle cells (SMCs) was discussed by Romana Nowak, Ph.D., University of Illinois, Urbana. In the studies presented, she found that in uterine smooth muscle and leiomyoma cells, both platelet-derived growth factor (PDGF) and epidermal growth factor (EGF) caused a detectable increase in ROS production in a time-course-dependent and dose-dependent manner. She demonstrated that when cells were exposed to a ROS inhibitor, a dose-dependent inhibition of increased proliferation by PDGF was observed, and that exogenous ROS mimicked the effect of the growth factor by showing a 20% increase in DNA synthesis.

Speculation on the role of angiotensin II and oleic acid in uterine leiomyoma cell growth was also addressed. Nowak noted that it has been shown binding of angiotensin II not only activates its own pathway, but also transactivates tyrosine kinase growth factor receptors including EGF, PDGF, and IGF-I (24). She suggested that this transactivation is dependent upon the production of ROS, and is one way that angiotensin II can affect uterine leiomyoma growth. Similarly, oleic acid is reportedly mitogenic for smooth muscle cells via increases in ROS production. In summary, Nowak commented on the importance of ROS-activated growth factor signaling pathways in stimulating uterine leiomyoma growth.

Developmental Programming: How Early Life Exposure Influences the Occurrence of Leiomyoma in Adults

To study the combination of genetic susceptibility and environmental exposure during uterine development, Cheryl Walker, Ph.D., University of Texas, Houston, M. D. Anderson Cancer Center, and her colleagues treated Eker rats (model with defect of the tuberous sclerosis complex 2 (Tsc-2) tumor-suppressor gene with diethylstilbestrol (DES) postnatally. They found that wild-type animals did not develop tumors at 16 months when exposed to DES, thus indicating that the environmental E exposure itself was not sufficient to induce tumors. Sixty-four percent of the Tsc-2 carrier rats that were exposed to the vehicle only developed tumors, a typical rate of occurrence; however, in carrier rats exposed to DES, tumors developed in 92% of the cases. In addition, increases in multiplicity and tumor size were observed when compared with the vehicle controls. In summary, Walker suggested that on the basis of the evidence

from her studies, early life exposure to DES may reprogram the normal response of the target tissue and, in association with a genetic defect, drive tumor development in genetically susceptible animals.

SESSION IV. POSTER WEBSITE

Excerpts of the meeting posters may be viewed online at http://orwh.od.nih.gov/health/uterinefibroidmtg.html.

SESSION V. ADVANCES IN CLINICAL MANAGEMENT AND TRANSLATIONAL FRONTIERS

What Do We Really Know about Management of Uterine Leiomyomas?

Duke University, in partnership with the Agency for Health Care Research and Quality (AHRQ) and a Technical Expert Advisory Group, conducted a review (25) on the topic of optimal management strategies for uterine leiomyomas as nominated by the American College of Obstetricians and Gynecologists (ACOG). Katherine Hartmann, M.D., Ph.D., University of North Carolina at Chapel Hill, reported that the primary finding of the systematic review of the literature on the management of uterine leiomyomas demonstrated almost no high-quality evidence upon which to base treatment strategies (14). Inconsistency in reporting the severity of symptoms, uterine and leiomyoma anatomy, and response to treatments prevented meaningful comparison of studies for most questions. Consequently, the investigators were unable to reach definitive conclusions about any of the selected research questions (14). Due to the lack of evidence-based results, standardization of treatment or determination of the most effective therapeutic options was not possible. Results of the systematic 2001 literature review were subject to many potential limitations, including the utilization of a less strict study design when compared with other reviews such as nonrandomized study designs, failure to search the literature before 1975, and reviewing only articles published in English (14).

In summary, Hartmann noted specific changes in the content of the literature during the last 4 years and reflected upon the degree to which progress is being made. Study designs have become more sophisticated, symptoms have been better described, characterization of anatomy has improved, and population covariates have been better measured. Long-term follow-up and direct comparison of treatment options remain consistent limitations. Considering the prevalence of the condition, research priorities should include methodologically rigorous studies of the effectiveness of nonsurgical treatments and development of standard measures of disease severity.

Alternatives to Hysterectomy

Valerie Montgomery Rice, M.D., Meharry Medical College, Nashville, Tennessee, provided an overview of the clinical management of uterine leiomyomas. As women delay childbearing, physicians will encounter with increasing frequency patients who wish to maintain their fertility in the presence of symptomatic leiomyomas. However, women are now increasingly seeking minimally invasive alternatives to hysterectomy, secondary to the desire for a shortened postoperative period and preservation of their fertility. Surgical management includes hysterectomy, myomectomy, myolysis, and uterine artery embolization (UAE). She discussed a large study in which the authors retrospectively analyzed reproductive performance before and after abdominal myomectomy for intramural and subserosal leiomyomas (26). The findings from the study suggest that conservative surgery for uterine fibroids effectively improves livebirth outcome. Factors of concern in clinical practice are the risk of leiomyoma recurrence, cesarean delivery, and reduced fertility due to surgical complications arising from the removal of multiple leiomyomas.

