Published in final edited form as:
Semin Reprod Med. 2013 September ; 31(5): 370–379. doi:10.1055/s-0033-1348896.

Racial and Ethnic Differences in the Pathogenesis and Clinical Manifestations of Uterine Leiomyoma

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Abstract

Uterine leiomyomas are the most common benign gynecologic condition. The prevalence is three times more common among women of African ethnicity. Disparity in this disease is evidenced by earlier age of onset, greater severity of symptoms, and different response to treatment. Although the pathogenesis of disease development is not completely known, growing evidence focuses on investigating the molecular mechanisms in disease development and the influence of ethnicity. Variation in the expression levels or function of estrogen and progesterone receptors, polymorphism of genes involved in estrogen synthesis and/or metabolism (*COMT*, *CYP17*), retinoic acid nuclear receptors (retinoid acid receptor-α, retinoid X receptor-α), and aberrant expression of micro-RNAs (miRNAs) are some of the molecular mechanisms that may be involved. Nutritional factors, such as vitamin D deficiency, might also contribute to the higher incidence in dark skinned populations who are also commonly suffer from hypovitaminosis D. Culture and environmental difference might have a role in disease development. Further analysis and better understanding of these mechanisms will provide insight into the molecular basis of racial disparities in leiomyoma formation and will help to develop new innovations in leiomyoma treatment.

Keywords

uterine leiomyoma; African American; ethnicity; molecular; risk factor

Uterine leiomyomas (uterine fibroids) are the most common benign reproductive tumor in women. By the age of 50 years, the cumulative incidence is approximately 70% in white women and more than 80% in black women based on ultrasound detection of fibroids.[1] African American women have three times the risk for developing leiomyoma when

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compared with white women.[2] They are more likely to be diagnosed with uterine fibroids at an earlier age, and have larger and more rapidly growing fibroids. They suffer from more severe symptoms (bleeding and pelvic pain) compared with white women.[3] In addition, African American women tend to undergo surgical treatment more often. There are also ethnic differences in response to treatment, as well as treatment complications. An estimated cost for uterine leiomyoma (ULM) and related care is up to 34 billion dollars annually in the United States, which represent a major burden on the health-care system.[4] The pathogenesis of ULM development is not fully understood. It is therefore important for research studies to focus on the molecular mechanisms in disease development and the influence of ethnicity.

Molecular Mechanisms Involved in the Development of Uterine Fibroids

The myometrium is the smooth muscle layer of the uterus that undergoes significant changes in size and cellular properties during reproductive years under certain conditions. For instance, during pregnancy, the uterus undergoes changes in the cellular phenotype with hypertrophy of myometrial smooth muscle cells.[5] Myometrial mass and morphology of smooth muscle cells are also modified in leiomyomas.[6] Leiomyomas share many characteristics with parturient myometrium such as increased production of extracellular matrix (ECM) components and expression of receptors for peptide and steroids hormones. However, ULM continues to grow and does not regress via apoptosis like the normal postpartum myometrium.[6,7] ULM arises from smooth muscle cells within the uterus.[8] They are formed mainly from ECM with less vascularization network compared with the surrounding uterine smooth muscles.[9] ECM provides the essential support for intracellular connection and is involved in regulating intercellular communication. The ECM in ULM is both plentiful and disorganized in its structure.[10,11]

Ovarian steroids play an important role in the development of leiomyoma. The rapid progression of leiomyoma during reproductive years and regression after menopause indicate that estrogen has a key role asa growth-promoting factor for these tumors. The mutagenic action of estrogen is mediated by the expression of autocrine/paracrine growth factors, cytokines, and chemokines. These mediators interact with their receptors to activate different signaling pathways that results in differentiation, cell growth, apoptosis, and expression of ECM.[9] Studies hope the molecular mechanisms of leiomyoma have shown considerable progress during the past decade by studying large-scale profiles of gene expression using microarray techniques and proteomic analysis. This leads to the identification of large number of genes and proteins that show different levels of expression of growth factors, cytokines, and chemokines in leiomyomas compared with myometrium.[12-17] Leiomyomas are more frequent in African American women compared with other ethnic groups, and differences are observed based on gene-specific manner, polymorphism of genes (*COMT, CYP17*) involved in estrogen synthesis and/or metabolism, variation in the expression levels, function of estrogen and progesterone receptors, retinoic acid nuclear receptors (retinoid acid receptor-α, retinoid X receptor-α), aromatase levels, or aberrant expression of miRNAs and vitamin D hypovitaminosis.[18]

