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NAMS Translational Science Symposium Report

NAMS 2018 Utian Translational Science Symposium, October 2018, San Diego, California
New therapies for leiomyomas: when surgery may not be the best option

Abstract

The North American Menopause Society (NAMS) held the 2018 Utian Translational Science Symposium on October 2, 2018, in San Diego, California, to discuss new therapeutic approaches to uterine leiomyomas when surgery is not the optimal choice.

Uterine leiomyomas arise from a single clonal cell and are the most common gynecologic disorder affecting reproductive and perimenopausal women worldwide. The prevalence of this disorder is approximately 40% to 70% in white women and 60% to 80% in black women. Recent research suggests that both estrogen and progesterone modulate the growth of leiomyomas, with progesterone being a major stimulator of leiomyoma growth.

Women with symptomatic uterine leiomyomas experience heavy uterine bleeding, bulk symptoms, miscarriages, and pregnancy complications. Surgical therapies such as myomectomy or hysterectomy are highly effective; however, medical therapy with progestin-predominant contraceptives or gonadotropin-releasing hormone (GnRH) agonists are in many ways inadequate to address the unmet need for better, noninvasive, and cost-effective treatments.

Recent advances in medical treatment, such as selective progesterone receptor modulators, new oral GnRH analogs, and clinical trials that provide new therapeutic approaches, were presented by speakers at the symposium. Research on why there is a prevalence of leiomyomas in black women, the racial and genetic effects on leiomyoma growth, and potential molecular mechanisms also were discussed.

Key Words: Gonadotropin-releasing hormone agonists – Medical therapy – Myomectomy – Racial disparities – Selective progesterone receptor modulators – Surgery – Ulipristal acetate – Uterine leiomyomas.

Uterine leiomyomas are one of the most common benign gynecologic disorders affecting reproductive and perimenopausal women worldwide. Although hysterectomy and myomectomy are effective surgical approaches for the treatment of uterine leiomyomas, over the past 2.5 decades there has been a struggle to find an effective long-term medical treatment. Current medical treatment with long-acting gonadotropin-releasing hormone (GnRH) agonists has many drawbacks.

The GnRH analog approach does not directly target the leiomyoma tissue, but induces a ''medical menopause'' through direct action on the pituitary gland. With the absence of ovarian function and lower estrogen levels, there are multiple, short-term adverse events (AEs), including hot flashes, joint stiffness, vaginal dryness, and reduced libido. Potential long-term AEs such as bone loss and the medical complications of early menopause make this approach inappropriate. Thus, there is a huge unmet need for safer, better-tolerated medications.

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Leading national and international experts were invited to the 2018 Utian Translational Science Symposium to provide a broad perspective on current knowledge; the effect of uterine leiomyomas with respect to their biology; their physiologic effect on clinical symptoms; their epidemiology; and the compounds that have shown promise in targeting them in clinical trials.

MANAGEMENT OF WOMEN WITH UTERINE LEIOMYOMAS: WHY WE NEED NEW OPTIONS

Wendy L. Wolfman, MD, FRCS(C), FACOG, NCMP

Uterine leiomyomas are monoclonal smooth-muscle tumors originating from the myometrium, affecting up to 70% of white women and 80% of black women by the age of menopause.[1,2] Fifty percent of women with leiomyomas experience significant health effects because of the triad of bleeding, bulk, or reproductive complications.[3,4] Loss of workdays, provider visits, and treatment of symptoms are responsible for increases in healthcare dollar spending, with an estimated cost in the billions of dollars.[5-7] Women with leiomyomas report that they affect their quality of life (QOL) in the areas of sexuality; relationships; and social, emotional, and physical well-being. Uterine leiomyomas are ultimately the responsible diagnosis for 200,000 of the 600,000 hysterectomies performed annually in the United States.[5,8] The acceptance of surgery as a solution reflects dissatisfaction with current medical therapies available to treat symptoms.

The most bothersome symptom in one-third of women with uterine leiomyomas requiring therapy is the increased amount, length, or timing of menstrual bleeding, often associated with dysmenorrhea, which can lead to anemia or emergency visits. The bleeding is postulated to be because of increased uterine surface area and vascularity, venous engorgement, endometrial ulceration, and impaired contractility.[9,10] Bulk symptoms may produce pelvic pressure; urinary frequency, urgency, and incontinence; abdominal distension; constipation; back pain; or dyspareunia.[4] Reproductive dysfunction, although usually a diagnosis of exclusion from other factors, may include difficulty conceiving and recurrent pregnancy loss. Pregnancies may be complicated by abnormal placentation, small-for-gestational-age infants, premature delivery, malpresentation, increases in caesarean delivery rates, or postpartum haemorrhage.[4,5]

Risks for uterine leiomyomas include uncontrollable factors such as increasing age, early menarche, late menopause, black ethnicity, and genetics. Lifestyle factors include obesity, dietary habits, and reduced physical activity, as well as early use of oral contraceptives (OCs). Increased parity and injectable progestins reduce the incidence.[4]