Montgomery Rice next discussed a large multicenter study that compared outcomes following UAE and hysterectomy for treatment of uterine leiomyomas. Overall, both UAE and hysterectomy improved symptoms not related to bleeding and enhanced quality of life for most patients; pelvic pain decreased at 12 months for patients with hysterectomy. She concluded by emphasizing the need for continued efforts to develop less invasive treatment strategies to help decrease the negative effect of leiomyomas on women's reproductive health.

Use of Antiprogestins for Treatment of Uterine Leiomyomas, Clinical Trials

Mifepristone is a selective progesterone receptor modulator (SPRM) that binds to progesterone receptors. Kevin Fiscella, M.D., University of Rochester, Rochester, New York, discussed his ongoing research determining the lowest effective dose of mifepristone in the treatment of uterine fibroids in a 6-month, randomized, double-blinded, placebo-controlled study. Primary outcomes will be determined by symptoms outlined in the Uterine Fibroid Symptom and Quality of Life (UFS-QOL) Questionnaire. This study is concentrating on the safety and efficacy of low-dose treatment. In summary, Fiscella stated that many of these medications are currently limited to short-term use because of their side effects, and more research is needed to determine long-term benefits and risks.

Translational Frontiers: Innovation in Fibroid Treatments for the 21st Century

Elizabeth Stewart, M.D., Harvard Medical School, Brigham and Women's Hospital, Boston, Massachusetts, is of the opinion that a critical first step in generating new treatments today is to have a strong scientific foundation. No early intervention is available for leiomyomas, and the effect of hysterectomy becomes more severe with increasing numbers of women delaying childbearing. Current approaches to uterine

leiomyoma treatment include surgical excision, hormonal manipulation, thermoablative coagulation, and angiographic-induced ischemia. Predictors of risk, early intervention, prevention, and genotypic and phenotypic relationships are lacking. MRI-guided, focused ultrasound surgery is one technique that provides real-time thermal mapping and precise anatomic visualization. In this procedure, the ultrasound beam penetrates soft tissues and focuses on target sites causing localized high temperatures. The resulting thermocoagulation results in necrosis of uterine leiomyomas.

Stewart described several of her research findings, including a short-term follow-up study of 109 patients, which reported 79.3% achieved a >10-point reduction in the UFS-QOL Questionnaire score at 3 and 6 months after treatment (27). The study indicated that a small reduction in uterine volume of 13.5% represented a marked symptomatic improvement in most patients at the 6-month follow-up. Although the MRI-guided, focused ultrasound therapy appears to be attractive compared with other leiomyoma procedures, larger definitive, randomized clinical trials are needed to determine long-term outcome and effect on childbearing. Stewart concluded by stating that more innovation is needed although fibroids are categorized as benign tumors. The high economic cost, significant morbidity, and effect on women's health warrants aggressive new avenues of treatments for leiomyoma (13).

SESSION VI. CLINICAL TRIALS AND TRIBULATIONS

Effectiveness of Asoprisnil in Treating Uterine Leiomyomas

Kristof Chwalisz, M.D., Ph.D., TAP Pharmaceutical Products, Inc., Lake Forest, Illinois, commented on Asoprisnil, the first SPRM to reach an advanced stage of clinical development for the treatment of symptomatic leiomyomas and endometriosis, and its high degree of tissue selectivity (28). Chwalisz described a study in which he and his colleagues determined the safety and efficacy of Asoprisnil in comparison with placebo in subjects with uterine leiomyomas. The study was a multicenter, randomized, placebo-controlled, double-blind, parallel-group study of three doses of Asoprisnil (5, 10, and 25 mg) administered orally once daily for 12 weeks. Subjects were premenopausal, and had leiomyomas previously diagnosed by ultrasound, regular menstrual cycles, and negative pregnancy tests at screening and day 1. Efficacy endpoints included fibroid volume (percent change in volume measured by ultrasound), bleeding pattern, and patient-reported outcomes recorded in the Leiomyoma Symptom Assessment Questionnaire (LSAQ) as well as a global efficacy questionnaire. Safety endpoints included endometrial biopsies (at screening and week 12), laboratory parameters, hormone measurements, and adverse events. Additional clinical trials to address safety and effectiveness are ongoing.

A Uterine Fibroid Symptom (UFS) and Quality of Life (QOL) Scoring Instrument

Relatively few studies have been conducted on the symptoms of uterine leiomyomas and their effect on quality of life before and after therapeutic intervention, most likely because symptomatic effects of uterine leiomyomas have been difficult to measure subjectively. James Spies, M.D., Georgetown University Medical Center, Washington, D.C., provided an overview on implementation of the UFS-QOL questionnaire. The development of this instrument was facilitated by clinicians, focus groups, and literature reviews. In summary, the UFS-QOL Questionnaire appears to provide a validated, patient-centered approach to measuring symptoms and health-related quality of life (29).