Racial/Ethnic Differences in the Pathogenesis of Fibroids

Polymorphism of Estrogen Receptors, Gene Expression

Microarray analysis has allowed wide genomic comparison of differently expressed genes involved in the molecular mechanisms of leiomyoma. Many studies investigated large-scale gene expression in myometrium and leiomyoma obtained from individuals without examining ethnic difference on overall gene expression.[17,19] Cumulative evidence supports the influence of ethnicity on ULM, as African American women are at increased risk for developing the disease. One study using microarray analysis and immuno-histochemistry reported some difference in the expression of several dysregulated proteins and their intensities in leiomyoma from African American compared with other ethnic groups.[14] Pan et al[20] investigated many genes by microarray analysis using Affymetrix (Affymetrix, Inc., Santa Clara, CA) platform. A total of 1,470 genes were identified to be differently expressed in leiomyoma compared with myometrium regardless of ethnicity. Of these, 268 genes were either overexpressed (177 genes) or underexpressed (91 genes) in leiomyoma obtained from African American compared with white women ($p < 0.01$). Also, the density/volume of 34 protein spots was 1.5-fold (26 increased and 8 decreased) in leiomyoma of African Americans compared with whites. They suggested that the level of expression of number of genes and proteins accounts for the difference of leiomyoma in African Americans and whites.

Al-Hendy et al[21] investigated the racial difference in leiomyoma and its effect on the function of estrogen receptors (ERs), rather than the expression level. The distribution of ER polymorphism was examined between black, Hispanic, and white women with or without ULM. The polymorphisms tested were in the first intron of the ER gene and included a *T/C* polymorphism, which is recognized by *t* restriction endonuclease *PvuII*, and an *A/G* polymorphism recognized by *XbaI* restriction enzyme. The *T* and *C* alleles represent the presence (*p* allele) or absence (*P* allele) of the restriction site. Similarly, the *A* and *G* alleles represent the presence (*x* allele) or absence (*X* allele) of the restriction site. Genotypes for *PvuII* and *XbaI* polymorphisms were termed *PP*, *Pp*, and *pp* and *XX*, *Xx*, and *xx*, respectively. Data showed that the *PP* genotype was statistically significant ($p < 0.05$) with increased risk for leiomyoma among black and white but not in Hispanic women. Black and Hispanic women were 9.7 and 2.4 times more likely to have ULM, respectively, while white women had the lowest risk for ULM. Women with *PP* genotype were 6.4 times more likely to have ULM compared with women with *pp* genotype regardless of ethnicity. In addition, *PP* genotype was more common in patients with severe disease (uterine weight > 400 g) and associated with earlier age of hysterectomy compared with *pp* genotype. Black women had higher frequency of *PP* genotype (35%) compared with white women (13%) and Hispanic women (16%); in contrast, *pp* genotype was the highest among white women (38%) and Hispanic (40%) compared with black women (27%). There was no difference in the *Pp* heterozygous genotype in the three ethnic groups. The reason why the polymorphism at the *Pvu II* locus located in the first intron of the ER receptor alters the estrogenic response is not yet understood. Theories suggest that the first intron may have a regulatory site (like an enhancer) to control the gene function that leads to differential messenger RNA (mRNA)

splicing and different functioning proteins, or this polymorphism may act as a marker in communication with other regulatory regions.