The diagnosis of uterine leiomyomas is made after a careful and thorough history and physical examination. Unusual complaints may include pain from ureteric obstruction, acute pain because of necrosis or torsion of a pedunculated leiomyoma, deep vein thrombosis because of physical obstruction, or even polycythemia because of erythropoietin produced by the leiomyoma.[11] A mass may be observed or palpated in the lower abdomen, and irregular uterine enlargement may be found during pelvic examination. A pelvic ultrasound will confirm the diagnosis. Magnetic resonance imaging (MRI) or 3-D ultrasound can be used for preoperative mapping and may be required to differentiate an ovarian from a uterine mass when the leiomyoma is located laterally, obscuring evaluation of the adnexa. Investigations for abnormal uterine bleeding (AUB) are individualized according to the patient's presentation, age, and risk factors, but may include cervical cultures for sexually transmitted diseases; a *Papanicolaou* (Pap) test; and endometrial biopsy, hysterosonogram, and/or hysteroscopy. Blood work includes a complete blood count, possibly a thyroid-stimulating hormone level test, a prolactin test, and a coagulation screen.

Leiomyomas have been classified by the International Federation of Gynecology and Obstetrics into eight subclassifications and the Society of European Hysteroscopy into four categories that assess the ability of removing a leiomyoma via hysteroscopy. Type 0 leiomyomas are fully inside the uterine cavity and preferentially removed via hysteroscope. Type I leiomyomas are more than 50% in the cavity and also amenable for removal via hysteroscope if not extending too close to the uterine wall. Type II is less than 50% in the cavity, and type III is outside the cavity (such as serosal or intramural in location).[12,13]

A history of rapid growth of uterine leiomyomas is not necessarily associated with malignancy. The rate of growth is unpredictable with shrinkage or growth, with a median of 9% a year enlargement.[14,15] Although malignancy is a fear, sarcomas are more common in women aged older than 50 years and usually only diagnosed in the postoperative specimen. The rate of leiomyosarcoma varies from 0.05% to 0.28%.[16] Risk factors for malignancy include age, previous radiation, and tamoxifen use.[17]

Medical and interventional options currently available for patients have varying effectiveness, with individualization based on the acuity of the patient's presentation, fertility wishes, age, and the number, size, and location of the leiomyomas.[4]

Medical options for bleeding include nonsteroidal anti-inflammatory drugs (NSAIDs), antifibrinolytics such as tranexamic acid, contraceptive steroids, progestin therapies such as progestin intrauterine devices (IUDs) and depot medroxyprogesterone acetate (DMPA), danazol, GnRH agonists, aromatase inhibitors (AIs), and, recently in Europe and Canada, selective progesterone receptor modulators (SPRMs).[9,18]

Nonhormone medications are used only with menses. NSAIDs reduce bleeding by 20% to 40%,[3,18] but are less effective than antifibrinolytics or the levonorgestrel IUD. The antifibrinolytic tranexamic acid at a dose of 1 g every 6 hours reduces bleeding by 9% in uterine leiomyomas and up to 95% with menorrhagia alone.[9,10] Steroidal contraceptive therapies are used throughout the cycle and include OCs, patches, and rings. In observational studies, these have been shown to reduce undifferentiated bleeding by 35% to 69% if used

cyclically and by 87% if used continuously.[18] They, however, do not reduce leiomyoma size and are contraindicated in smokers aged older than 35 years. Depo MPA can decrease bleeding by 20%, but up to 90% if used for more than 5 years.[3] The levonorgestrel IUD (20 μg/d) decreases the amount of leiomyoma bleeding by up to 80% to 90% at 1 year and is an effective and safe treatment. It may also have uterine AEs.[3,9,19] There is, however, a higher expulsion rate with submucosal leiomyomas, and success may be limited with larger uterine cavities.[4]

For conservative bulk management treatments, no therapy is necessary if the patient is asymptomatic. If the patient is symptomatic, medical options include GnRH agonists with steroid add-back, SPRMs, or AIs. GnRH agonists reduce estrogen levels by initially competing for the pituitary GnRH receptor, then producing a flare gonadotropin response followed by downregulation of GnRH pituitary receptors leading to inhibition of the hypothalamic–pituitary–ovarian axis.[9] GnRH agonists with or without add-back hormone therapies are recommended for preoperative treatment for both hysterectomy and myomectomy and have been shown to reduce uterine and leiomyoma volume (up to 67%), anemia, and intraoperative blood loss, enabling more minimalistic surgery and reducing complications. The effects of GnRH are temporary, and leiomyomas regrow when therapy is discontinued.[20] Their usage is limited by their estrogen deficiency AEs, including hot flashes, vaginal dryness, low mood, and loss of bone mass. Add-back options for longer therapeutic use include low-dose hormone therapies, progestins, tibolone, or, most recently, tissue selective estrogen complexes (conjugated equine estrogens with bazedoxifene).