SESSION VII. THERAPEUTIC TARGETS

Transforming Growth Factor (TGF)-β Collagen-Keloid and Abnormal Mature Collagen Hypothesis

James Segars, M.D., NICHD, NIH, in collaboration with the National Naval Medical Center and the Departments of Obstetrics and Gynecology at Uniformed Services University of the Health Sciences (USUHS) and the University of South Florida, Tampa, characterized the genetic features of leiomyomas using Affymetrix™ U133 A&B microarray chips (Affymetrix, Inc., Santa Clara, CA). These investigators found that genes involved in formation of collagen, other extracellular matrix (ECM) components, and cellular cytoskeleton were differentially expressed (30). Ultrastructural studies performed by Phyllis Leppert, M.D., NICHD, NIH (31), indicated that the ECM was altered in leiomyomas—a finding of note because the ECM of fibroids might contribute to the cell phenotype of leiomyomas, or that degradation of the ECM may be altered in leiomyomas.

Furthermore, when the list of differentially expressed genes was compared with published lists obtained using a similar methodology, six transcripts were consistently identified. One transcript encoded dermatopontin, a 22 kd extracellular protein known to bind the collagen-binding protein decorin, as well as TGF-β. Subsequent experiments confirmed the reduction in dermatopontin in fibroids, as has been previously described in hypertrophic scar and keloid, which are two disorders of tissue remodeling in skin. Segars suggested that leiomyomas may arise from normal uterine cells that undergo alteration in response to disordered extracellular signals. Results of these studies raise the possibility that abnormal tissue repair may contribute to leiomyoma development. On the basis of these findings, trials of antifibrotic agents or medical treatments on the basis of abnormal fibrosis and wound repair appear to hold promise.

Regulation of Estrogen Biosynthesis in Uterine Leiomyomas

Given the pivotal importance of estrogen in leiomyoma growth, and based on the translational studies of aromatase in breast cancer, Serdar Bulun, M.D., Northwestern University, Chicago,

Illinois, presented studies on estrogen biosynthesis and aromatase in uterine leiomyomas. Experiments at Northwestern University indicate that promoters I.3 and II (with a limited presence of I.4) are the primary promoters in leiomyomas, whereas reports from Japan revealed that the I.4 promoter was most prevalent in leiomyomas (32). Bulun suggested that the difference in prevalence of the I.4 promoter may be related to the racial composition of the populations studied because the studies at Northwestern University were conducted in primarily African American with some White and Hispanic women, but none of Asian heritage, whereas the results in Japan were obtained from Asian women. Results of these experiments suggest that aromatase-inhibiting medications may hold promise as therapeutic agents.

SESSION VIII. FUTURE DIRECTIONS: CHARTING THE COURSE

A common problem among investigators conducting clinical or translational leiomyoma research, or testing efficacy of medical, radiological, and/or surgical therapies is the current lack of a standardized, clinical system for classification of these tumors. Uterine leiomyomas by nature are difficult to classify because they can be single or multiple, of different sizes and located within different regions of the uterus. Furthermore, there are clear genetic syndromes that feature leiomyoma development, yet the molecular and clinical features of these rare genetic conditions may or may not resemble those of common leiomyomas. Several attendees suggested that a consensus or state-of-the-art conference be organized to facilitate the establishment of a scoring system or clinical classification scheme for leiomyomas. This suggestion was endorsed by comments from several scientists, clinicians, and other participants, and it was emphasized that the classifications should be interchangeable between disciplines and useful to clinicians, as well as basic and clinical researchers.

Overwhelmingly, participants recommended convening a Third International Congress within the next 3–5 years and including working group sessions on specific subtopics of interest to investigators. These working group sessions would facilitate and stimulate interactions among the scientists and foster future interdisciplinary collaborations. The incorporation of breakout sessions, in which patients could directly interact with clinicians and researchers in a smaller setting, was suggested. In addition, the recommendation was offered to encourage professional organizations to promote uterine leiomyoma research and scientific interactions at their national meetings.

Research themes identified as needing further exploration included: developing randomized clinical trials focusing on comparison of standard treatments with new therapeutic and surgical modalities, developing natural history studies and factors influencing racial differences, acquiring a better understanding of the genetic and molecular bases of uterine leiomyomas, underscoring the need for translational research linking biology and symptomatology, determining how hormonal and environmental influences affect the biology and clinical manifestations of leiomyomas, and standardizing microarray data between laboratories. Lastly, the attendees recommended the establishment of a NIH-based tissue repository for (frozen and fixed) uterine leiomyoma and normal myometrial samples, and that the Office of Research on Women's Health (ORWH), NIH, foster interactions among scientists and clinicians by supporting small interdisciplinary research efforts.

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