Micro-RNAs Aberrant Expression in Leiomyoma

Growing evidence has provided strong support to the key regulatory role of miRNA on protein-coding gene expression stability by interacting with their 3′UTR.[22] Several thousand miRNAs have been identified and the expression of large number of them has been outlined in cellular activities as cell growth, differentiation, and apoptosis.[23-26] Their aberrant expression has been related to various disorders including cellular transition, tumorigenesis, and tissue fibrosis.[22,27-29] Chuang et al[30] examined miRNA-200c (miR-200c) function and expression in leiomyoma and matched myometrium tissues and their association with ethnicity, and they found that miR-200 was significantly expressed in lower levels ($p < 0.05$) in leiomyoma compared with myometrium. Moreover, levels of miR-200 were lower in both leiomyoma and myometrium tissues obtained from African American women compared with white ($p < 0.05$). In addition, Wang et al[31] investigated 24 miRNAs that were significantly overexpressed in leiomyoma compared with matched myometrium; some miRNAs (miR-21, miR-23b, miR-16–1, miR-197, and Let-7e) were significantly overexpressed more than twofold ($p < 0.05$) among African American compared with white. MiR-21 was found to be the most highly up-regulated miRNA in ULM. Pan et al[20] also reported miR-21 overexpression in leiomyoma specifically during secretory phase and in women on oral contraceptives and Depo-Provera, while reduced in patients who received gonadotropin-releasing hormone analog therapy ($p < 0.05$).

Polymorphism of Genes Involved in Estrogen Synthesis

Catechol-*O*-Methyltransferase—Another aspect that has been also investigated is the different enzymes that involved in estrogen synthesis/metabolism and the polymorphism of their encoded genes. One of these enzymes is the catechol-*O*-methyltransferase (COMT). It is a ubiquitous enzyme that introduces a methyl group to the hydroxyl groups of catechol estrogen resulting in conversion of 2.4 hydroxy oestradiol to 2.4 methoxy oestradiol. Regulation of COMT activity may modify the biological effect of estrogen and may have a role in leiomyoma formation.[32] Three genotypes have been identified. The Met/Met genotypes caused decreased enzymatic activity, the Val/Val associated with high enzymatic activity, and Val/Met genotypes showed intermediate enzymatic activities.[32]

The associations of ULM with *COMT Val158Met* polymorphism have been observed in patients from different ethnic groups. The genotypes frequencies of COMT polymorphism among different ethnic groups showed variations associated with ethnicity.[23–26]

Al-Hendy and Salama[25] compared the genotype frequencies of the functional *COMT Val158Met* polymorphism among participant women with or without fibroids and its relation to ethnicity; the results showed that women with the high-activity *COMT Val/Val* genotype are 2.5 times more likely to develop ULMs than women with other genotypes ($p < 0.01$). Interestingly, the frequency of *COMT Val158Met* genotype was significantly higher in African American women (47%) compared with white (19%) or Hispanic (30%) women ($p = 0.003$). While Ates et al[29] found no association between *COMT G158A* polymorphism and

ULM, both de Oliveira et al[27] and Ates et al[29] reported significant association between *COMT 1581 Met* allele and large fibroids. COMT is highly expressed in ULM tissue compared with normal myometrium; inhibition of its activity resulted in decrease clearance of 2-hydroxy E2 (a COMT substrate) that has an antiestrogenic effect.[28] Therefore, the biological effect of E2 and its metabolites can be modulated through COMT inhibitor, with potential therapeutic benefit for uterine fibroids.