Aromatase inhibitors that reduce estrogen levels by blocking peripheral and ovarian conversion of androgens to estrogens[3,9] have been shown to reduce leiomyoma volume, operative time, and bleeding during hysteroscopic and laparoscopic myomectomies. Their use is limited by ovarian cyst formation and ovulation induction in premenopausal women. Currently, insufficient clinical experience is available to recommend them for therapeutic use for this purpose.[3,9,21,22] Other agents that may be effective but require more study include GnRH antagonists such as elagolix[23] and possibly the selective estrogen receptor (ER) modulator raloxifene.[24]

Nonexcisional therapeutic options include uterine artery embolization (UAE), high-intensity focused ultrasound ablation, and radiofrequency volumetric thermal ablation.[2-4] Uterine artery embolization blocks arterial blood flow to the uterus via embolic agents injected during an angiogram, producing tissue infarction and necrosis.[3,25] It has been shown to improve QOL, reduce hospital stay after treatment, reduce the need for blood transfusion, reduce time off work (compared with hysterectomy), and produce similar patient satisfaction. The disadvantages are increased need for further surgical treatments; size restrictions for very large uterine leiomyomas; complications of pelvic pain, fever, and earlier menopause; and rarely, sepsis. Pregnancy is not currently recommended after this procedure. MRI-guided high-intensity focused ultrasound delivers focused thermal energy with MRI guidance to produce coagulative necrosis and loss of perfusion to specific fibroids. It is limited by its cost, availability, and limited criteria for use (leiomyomas <10 cm), as well as a higher reintervention rate after 5 years of 54% compared with 14% for UAE and 12% for myomectomy.[26] Radiofrequency volumetric thermal ablation is a new form of myolysis performed with the energy source inserted directly into the leiomyomas during laparoscopy or inserted transvaginally. Initial results suggest a reintervention rate of 11% after 3 years, with promising pregnancy rates.[3]

Conservative surgical options include hysteroscopic myomectomy (treatment of choice for submucosal leiomyomas); endometrial ablation using mechanical, heat, or cold options to destroy the endometrium[4]; and laparoscopic or abdominal myomectomies. Myomectomies, however, may have a 3% to 4% risk of hysterectomy, usually because of bleeding complications.

There is a significant recurrence and failure rate with these conservative medical or surgical therapies, whereas hysterectomy by laparoscopic, vaginal, abdominal, or robotic means is the definitive cure. Especially in young women (disproportionately composed of black women) with significant symptoms who have failed conservative medical therapies, the surgical and nonexcisional options remain unattractive because of risks, adhesion formation, potential reproductive implications, fear of sexual AEs,[5] and possible earlier menopause. Many women prefer to retain their uteri despite disabling symptoms, and others have medical contraindications for definitive therapy.

During the perimenopausal transition, women commonly notice increasing symptoms because of fluctuations in ovarian hormone levels that accentuate the anatomic aberrations associated with leiomyomas. The clinical goal in perimenopause is to temporize until menopause, when amenorrhea and shrinkage of uterine leiomyomas occur naturally. The goals of medical management are to ensure sustained reduction of bulk, restoration of anatomy, normalization of bleeding, and fertility optimization without the surgical risks. The QOL for many reproductive-aged women would be improved with the advent of more effective medical therapies.[5]

UTERINE LEIOMYOMAS AND RACIAL DISPARITIES

Ayman Al-Hendy, MD, PhD, FRCSC, FACOG, CCRP

Uterine leiomyomas are the most common benign growths arising from a single, genetically altered mesenchymal cell under the influence of gonadal hormones, progesterone, and 17β-estradiol. Signs and symptoms vary from patient to patient; the abnormal cell proliferation frequently distorts the uterus and causes pelvic pain, AUB, and reproductive dysfunction.[27] Less-invasive treatment options for uterine leiomyomas are available that include procedures to extirpate the leiomyoma; UAE; thermoablative therapies; and several

medical therapies.[28] The leiomyoma pathology causes a significant burden in the US public health system, with an estimated annual cost of approximately $5.9 to $34.4 billion.[29] Despite the high prevalence of leiomyomas, this pathogeneses is far from being completely understood.[30]

Risk factors and ethnic disparity

Several risk factors associated with leiomyomas include age, race, genetics, hormone changes, lifestyle, diet, obesity, and endocrine disruptors (EDs).[30] A combination of factors can be found in the population of black women, in whom cumulative risk factors put these women at higher risk for uterine leiomyomas compared with other ethnicities.[31]

The peak incidence of diagnosis of uterine leiomyomas is in women aged 50 years. Uterine leiomyomas do not occur before puberty, and their frequency decreases with menopause. The incidence of leiomyomas by the age of 35 years is approximately 60% in black women, increasing to 80% by the age of 50 years.[31] White women have an incidence of 40% by age 35 years and almost 70% by the age of 50 years.

A two- to threefold incidence of leiomyomas has been found in black women.[31] This racial disparity has been associated with estrogen biosynthesis and/or metabolism, probably because of genetic variation.[32] A study by Marsh et al analyzed estrogen levels in women across different racial groups.[33] This study found higher levels of estrogen across the menstrual cycle of black women in particular and concluded that increased estrogen production may be because of polymorphism in aromatase enzyme levels.

