Endocrine-disrupting chemicals and uterine fibroids

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Uterine fibroids are the most frequent gynecologic tumor, affecting 70% to 80% of women over their lifetime. Although these tumors are benign, they can cause significant morbidity and may require invasive treatments such as myomectomy and hysterectomy. Many risk factors for these tumors have been identified, including environmental exposures to endocrine-disrupting chemicals (EDCs) such as genistein and diethylstilbestrol. Uterine development may be a particularly sensitive window to environmental exposures, as some perinatal EDC exposures have been shown to increase tumorigenesis in both rodent models and human epidemiologic studies. The mechanisms by which EDC exposures may increase tumorigenesis are still being elucidated, but epigenetic reprogramming of the developing uterus is an emerging hypothesis. Given the remarkably high incidence of uterine fibroids and their significant impact on women's health, understanding more about how prenatal exposures to EDCs (and other environmental agents) may increase fibroid risk could be key to developing prevention and treatment strategies in the future. (Fertil Steril® 2016;106:967–77. ©2016 by American Society for Reproductive Medicine.)

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GENERAL OVERVIEW

Uterine Fibroids: The Human Disease

Uterine fibroids (UFs) affect 70% to 80% of women during their lifetime and are the leading indication for hysterectomies in premenopausal women, with over 200,000 per year performed in the United States (1–4) at a cost of up to $34 billion each year (5). Medical management and uterine-preserving procedures are available to treat this disease, but the lack of comprehensive data comparing treatment options leads most practitioners to resort to the classic treatment of hysterectomy (6). Although UFs are benign tumors, they can cause a variety of symptoms such as pain, bleeding, and bladder dysfunction as well as complications leading to infertility, miscarriage, and other reproductive disorders (7–10).

Arising in the myometrial layer of the uterus, UFs are hormonally responsive to estradiol and progesterone as well as other steroid hormones, and they regress after menopause (11). The cause of uterine fibroids is largely unknown, but there are established risk factors: increased age up to menopause, increased body mass index, nulliparity, early age at menarche, family history, and African American ethnicity (11, 12). Although many of the risk factors for this disease are hormone related, the mechanism underlying the increase in risk for African American women compared with Caucasians remains to be identified (1, 2, 13–16).

The incidence of UFs is likely underestimated, as only 20% to 50% of women with fibroids will develop symptoms (1, 17). Data on the latency for development of these tumors is limited, although the time of onset is thought to be 10 to 15 years earlier for African American women (1, 12, 18). Ultrasound has been used to find clinically undiagnosed UFs (1, 18–20), but only one study has found fibroid-free women prospectively to ascertain the timing of fibroid onset (21). The Study of Environment, Lifestyle, and Fibroids (SELF) was designed to investigate the timing of UF onset. The SELF study enrolled 1,696 African American

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women aged 23 to 34 years without UFs in the Detroit area from 2010 to 2012 and plans follow-up evaluations every 20 months with ultrasound assessment to determine more precisely the onset of UFs (21).

In addition to hormones, these lesions are influenced by genetic aberrations as well as growth factor signaling pathways. Translocations in the high mobility group genes *HMGA1* and *HMGA2* have been described, possibly influencing fibroblast growth factor pathway activity and resulting in increased tumor size (22, 23). The mediator complex subunit 12 (*MED12*) gene has been reported to be mutated in UFs in multiple cohorts of women, including American, South African, and Finnish studies (24–28). There are also genetic factors that predispose to these tumors as part of heritable cancer syndromes, including mutations in fumarate hydratase (*FH*) seen in patients with hereditary leiomyomatosis and renal cancer (29, 30). An enzyme in the tricarboxylic acid cycle, *FH* acts as a classic tumor suppressor, with mutations in *FH* significantly increasing the risk of fibroids in the uterus and other tissues in patients with hereditary leiomyomatosis and renal cancer (31).