A recent study examined Ro 41–0960, a synthetic COMT inhibitor, and its therapeutic effect on Eker rats bearing uterine fibroids, which demonstrated shrinkage in size uterine fibroids to maximum levels after 2 weeks of treatment, together with specific changes in leiomyoma structure through modulating estrogen-dependent genes that regulate apoptosis (*P53, PARPI*), proliferation (*PCNA, cyclin-D* I), and ECM formation (transforming growth factor-β [*TGF*-β]).[33]

CYP17 and CYP1A1—The *CYP17* gene encodes the cytochrome P450C17α enzyme, the enzyme that mediates steroid 17α-hydroxylase and 17,20-lyase activities. The 5′-untranslated region of *CYP17* has one base pair polymorphism, a T (designated as A1) to a C (designated as A2), 34 base pairs upstream from the initiation of translation, and 27 base pairs downstream from the transcription star site.[34] *CYP17* genotype is associated with steroidogenesis in premenopausal women, with possible evidence of direct genetic control of serum hormone.[35] Other polymorphic genes, such as *CYP1A1, CYP1B1, CYP19,* and *GST*, are also involved in steroid hormone metabolism and steroid hormone-dependent tumors. These polymorphic genes contribute to the ethnic difference in ULM pathogenesis.

Amant et al[36] investigated the role of *CYP17* gene polymorphism in the risk for leiomyoma development among black South African and white women and found that 16.9% of affected black South Africans were homozygous for the *CYP17A2* allele compared with 9.5% of affected white women. Further analysis concluded that age, race, parity, and *CYP17* polymorphism affect incidence of ULM (*p*-values are 0.0006, 0.0001, and 0.03, respectively) in black South African women.[36] One meta-analysis revealed an association of *CYP17A1* polymorphism with multiple ULM but not with all ULM.[37]

CYP1A1 gene polymorphism involved in the hydroxylation of estrogen may have influence on the degree of estrogen metabolism via C-2 hydroxylation. The presence of homozygous allele for *CYP1A1* gene was increased in African American compared with white women affected with breast cancer.[38] Recent studies reported the association between *CYP1A1* gene polymorphism and increased risk for development of ULMs.[39-41] However, more studies are needed to investigate the polymorphism of these genes and develop better understanding of the pathogenesis of ULM and their association to ethnicity.

Transforming Growth Factor-β Receptors and Over Expression

TGF-β) expression is elevated in a wide array of fibrotic processes, including pulmonary fibrosis, liver cirrhosis, scleroderma, keloids, as well as leiomyomas.[42-48] TGF-β directly affects leiomyoma ECM production, stimulating COL1A1 template expression as well as plasminogen activator inhibitor-1 expression.[49] Anti-TGF-β antibody, when used to treat

primary human leiomyoma cell cultures, decreased expression of COL1A1 and COL3A1, suggesting that TGF-β stimulates the production of these collagens in leiomyoma cells.[50]

While TGF-β is elevated in a wide range of fibrotic diseases, TGF-β may also play a role in the greater prevalence of leiomyomas in women of African descent. Eiser[51] hypothesized that heritable polymorphisms in TGF-β may not only result in elevated leiomyoma formation but also elevation in other diseases characterized by aberrant fibrosis, including hypertension, diabetic glomerulosclerosis, keloids formation, and sarcoidosis. Future analysis and understanding of TGF-β may provide insight into racial disparities in leiomyoma formation.

There is evidence of differential regulation of ECM components depending on the specific TGF ligand. While Ding and colleagues[49] found that TGF-β_1 treatment inhibited fibronectin expression, Arici and Sozen[52] demonstrated that TGF-β_1 did not alter fibronectin template expression. However, a different isoform, TGF-β_3, induced fibronectin expression.[52] In tissues of mesenchymal origin, including myometrium and leiomyomas, the dominant TGF-β isoform was TGF-β_3.[53] These findings suggest that regulating the specific TGF-β receptor ligand can result in different effects in leiomyoma cells. In studies evaluating versican variants, TGF-β_3 stimulated and anti-TGF-β inhibited versican variant V0 expression in immortalized human leiomyoma cell culture.[54] Taken together, these data suggest that endogenous overexpression of TGF-β_3 maintains a fibrotic phenotype in human leiomyomas.