Aromatase is an enzyme that belongs to the CYP450 family, which catalyzes the conversion of androgens and estrogens. This enzyme is ubiquitous and has been isolated in leiomyoma tissue.[34] Shaw et al found higher levels of aromatase enzyme in the granulosa cells of the ovaries from black women compared with white women.[35]

Another enzyme is catechol-O-methyltransferase (COMT), an enzyme that modifies the biologic effect of estrogen by converting estrogen to catechol estrogens. Women with high levels of COMT enzyme have been found to have a 2.5 times increased likelihood to develop leiomyomas. Three genotypes associated with varying levels of enzyme activity are the valine form *(Val/Val)* genotype with high enzyme activity; the methionine variant *(Val/Met*) genotype with intermediate enzyme activity; and *Met/Met*, with lower enzyme activity. Black women were found to have a high frequency of the *Val/Val* genotype (47%), whereas white women were found to have a higher frequency of the *Met/Met* genotype (33%) with lower activity.

Women found to have a decreased ER function were more likely to have leiomyomas than women with higher ER function.[35] A lower ER function could theoretically lead to a compensatory higher circulating level of estrogen. Black ethnicity showed higher rates of decreased ER function, which predisposed them for severe clinical manifestations and earlier age of hysterectomy. Higher levels of estrogen in black women may explain the higher uterine weights, increased number of leiomyomas, higher likelihood of preoperative anemia, and more severe pelvic pain at time of hysterectomy.[36]

Baird et al found an inverse association between the effects of exercise on the development of leiomyomas.[37] As body mass index (BMI) increased, so did the risk for developing leiomyomas but only in black women.[38] The California Teachers study found that the increase in BMI after the age of 18 years was associated with higher rates of surgically confirmed leiomyomas.[39] Several studies suggest that diet may play a role in the development of leiomyomas, but many confounding variables prevent a clear consensus.[30] Recent studies have found vitamin D deficiency to be related to the development of leiomyomas.[40] Black women have a 10-fold increased risk of vitamin D deficiency compared with white women. Higher levels of melanin found in dark skin block vitamin D receptors, leading to decreased vitamin absorption and depriving them of the regulatory effect this vitamin offers. Vitamin D displays an antiangiogenic effect, plays an important role in regulating the cell cycle, and contributes to apoptosis.[32,40] Blauer et al showed the relationship between 1,25(OH) vitamin D levels and the growth of leiomyoma cells.[41] In vitro studies of myometrium and leiomyoma tissue demonstrate significant suppressed growth at 1,25(OH) vitamin D concentrations of 40 ng/mL with approximately 62% growth inhibition.

Recent exposure to endocrine disruptor modulators (EDMs) has been associated with increased risk of uterine leiomyomas because they can reprogram gene expression and lead to increased rates of myometrial stem cell (MMSC) proliferation.[42,43] A large prospective cohort study in the United States and Puerto Rico that was focused on black women found a strong association with early-onset leiomyomas in women who were exposed to diethylstilbestrol (DES) in utero.[44] Other risk factors were maternal prepregnancy diabetes or gestational diabetes and being fed soy formula. Wise et al identified constant exposure of black women with phthalates, a chemical contaminant easily absorbed through skin and with inhalation, commonly found in hair relaxers, which has shown estrogenic effect in cell models and experimental animal as an EDM.[45] In this study, 94% of black women had used hair relaxers at least once a year, with a positive relationship between use of this chemical and risk of developing leiomyomas. Additional studies have associated higher rates of leiomyomas with exposure to EDMs.[46,47]

The role of epigenetics in uterine leiomyomas

Gene expression profile studies have demonstrated that hundreds of genes with critical functions in differentiation, apoptosis, proliferation, and extracellular matrix formation are dysregulated in leiomyomas.[48] In humans, three main epigenetic mechanisms modulate gene expression: DNA methylation, adding CpG to the promoter region, results in decreased gene expression, whereas hypomethylation leads to the opposite effect of active gene transcription. Other

mechanisms of altering gene expression include modification of histone proteins and microRNA, which play an essential role in transcription and posttranscriptional regulation of gene expression.[49]

Interestingly, uterine leiomyomas are associated with alterations in DNA methylation during replication.[49] Estrogen and progesterone influence leiomyoma development by regulating growth factors and their signaling pathways. The activation of steroid hormone receptors has multiple effects in the upregulation of growth factors and receptor tyrosine kinase through the downstream effector proteins such as mitogen-activated protein kinase p44/42 that are capable of mediating transcription, translation, and cell proliferation.