Endocrine-disrupting Chemicals and Uterine Fibroids

As defined by the U.S. National Institute of Environmental Health Sciences (NIEHS), endocrine-disrupting chemicals (EDCs) are "chemicals that interfere with the body's endocrine system and produce adverse developmental, reproductive, neurological and immune effects." The endocrine system is composed of glands that are distributed throughout the body that synthesize the hormones that are released in the circulatory system to regulate development, physiologic processes, and homeostatic functions. These glands include, but are not limited to, the hypothalamus, pituitary, thyroid, and reproductive organs. Endocrine-disrupting chemicals can be natural or man-made, such as pharmaceuticals, plasticizers, dioxins, polychlorinated biphenyls (PCBs), organochlorines, polyfluoroalkyls (PFOAs), phthalates, and pesticides. Although the route of exposure depends on the individual EDC, common routes of exposure in humans are ingestion, inhalation, and dermal absorption. Importantly, EDCs can exhibit non-monotonic dose–response curves, and low doses of EDCs can produce a pathophysiologic effect (32).

Numerous EDCs have been shown to interact with nuclear receptors to exert their actions in target tissues (32). The binding of EDCs to nuclear receptors can alter hormone functions by mimicking naturally occurring hormones in the body, blocking the endogenous hormone from binding or interfering with the production or regulation of hormones and/or their receptors. An individual EDC may interact with more than one receptor, and multiple EDCs can interact with the same receptor, highlighting the complexity of the response of animals and humans to environmental EDC exposures. For example, the xenoestrogen bisphenol A (BPA) has been shown to bind and activate estrogen receptor (ER) (33, 34), estrogen-related receptor γ (35), and pregnane X receptor (36). In addition to BPA, a variety of other EDCs, such as diethylstilbestrol (DES), polychlorinated biphenyls (PCBs), polyfluoroalkyl (PFOA), and phthalates, can also bind to ERs (33, 37–40).

Liganded nuclear hormone receptors that function as transcription factors interact with DNA, producing what are termed "genomic" effects that regulate gene transcription, but they are also capable of action outside the nucleus via what is termed "nongenomic signaling" (41, 42). Endocrine-disrupting chemicals are also capable of inducing both genomic and nongenomic signaling: both BPA and DES, for example, have been shown to activate nongenomic signaling pathways through the ER (43–48). Regardless of the mode of action, EDCs have been linked to several adverse health outcomes including diabetes, obesity, cardiovascular disease, reproductive tract disorders, and neurodevelopmental disorders (32).

PATHOGENESIS OF UTERINE FIBROIDS

Chromosomal Alterations and *MED12* Mutations

In contrast to mutations that are inherited from a parent and present throughout a person's life in virtually every cell in the body, somatic mutations associated with clonal tumors such as fibroids occur in a single progenitor cell in tissues, from which the tumor arises. Most UFs cases are sporadic in nature, but a few rare familial syndromes are associated with development of UFs. In these syndromes, genetic alterations occur in the *FH*, *COL4A5*, and *COL4A6* genes (49). In sporadic tumors, several recurrent genetic aberrations have been identified, including deletions in 7q, trisomy of chromosome 12, reciprocal translocation of chromosome 12, and monosomy of chromosome 22, among others (50–52). However, these genetic alterations occur at relatively low frequency.

By contrast, *MED12* somatic gene mutations have been found in sporadic UFs with a very high frequency (70% to 80%) (25). The *MED12* gene encodes one of the components of the Mediator complex, which consists of 26 subunits that bridge DNA regulatory sequences to the RNA polymerase II initiation complex. The Mediator complex is highly conserved in eukaryotes and can participate in transcriptional repression or act as a positive coregulator (25, 53). Pathway analysis in *MED12*-deficient UFs demonstrated that focal adhesion, extracellular matrix receptor interaction, and Wnt signaling are substantially altered in these tumors (25). Subsequent studies have confirmed the important role of *MED12* mutation in UFs (24, 25, 28, 54–56), making *MED12* somatic mutations the most widely detected DNA mutation in human fibroid lesions.

Nuclear Hormone Receptors

Estrogen receptors. A striking feature of UFs is their dependency on the ovarian steroids estrogen and progesterone (50, 57). Both clinical and experimental data suggest that estrogen stimulates the growth of UFs during reproductive years. Regression is seen after menopause, and continuous gonadotropin-releasing hormone agonist treatment inhibits UF growth by decreasing ovarian hormone production. Estrogens, such as 17β-estradiol, exert their biologic effects