To test this hypothesis, further studies determined whether myometrial cells would develop a fibrotic phenotype similar to leiomyoma cells when treated with TGF-β_3. Results showed COL1A1, fibronectin-1, and CTGF expression increased to levels comparable with expression levels found in leiomyoma cells.[55] Furthermore, MMP-11, but not MMP-2, was regulated in leiomyoma cells. These studies demonstrated a central role of TGF-β_3 in the development of the fibrotic phenotype that defines leiomyomas.

Based on these insights, regulation of TGF-β might be exploited for therapeutic benefit. Promising therapeutics that inhibit TGF-β function include leuprolide acetate,[56] epigallocatechin gallate,[57] 1,25-dihydroxyvitamin D3,[58] Ro 41–0960,[33] genestein,[59] halofuginone,[60] rosiglitazone,[61] asoprisnil,[62] and various Korean medicinal ingredients.[63] Future studies to rapidly assess which of these compounds has the greatest impact on TGF-β function and ECM formation in formed leiomyomas might result in advances in the management of ULMs.[64]

Retinoic Acid Nuclear Receptors

The retinoic acid metabolic pathway is dramatically disrupted in human leiomyomas, compared with patient-matched myometrium.[65] The molecular pattern minimizes cellular exposure to retinoic acid by decreasing cellular retinol binding protein, alcohol dehydrogenase, aldehyde dehydrogenase, and cellular retinoic acid–binding protein. Any produced retinoic acid is metabolized at a greater rate by increased CYP26A1 in leiomyomas compared with myometrium. Furthermore, retinoic acid receptor α (RARα) expression is decreased in leiomyoma compared with normal myometrium in African

American women.[14] This represents a further inhibition of retinoic acid signaling in women of African descent and contribute to the increased prevalence of leioyomas in this group.

Human leiomyoma cells in culture, when treated with all-trans retinoic acid (ATRA), proliferate more slowly. Molecular analysis demonstrated expression of RARs and retinoic acid X receptors (RXRs).[66] However, RXRα concentration is higher in leiomyoma tissue compared with myometrial tissue during the follicular phase.[67] Retinoic acid is a differentiating agent tested on human leiomyoma cells to determine whether ATRA can influence ECM production. With increasing concentration of ATRA, expression of COL1A1, COL4A1, COL7A1, fibronectin, and versican V0, V1, and V3 isotypes approach expression levels found in myometrial cells.[68] Furthermore, leiomyoma cell soluble collagen concentrations decrease with ATRA treatment, and fibronectin protein inhibited by ATRA treatment as assessed by cytoimmunofluorescence.

Therapeutically, retinoic acid has been used for various cancers of differentiation.[69–71] However, treatment results in significant side effects,[72] and is therefore not acceptable as a short- or long-term therapy for human leiomyomas. Alternative therapies that regulate the retinoic acid signaling pathway, however, have demonstrated promise. In animal studies, the retinoic acid agonist targretin inhibited tumor formation and size.[73] Liarozole, a retinoic acid metabolic blocking agent,[74] increases intracellular retinoic acid without inducing significant side effects.[75] Liarozole inhibits leiomyoma cell proliferation and ECM formation in human leiomyoma cells.[76] Future studies elucidating the mechanism of retinoic acid function in the development of human leiomyomas, and in particular how this pathway may be exploited to lower the health disparities in women of color, along with novel low-toxicity therapies, will provide additional therapeutic options to women suffering from leiomyomas.

Higher Aromatase Levels in Myometrium from African American Women

As mentioned earlier, leiomyoma growth is dependent on estrogen. Although there are extra ovarian resources for estrogen, the ovary is the most important source for estrogen production. Aromatase enzyme catalyzes the conversion of C19 steroids to estrogen; it is expressed in number of human cells, including ovarian granulose cell, placental syncytiotrophoblast, testicular Leydig cells, and adipose fibroblast.[77,78]