Through epigenetic analysis, changes in phenotype from altered gene expression because of hypermethylation have been identified. It is known that epigenetic changes have a major role in the incidence of complex diseases, including cancer, cardiovascular and respiratory diseases, metabolic syndrome, neurologic impairment, and developmental defects. Alterations of chromatin structure, gene expression, and genomic structure are major features of epigenomic modifications.[50,51] Endocrine disruptor compounds (EDCs) have complex actions in some cells. For instance, an individual EDC may interact with more than one hormone receptor, and multiple EDCs can interact with the same receptor. The xenoestrogen bisphenol A (BPA) has been shown to bind and activate several receptors: ER, estrogen-related receptor gamma, and pregnane X receptor.[52] In addition to BPA, a variety of other EDCs (DES and phthalates) can also bind to ERs, leading to changes in replication of DNA.[46] Activation of replication can be initiated by environmental chemicals, achieving a direct link between xenoestrogen-induced nuclear hormone receptor signaling and modulating of epigenetic machinery.

Other epigenetic changes that have been related to leiomyomas are the enhancement of zeste homologous 2 (EZH2) mediated by histone methyltransferase. Xenoestrogens induce regulation of EZH2 and histone methylation via ER signaling to phosphatidylinositol 3-kinase/serine-threonine protein kinase. This can lead to hypermethylation of tumor suppressor genes and hypomethylation of oncogenes that contribute to the development of tumorigenesis. Additional studies done in black women have shown variations in 55 genes in promoter methylation with concomitant differences in mRNA expression in uterine leiomyoma when compared with normal myometrium.[52]

Higher levels of estrogen and progesterone are important for the growth of uterine leiomyomas. Endogenous estrogen metabolism is primarily oxidative and involves hydroxylation of the steroid or carbon-2 (2-OHE1) or carbon-16 (16-OHE1). The 2-OHE1 metabolites are primarily responsible for the biologic activity, whereas 16-OHE1 is agonist for this receptor. The CYPA1 gene seems to play a role in estradiol oxidation on carbon 2, and in black women, the wild type of CYPA1 showed increased ratio of estradiol derivate hydroxylated in position 2, compared with derivate hydroxylated in position 16. This position has been associated with leiomyomas in black women.[49]

There are a variety of pathway changes that lead to changes in DNA methylation, histone modification, and microRNAs production, a common epigenetic mechanism that contributes to tumorigenesis, including uterine leiomyomas. Further studies are needed to fully understand the role of epigenetics in the pathology of disease.

Defective DNA repair in uterine leiomyomas

Several genetic abnormalities have been related to uterine leiomyomas; for example, deletion in 7q, trisomy/translocation of chromosome 12, and monosomy of chromosome 22. These, however, occur in a very small percentage of cases. In contrast to hereditary mutations, somatic mutations are associated with clonal tumors such as leiomyomas that occur from a single progenitor cell. Most leiomyoma mutations are sporadic.[46] The most frequent somatic mutation is MED 12, located on gene Xq13.1 in chromosome 1 and 2.[53,54]

Although the cause of MED 12 mutation is unknown, it is well accepted that defects in DNA repair are increased in somatic tumors. Tissues with high mitotic events such as the myometrium are at increased risk for genomic instability because of increased risk of random mutations occurring during normal physiologic processes such as DNA replication. Constant repair is needed to maintain integrity of DNA, a role that requires homologous recombination or nonhomologous end-joining to maintain genome integrity. Reduced expression of DNA repair genes are found in several cancers and is a common defect identified in breast cancers. Growth of mammary stem cells of the breast is regulated by sex steroid hormones, and as the level of estrogen increases, so do the proliferation rates. Women with a mutation in breast cancer suppressor genes have increased risk for breast cancer.[42,55]

Sex hormone-regulated tumors such as leiomyomas are also at risk for replication errors. The myometrium stem-cell population may be implicated during this process, leading to transformation of these cells into tumor-forming cells and the development of leiomyomas. The team at the University of Illinois at Chicago has recently shown that several DNA repair genes are downregulated in leiomyoma tissue.[56] Recently, vitamin D has proved to attenuate the levels of DNA damage and modulate the induction of DNA repair gene expression. This vitamin has been shown to regulate the expression of double-strand repair proteins. Importantly, two sex steroid-dependent cancers, breast and prostate, have shown that vitamin D deficiency is associated with increased risk of tumor development.[57] Recent evidence has shown that vitamin D attenuates DNA damage and modulates the DNA damage response via induction of DNA repair gene expression.[32,41,57] Studies by Ali et al demonstrate that vitamin D effectively suppresses uterine leiomyoma growth that may become a therapeutic option for the prevention and early treatment of leiomyomas.[57]

Reprogramming of myometrial stem cells and uterine leiomyoma development

The human female reproductive tract is a target for development and reprogramming as a result of inappropriate early life hormone exposure.[43] Stem cells are undifferentiated cells residing in adult organs that can self-renew and differentiate into specialized tissue or organ-specific cell type. They are usually located in a specific anatomic location. Growth of these myometrial stem cells is because of stimulation of high levels of estrogen and progesterone.[27] This is a special characteristic of the human female reproductive tract because it regenerates and grows continuously each menstrual cycle and throughout pregnancy.[58] These cells have shown the ability to generate functional human myometrial tissue when transplanted into the uteri of severely immunodeficient mice.[46] Mas et al identified mesenchymal stem cells as well as tumor-initiating cells in myometrium and leiomyomas using $Stro1^{+}/CD44^{+}$.[59] CD44 is a well-known cell surface marker for stem and cancer cells, composed of a glycoprotein molecule with the main ligands being hyaluronic acid and osteopontin. $Stro1^{+}$ is used as a marker for pure primitive MSC.[60]

