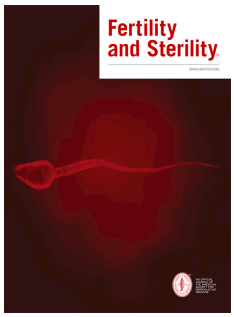

Solving the mysteries surrounding uterine fibroids: are we almost there?

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Introduction to V&R 2024 on fibroids

Solving the mysteries surrounding uterine fibroids: are we almost there?

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Keywords: Fibroids, pathogenesis, diagnosis, abnormal uterine bleeding.

Capsule: Shedding light on uterine fibroids

Short narrative abstract: A better understanding of uterine fibroid-related pathogenesis and symptoms like uterine bleeding and infertility is mandatory.

Uterine fibroids are the most commonly encountered female benign pelvic tumors, affecting over 50% of patients aged 35-50 years. This Views and Reviews piece encompasses 4 manuscripts. The goal is to acquire a better understanding of uterine fibroid-related pathogenesis and symptoms like uterine bleeding and infertility in order to pinpoint new strategies and an individualized approach.

In a first manuscript, Dolmans et al (1) evaluated the widely accepted pathogenesis and identified risk factors and future directions for clinical and basic research into fibroids. Their

prevalence depends upon ethnicity, age, age at menarche and parity, which has a protective effect. Indeed, delaying the first pregnancy until the third decade of life is known to place women at higher risk of myomas. Other risk factors including some genetic alterations are also in play.

Dolmans et al (1) pointed out that ovarian steroid hormones, and especially progesterone, are major actors in the pathogenesis of uterine fibroids. Sex steroids are crucial to fibroid development and growth, but a number of autocrine and paracrine messengers are also involved in this process. A single myometrial stem cells is genetically transformed into a tumor-initiating cell because of various factors, including genomic instability, inflammatory microenvironment, and developmental and environmental insults. It has been suggested that MED-12 exon 2 mutations could give myometrial stem/progenitor cells a selective advantage by altering their growth and/or trajectory of differentiation, leading to formation of uterine fibroid stem cells. The adverse effects of endocrine-disrupting chemicals present in plasticizers, dioxins, polychlorinated biphenyls, organochlorines, phthalates and diethylstilbestrol and their direct association with the estrogen receptor and epigenetic reprogramming of the developing uterus are also considered a conceivable hypothesis. Epigenomic changes found in uterine fibroids like aberrant DNA methylation and histone tail modifications can dysregulate gene expression, which helps form the uterine fibroid phenotype. The role of vitamin D, which acts as an antiproliferative compound against small uterine fibroids by arresting cell growth is also discussed.

In their manuscript, Mension et al (2) analyzed different diagnostic tools to characterize the number and location of myomas. They believe that standardizing descriptions of transvaginal ultrasound (TVUS) images according to updated classifications and individualizing use of various complementary tools is crucial to achieving precise uterine

mapping. When a uterine fibroid is suspected, the first diagnostic tool is TVUS, thanks to its high sensitivity and specificity, low cost and easy accessibility. In certain cases, however, magnetic resonance imaging (MRI) may prove to be more accurate. MRI was shown to be a helpful complementary imaging technique to TVUS for assessment of women presenting with coexisting endometriosis and adenomyosis. In case of multiple fibroids (>4), a large uterus (>375 cm^3) or suspected malignancy, MRI appears to be superior to TVUS. Other emerging techniques like saline infusion sonohysterography, elastography and contrast-enhanced ultrasonography are also discussed, as is the role of artificial intelligence that has truly begun to show its worth as a complementary tool to improve diagnostic efficacy.

In their manuscript, Vannuccini et al (3) highlight that uterine fibroids may affect quality of life and women's health in around 30% of cases. Abnormal uterine bleeding (AUB) and heavy menstrual bleeding (HMB) are the most common complaints, accompanied by iron deficiency and anemia. Fibroids represent a considerable health burden and current management strategies are mainly surgical and expensive. One-third of 600,000 hysterectomies carried out every year in the United States are for fibroids. Vannuccini et al (3) evaluated existing medical treatments for uterine fibroid-related AUB, including symptomatic agents, like nonsteroidal anti-inflammatory drugs and tranexamic acid, and hormonal therapies like combined oral contraceptives, gonadotropin-releasing hormone (GnRH) agonists or antagonists, levonorgestrel intrauterine systems, selective progesterone receptor modulators and aromatase inhibitors. Surgical options and nonsurgical techniques such as uterine artery embolization, high-intensity focused ultrasound or magnetic resonance-guided focused ultrasound and radiofrequency ablation were all considered. As stressed by the authors (3), therapy should be individualized based on clinical profile and fibroid characteristics (location, size, multiple myomas or coexistent adenomyosis), as well as patient preference and

reproductive wishes. Shared decision-making should be the basis for treatment selection, considering both long- and short-term treatment goals of patients.

In the fourth manuscript, Donnez et al (4) reported that fibroids are being increasingly encountered in women seeking a medical opinion for infertility issues for two main reasons: a longer reproductive timeline, and the current trend for women to postpone childbearing. As the focus of this review was infertility, the mechanisms by which fertility may be impaired by the presence of fibroids were analyzed in detail. The first widely documented mechanism is uterine cavity distortion responsible for defective blastocyst implantation due to changes in endometrial receptivity. Others include impaired endometrial and myometrial blood supply and increased uterine contractility, which interfere with embryo implantation. Complex series of interactions allow successful implantation of the embryo during the window of implantation, but fibroids can alter expression of genes important for implantation. Diminished release of cytokines critical to implantation, such as leukemia inhibitory factor and cell adhesion molecules, are attributed to the presence of myomas. The roles of transforming growth factor beta-3 (TGF-β3) and HOXA-10 in endometrial receptivity are well documented.

Concerning treatment, the real question is this: is there a place for surgical management of uterine fibroid-related infertility? According to the literature, there are areas of uncertainty surrounding the management of myomas, so the risks and benefits of each option should be discussed with patients. Although current management strategies involve mainly surgical interventions, new drugs (GnRH antagonists) may play a role, as they can induce a significant reduction in fibroid volume. Donnez et al (4) suggest therapy with GnRH antagonists without add-back therapy for a short period of 3 months, which may help restore distorted uterine cavities that impede fertility, thereby reducing the need for uterine surgery.

In conclusion, fibroids are a common pathology increasingly observed in women suffering from infertility. The current trend for women to postpone childbearing is making myoma-related infertility increasingly common and new algorithms are urgently needed.

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