Leiomyoma tissues were found to have high levels of aromatase mRNA and high estrogen levels compared with surrounding myometrial tissues. Furthermore, conversion of androstenedione to estrone occurs in leiomyoma tissues and leiomyoma smooth muscles cells. This conversion does not occur in normal myometrial tissues and cells.[79,80] It was also noted that local aromatase activity caused in situ estrogen production in leiomyoma tissues and increase cell growth in an intracrine manner.[81] *CYP19* is a single gene that encodes aromatase, and suppression of its expression inhibits estrogen production in the entire body. The downstream 30-kb region consists of nine coding exons (II–X). The upstream 93-kb portion of the *CYP19* gene is composed of multiple promoters that direct transcription of alternative first exons giving rise to aromatase mRNA parts with unique 5′-translated region.[77] Gene expression is regulated by activation of several promoters.[77] identification of alternative aromatase promoters in estrogen-dependent tissues provides important

information on signaling mechanisms that regulate aromatase expression. Leiomyoma tissues are regulated by promoter I.3/II region in African American and white women,[82] while promoter I.4 regulates aromatase expression in leiomyoma tissue of Japanese women.[83] Ishikawa et al[84] compared the mRNA levels of aromatase in leiomyoma tissues and adjacent myometrial tissues obtained from women with same age and cycle phase but with different ethnicity. The authors reported strikingly higher levels of aromatase mRNA 83-fold in African American, 38-fold in white, and 33-fold in Japanese women.

Vitamin D deficiency as a Risk Factor for Uterine Fibroids

Vitamin D is one of the fat-soluble vitamins that primarily produced endogenously by exposure of skin to sunlight. It converts mainly in the liver and kidney to the active metabolite 1,25-dihydroxyvitamin D [$1,25(OH)_2D_3$]. It can be obtained exogenously by ingestion of D-fortified food and dietary supplements.[85] Vitamin D is a potent antiproliferative and immune modulator secosteroid hormone that activates vitamin D receptor (VDR) via a ubiquitous signaling pathway to initiate target gene expression. VDRs are expressed in the myometrium and endometrium throughout the menstrual cycle.[86-88] Vitamin D [$1,25(OH)_2D_3$] antiproliferative action is mediated via a G_1/S phase block of the cell cycle. It regulates many of the regulatory genes in the cell cycle and modify the kinase activities of the cyclin-dependent kinase resulting in decreased numbers of cell in the S phase and accumulation of cells in the G0–G1 phase in cancer cells.[89–91] Vitamin D3 also prevents mutagenic signaling from estrogen, epidermal growth factor, insulin-like growth factor, and increase growth factors inhibitor.[92] Recent studies showed that vitamin D inhibited extracellular signal regulation for kinase activity and downregulated the expression of antiapoptotic (BCL-2, BCL-w) cell cycle regulating (cyclin-dependent kinase 1) and cell proliferating genes (proliferating cell nuclear antigen) in cultured human fibroid cells.[93]

Vitamin D produces its antifibrotic effect on fibroid cells in a dose-dependent fashion by reducing (TGF-β_3) its mediated effect on fibronectin and collagen type 1 protein expression and protein expression of plasminogen activator inhibitor-1. In addition, vitamin D suppresses TGF-β_3–induced phosphorylation of *smad2* and nuclear translocation of *smad2* and *smad3* in fibroid cells.[58]

Vitamin D deficiency is estimated to be 10 times more common in African American women (40%) compared with white (4%) and the reason for this high prevalence of vitamin D deficiency among African American is still unknown.[94] Recent data showed significant association between lower serum vitamin D levels and ULM ($p < 0.05$) among different ethnic groups. Further analysis showed negative correlation between serum vitamin D levels and ULM size ($r = -0.42$; $p < 0.001$) among black individuals.[95]

Vitamin D treatment used in Eker rats showed significant reduction and shrinkage in ULM size by suppressing cell growth and proliferation-related genes (*Pcna, cyclin D1* [*Ccnd1*], *Myc*, *Cdk1*, *Cdk2*, and *Cdk4*) and antiapoptotic genes (*Bcl2* and *Bcl2l1* [*Bcl-x*]), with decreased expression of PCNA and MKI67 (a marker of proliferation) and increased expression of caspase 3, after 3 weeks of treatment and with no adverse effect.[96] Further studies are needed to test vitamin D treatment effect and safety as an alternative therapy.