Eker strain rats have been used as an animal model to determine the interaction between genes and environment.[61] These rats are carriers of mutated tuberous sclerosis complex 2 (Tsc2) gene, and 65% of them will develop leiomyomas because of loss of tuberin expression. The development of leiomyomas in these rats is dependent on ovarian hormones, confirmed because removal of ovaries prevents tumor development. Experimental studies have shown that in early life (during the period of uteri development), exposure to DES and genistein increased the penetrance from 65% to 100%.

To determine the molecular mechanism by which early life exposure to EDCs alters the characteristics of MMSCs, the Eker rat pups were exposed to DES at the postneonatal day.[62] Myometrium tissues were collected at the age of 5 months and subjected to stem cell isolation using $Stro^{-1}$/CD44 surface markers. Genome-wide epigenomic analysis was performed, coupled with high-throughput RNA-seq analysis and targeted next-generation seq (NGS) in vehicle versus EDC-exposed MMSCs. The studies demonstrated that MMSCs are the targets of environmental exposure. Developmental exposure to DES reprogrammed many signaling pathways that play key roles in pathogenesis of leiomyomas. Gene set enrichment analysis on the ChIP-sequencing data demonstrated that enrichment of active mark H3K4me3 at the promoters of estrogen-responsive genes and others were observed in DES-treated MMSCs compared with vehicle-treated MMSCs. Furthermore, targeted NGS analysis demonstrated that estrogen-responsive genes and others exhibit hypomethylation within their CpG islands in DES-treated MMSCs compared with vehicle-treated MMSCs. The study suggested that early life exposure to EDCs during crucial periods of uterine development increased the risk of leiomyoma pathogenesis by reprogramming the epigenome of MMSCs toward a pro-leiomyoma epigenomic landscape.

Early life exposure to EDCs has been connected to increased risk of adult onset of leiomyomas in women and confirmed using experimental animal models. Minority communities are particularly at risk for hazardous environmental exposures, making them susceptible for phenotypical alteration and future development of multiple diseases.

Despite the high prevalence and major effect of uterine leiomyomas on black women, there is no conclusive evidence for why this ethnicity is more affected. The possible cumulative addition of risk factors and polymorphism found in several enzymes might put them at higher risk for leiomyomas. Cultural and environmental differences might alter stem cell characteristics via an epigenomic reprogramming mechanism that leads to alteration of MMSC phenotype. Developmental insult exposures may cause DNA damage to the stem cell population and impair DNA repair and many other key pathways. Additional investigations should focus on localized systemic treatment and identify strategies for preventions of uterine leiomyomas. [Dr. Al-Hendy's work was conducted in collaboration with Mara Ulin, MD, and Qiwei Yang, PhD, and supported in part by the National Institutes of Health grants: R01 HD094378, R01 ES028615, and U54 MD007602.]

ROLE OF PROGESTERONE PATHWAYS IN THE PATHOPHYSIOLOGY OF LEIOMYOMAS: THE EVIDENCE

Elizabeth A. Stewart, MD

The evidence of steroidal modulation of uterine leiomyomas has long been recognized.[4,63] Uterine leiomyomas are primarily a disease of reproductive-aged women, their incidence increases with age during the reproductive years, and they tend to regress at the time of menopause.

Initially, the focus was on estrogen because of experimental data from the guinea pig model.[64,65] These experiments, however, used different estrogens, a variety of doses, and different lengths of treatment and caused many other kinds of growth.

With the clinical introduction of GnRH analogs in the 1990s, the regression of leiomyomas with treatment with these agents reinforced this paradigm; as the hypogonadal hyposteroidal downregulation phase of treatment was reached, leiomyomas shrank, and amenorrhea was achieved. The common interpretation was, however, that estrogen was the only important steroidal hormone responsible for this clinical result. Both clinical and biomedical discovery set this stage for the understanding of the primacy of progesterone over estrogen in this disease process.

First, clinical studies suggested that progestins inhibited the volume reduction of leiomyomas when used as add-back therapy with GnRH agonists.[66] Subsequently, in vitro experiments showed that estrogen was chiefly important for inducing the progesterone receptor, and progesterone was the key driver of leiomyoma growth.[67] Thus, the development of

SPRMs seemed to be agents with utility for leiomyoma treatment. The earliest studies were with mifepristone and showed substantial volume reduction yet maintenance of follicular-phase estradiol.[68] Both the unusual pattern of endometrial histology that occurs after treatment with SPRMs (PRM-associated endometrial changes) and the politics of abortion, however, played a role in this agent failing to gain approval for use for uterine leiomyoma treatment despite its efficacy.[69-71]

Both Cochrane and Agency for Healthcare Research and Quality reviews conclude that there is strong and consistent evidence on the effectiveness of SPRMs for leiomyoma treatment.[72,73] The agent ulipristal acetate (UPA) has achieved widespread clinical use outside the United States, and trials in US populations were conducted in preparation for approval by FDA.[74,75] Several cases of liver failure, some requiring liver transplantation, however, led to new guidance for use in Europe.[76] The current state of a US-based application is unclear.

LONG-TERM INTERMITTENT ADMINISTRATION OF SELECTIVE PROGESTERONE RECEPTOR MODULATORS: EXPANDING NEW TREATMENT OPTIONS

James H. Liu, MD, NCMP

Current evidence indicates a major biologic role for estrogens and progesterone in stimulating uterine leiomyoma growth and development because leiomyomas are rare before menarche and regress during menopause.[67] A number of steroidal analogs have been developed to target the progesterone receptors with a minimum of biologic activity.[72] These compounds are classified as SPRMs and include mifepristone, UPA, and vilaprisan (VPR).[74,75,77] Available animal studies and recent clinical trials have demonstrated that SPRMs have multiple effects on leiomyoma tissues, including (1) blocking of progesterone receptors without antiglucocorticoid effects (UPA and VPR); (2) inhibition of leiomyoma cell proliferation; (3) stimulation of leiomyoma cell apoptosis; and (4) maintaining follicular-phase estrogen levels in reproductive-aged women. The other shared characteristics of SPRMs are excellent oral bioavailability and a long half-life of 38 to 53 hours, allowing for daily-dosing options.[77]

Ulipristal acetate is the first SPRM approved for intermittent treatment of uterine leiomyomas in the European Union and Canada, at a dose of 5 mg per day.[78,79] Published randomized clinical trials of UPA in Europe in a white population demonstrated an amenorrhea rate of more than 90% in women with symptomatic leiomyomas treated with 5 or 10 mg per day.[75,76] These findings are comparable to leuprolide acetate treatment. In US trials with a predominantly black population, amenorrhea rates were 42% and 55% at the 5 and 10 mg dose per day, respectively.[80] Time to amenorrhea was less than 10 days. These responses seem to be different from the original PEARL trials conducted in a predominantly white European population.[75,76] There was also a small reduction in leiomyoma volume of 10% to 20% compared with placebo.[80] These studies were designed with 12 weeks of active treatment followed by a recovery cycle and another 12-week treatment with recovery. Uterine symptom QOL assessments showed significant improvement in daily activities, hematocrit, energy, and sexual function. Limited clinical trials with VPR demonstrated similar amenorrhea rates at doses between 2 and 5 mg per day.[81]

Overall, AEs of SPRMs seem to be minimal, with mild hot flashes (1%-12%) and occasional headaches. All SPRMs are metabolized by the Cyp3A4 cytochrome system and processed primarily in the liver. Although no liver function changes were detected in clinical trials to date, there have been rare cases of severe liver injury in patients on UPA in Europe. The European Medicine Agency has evaluated these cases and recommends regular alanine transaminase and aspartate transaminase testing to monitor liver health. Ulipristal acetate should not be used in patients with liver disease.[76]

Once they become available in the United States, UPA and, possibly, VPR can be treatment options for women with symptomatic uterine leiomyomas who desire conservative management of their uterine bleeding and preservation for future fertility.

HELPING WOMEN WITH FIBROIDS NAVIGATE THE MENOPAUSE TRANSITION AND POSTMENOPAUSE HORMONE THERAPY

Nanette F. Santoro, MD

Uterine leiomyomas are the most common tumors of the female genital tract, occurring in 20% to 80% of women. Uterine leiomyomas are often clinically silent, but depending on their size and location, they can cause symptoms because of compression of adjacent organs, irregular or profuse vaginal bleeding, infertility, and pain because of degeneration. Estradiol and progesterone both seem to fuel the growth of leiomyomas; therefore, leiomyomas are expected to shrink and/or disappear once a woman has completed the transition.[82] In the timeframe that encompasses the end of childbearing to the last menstrual period, leiomyomas can, however, become symptomatic and present a challenge for clinical management.

There are several medical strategies that can avoid surgical intervention in the late-reproductive years. Hormone contraception such as a progestin-releasing intrauterine system is an inexpensive and simple option, particularly attractive for the woman who also has contraceptive needs.[83] When this simple strategy is not effective, other agents that can be used include DMPA, a GnRH agonist, a GnRH antagonist, and UPA.[84] Depo MPA will reduce estradiol stimulation of leiomyomas, but provides long-acting progestin that can counteract the benefit of the lowered estradiol. A 2- to 3-month course of GnRH agonist treatment may shrink leiomyomas by as much as 50% and allow a woman to avoid surgery, providing she is

close to her final menstrual period. A new, oral GnRH antagonist, elagolix, is becoming available and may allow a woman to undergo a short course of treatment, followed by observation.[23,84,85] Ulipristal acetate is a SPRM that can be administered in multiple courses and provides rapid relief from leiomyoma symptoms.