Understanding the molecular differences in vitamin D action may help to explain ethnic differences in ULM.

Ethnic Differences in Clinical Manifestation and Treatment of the Disease

Uterine fibroids are three times more common in African American women and two times more common in Hispanic women compared to white women.[25,97] African American ethnicity is thought to be a risk factor for the development of leiomyoma probably due to earlier age of diagnosis, more severe symptoms, and different responses to treatment in this group.[98] Ultrasound screening indicated that age of onset is earlier by 10 to15 years in African American women.[99] The size, multiplicity, and growth rates of ULM are higher in African American women and these women are more likely to undergo surgical intervention.[99]

In the United States, 42 per 10,000 women are annually hospitalized due to leiomyoma. African American women had increased rates of hospitalization, myomectomy, and hysterectomy (relative risk, 3.5, 6.8, and 2.4, respectively) compared with white women.[100] Wilcox et al[101] evaluated data on hysterectomy in the United States and demonstrated that 61% of African American women had hysterectomies, and fibroids was the main indication compared with 29% in white women.

Postoperative complications as well as surgical procedures were more common in African American women. Kjerulff et al[3] estimated postsurgical complications in 1,200 women who had hysterectomies. Data showed that African American women experienced severe postsurgical pain (59%) and suffered from anemia (56%) compared with Caucasian women who experienced less postsurgical pain (41%) and anemia (38%). The higher complication rate may be a result of larger uterine size in African American women. The average uterine weight was significantly higher among African American women (421 g) compared with Caucasian women (319 g). Another study estimated postoperative complications after myomectomy twofold higher in African American women compared with white women (odds ratio [OR], 2.5; 95% confidence interval [CI], 1.5–4.8). Furthermore, blood transfusions were significantly higher among the African American patients (OR, 2.3; 95% CI, 1.1–5.0).[102]

In addition to more severe disease and higher complication rates, African American women also have disparate access to care. One large cohort study that compared laparoscopic hysterectomies rates among different races for the treatment of ULM and menorrhagia between 1998 and 2002 reported that even with same median household income, African American, Hispanic, and women of other ethnic minorities were less likely to undergo laparoscopic hysterectomies when compared with white women, who have the highest rates for laparoscopic hysterectomies (62%).[103]

Culture and Environmental Effects

ULM is a multifactorial disease. Culture/environmental interactions in the pathogenesis of disease are all variables that should be considered. In the following section, we will focus on published data examining the effect of culture/environmental variation on ULMs.

ULMs are hormonally responsive tumors; therefore, early life or in utero exposure influences uterine development and uterine sensitivity to steroid hormones later in adult life.[104] This theory was supported by epidemiological studies reporting an increased risk of UL with early menarche and prenatal exposure to diethylstilbestrol (DES).[105–107] D'Aloisio et al[108] found increased risk of early-onset ULM in black and white women associated with early-life factors such as in utero exposure to DES, maternal pre-pregnancy diabetes, or gestational diabetes, with the exception of hypertensive disorders in pregnancy and multiple birth. Interestingly, childhood height and weight, but not socioeconomic status, was associated with early-onset ULM in black women.

Adults who have been exposed to childhood abuse are more likely to have various health-related problems, such as behavioral, mental, and physical health problems, than those without this experience.[109–111] Recent epidemiological study by Boynton-Jarrett et al[112] reported an association between early-life exposure to physical, sexual, and emotional abuse and risk of clinically detected ULM. In addition, cumulative exposure, severity of abuse, and duration of exposure were all related to ULM risk in a dose-dependent pattern; increased health utilization, pelvic examination, and ultrasound examination in women exposed to abuse might explain this association.[113]

National surveys showed that African American adults have lower intake of fruits, vegetable, fiber, and carotids and less likely to take vitamin and mineral supplement.[114–116] Wise et al[117] examined the association between ULM and dietary intake of fruit and vegetables in African American and found that fruit intake, specifically citrus fruit, was associated with stronger risk reduction in ULM development. Also, dietary vitamin A derived from animal sources was inversely associated with ULM risk.