More invasive strategies to reduce leiomyoma morbidity in midlife women include embolization[86] and focused ultrasound. Both these methods can be highly effective in appropriately selected patients.

AREAS OF FUTURE RESEARCH IN FIBROID THERAPY

William Catherino, MD, PhD

Uterine leiomyomas are associated with menorrhagia, pelvic pain, pelvic pressure, miscarriage, and various pregnancy complications.[87] Their high prevalence and similarity to leiomyosarcoma by pelvic examination and imaging can delay diagnosis and worsen outcomes for women with leiomyosarcomas and leiomyomas. Leiomyomas are exceedingly rare before menarche and regress after menopause, suggesting that they are hormonally stimulated tumors. The advent of GnRH analogs, and specifically leuprolide acetate, resulted in the first and only FDA-approved medical therapy for uterine leiomyomas. More recently, an oral active GnRH antagonist, elagolix, is undergoing phase 3 trials for AUB related to leiomyomas.[23] These compounds disrupt gonadotropin release, resulting in a hypoestrogenic state, inducing amenorrhea, and resulting in a decrease in leiomyoma size. These compounds are, however, also associated with other symptoms associated with a hypoestrogenic state, including hot flashes, vaginal dryness, and bone loss. Given the limitations of surgical and minimally invasive options for leiomyoma therapy, there is substantial interest in novel medical therapies.

Selective estrogen receptor modulators have, unfortunately, not proven to be helpful for leiomyoma therapy.[21,22] In addition, hormone regulation via combined OCs or progestin-based contraceptives do not alter the disease process, although they may transiently decrease menstrual flow.[19] Selective progesterone receptor modulators, however, have demonstrable benefit as a leiomyoma therapeutic.[88,89] These compounds provide a similar beneficial effect as GnRH analogs, but are not associated with hypoestrogenic AEs. Such compounds represent near-term therapeutic options.

In the intermediate term, there are various therapies that have an effect on leiomyoma development, but do not function by regulating gonadal hormones in a manner similar to GnRH analogs and SPRMs. These categories include compounds that function as vitamins,[90,91] HMG-CoA inhibitors (statins), antifibrotics,[92] and nutritional supplements.[93,94] The nutritional supplements are particularly exciting because they provide the only potential mechanism of intervening in a woman who has asymptomatic leiomyomas but who is at high risk of disease progression. In the future, medical therapies for women suffering from leiomyomas will provide excellent alternatives to surgery.

CONCLUSION

JoAnn V. Pinkerton, MD, NCMP

Leiomyomas have clinical significance in reproductive women because of bleeding, bulk issues, or difficulty with fertility. Racial disparities are seen, with a higher incidence in black women associated with estrogen biosynthesis and/or metabolism and most likely because of genetic variations. The definitive treatment is hysterectomy or myomectomy. Minimally invasive techniques have been developed, but the fear of leiomyosarcoma, or spreading cancer cells, has slowed the use of minimally invasive surgery.

Nonsurgical modalities include NSAIDs, OCs, progestin-containing IUDs, depo-progesterone injections, tranexamic acid, GnRHs, and possibly AIs, many of which control bleeding but do not treat the leiomyomas. Newer therapies are needed. Select women are candidates for UAE and focused ultrasound, but concerns have been raised if later fertility is desired.

Progesterone has been identified as the key steroid modulator of proliferation of leiomyomas, not estrogen as long supposed. This has led to the investigation of SPRMs such as UPA, which has shown to be effective in large clinical trials providing rapid control with decreased bleeding and increased amenorrhea with improved QOL. Leiomyoma size decreases are reported in the 10% to 24% range. AEs include hot flashes and mild headaches. Cystic endometrial changes occur but either regress or are reversible. It is important to remember that UPA does not provide contraceptive protection. Liver problems are rare, but have raised concerns about FDA approval in the United States, whereas this product is already available in Canada and Europe with extensive use.

Other nonsurgical options include GnRH agonists and antagonists, which affect gonadal hormones and their effect on leiomyoma size and bleeding, but have not been able to be used for long periods of time because of AEs. Simvastatin has been shown to lead to cell death and has an antiproliferative effect on leiomyomas. Retinoic acid seems to have an intracellular effect (leiomyoma cell death), but fibrosis persists. Areas being pursued include environmental disrupters for their role in etiology or growth of leiomyomas. Vitamin D seems to be antiproliferative and associated with apoptosis and may play a role. Nutritional supplements being evaluated include green tea extract and berberine.

Symptomatic leiomyomas need more treatment options because current surgical treatment and medical treatment with long-acting GnRH agonists have drawbacks. As the etiology and proliferative stimuli of leiomyomas are better understood, improved medical therapies, such as SPRMs, or nonprescription options, such as vitamin D or nutritional supplements, will hopefully lead to improved prevention and treatment management options and improve QOL for women who suffer from leiomyomas.

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