Tobacco, alcohol, and caffeine consumptions are risk factors that may affect ovarian function and cause alterations in hormone levels and metabolism. To assess influence of the risk factor on ULM development, Wise et al[118] examined the relationship between alcohol and caffeine consumption and cigarette smoking and the development of leiomyoma. The authors reported a positive correlation between duration of alcohol consumption, mainly beer, and risk for ULM among African American women who drink compared with those who do not drink. No association was found with cigarette smoking and caffeine consumption.

Many black women use hair relaxers; the main ingredient of relaxers is sodium hydroxide (lye); no-lye relaxers contain calcium hydroxide and guanidine carbonate; and "thio" relaxers contain thioglycolic acid salts.[119] Relaxers may also contain hormonally active ingredients such as phthalates that can be absorbed from skin or by inhalation. Phthalates have been shown to have an estrogenic effect in cell models and experimental animals, but there is little human data.[120]

The third National Health and Nutrition Examination Survey (NHANES) reported that risk for ULM is positively correlated to urinary levels of monobutyl phthalate with negative association of urinary levels of mono(2-ethylhexyl) phthalate to ULM risk.[121] Another case–control study found higher levels of total urinary monoethylhexyl phthalate in ULM among

studied cases.[122] In addition, increased risk for ULM was found among hair relaxer users, and positive association between frequency/duration of use and ULM risk was also observed.[123]

Stress from major life event (MLE) is considered a risk factor for poor mental and physical health outcome especially with acute changes (e.g., loss of spouse/child, divorce, birth of first child) in life that result in behavioral misjudgment.[124] There is evidence indicating that stress may increase risk for ULM probably due to fluctuations in estrogen and progesterone hormone levels, which play major role in fibroid development. Stress results in activation of the hypothalamic– pituitary–adrenal axis and the release of cortisol, which is a stress hormone.[125] Epidemiological studies reported higher incidence of MLE among African American women compared with white women. The factors related to this difference in MLE appear to be relationships, financial issues, residential changes, and discrimination.[126,127] Vines et al[128] reported positive association between the number of events and the prevalence of fibroids, with average two MLEs among participants. After adjusting other ULM risk factors, the presence of ULM among African American were significant in the high stress group compared with those without an experienced event (prevalence ratios (PR), 1.2; 95% CI, 1.1–1.4). However, these data suggest a need for further studies to improve knowledge about MLE as a risk factor for onset of disease and progression.

Conclusion

Although ULMs are a very common gynecologic disease worldwide that can adversely affect a women's reproductive health, fertility, and birth outcome, complete understanding of ULM pathogenesis remains unclear. Advances in research during the past decade have revealed racial disparities based on molecular differences in leiomyoma development, clinical course, and response to treatment. African American ethnicity is considered a risk factor, with a higher prevalence than for other races. Discrepancy in levels of genes expression, polymorphism of genes involved in estrogen synthesis and/or metabolism (*COMT, CYP17*), aberrant expression of micro-RNAs, variation in the expression levels of retinoic acid nuclear receptors (retinoid acid receptor-α, retinoid X receptor-α), aromatase levels, and vitamin D deficiency are some of the molecular mechanisms that have been investigated. Epidemiological studies have demonstrated a significant association between race and environmental effects on ULM onset and growth. Future studies are required to develop insight into difference in leiomyoma formation among ethnic groups.

Acknowledgments

The authors acknowledge the support and assistance of Drs. DeCherney and Zahn. This research was supported, in part, by NIH grants to authors A.A. and W.C.

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