Fibroid growth and medical options for treatment

Nathalie Chabbert-Buffet, M.D., Ph.D.,[a] Nathalie Esber, M.Sc.,[b,c] and Philippe Bouchard, M.D.[d,e]

[a] Obstetrics, Gynecology and Reproductive Medicine Department, AP-HP, Hospital Tenon, Paris; [b] INSERM, U693, Le Kremlin-Bicêtre; [c] Faculté de Médecine Paris-Sud, Le Kremlin-Bicêtre; [d] Univ Paris-Sud, UMR-S693, Le Kremlin-Bicêtre; and [e] UPMC Paris 06, Paris, France

Although fibroids are common benign tumors, their impact on women's quality of life can be considerable. The most frequent symptoms are uterine bleeding, resulting in anemia, and pelvic pain. Fibroids can be of genetic or hormonal origin or arise from intrauterine events. Current options for medical treatment include control of estradiol and progesterone production or action and are discussed in this review. Although curative treatment of fibroids relies on surgical strategies, the current trend is for uterine-sparing treatment to preserve fertility and avoid unnecessary surgery. Currently approved medical treatments include intrauterine progestin delivery to reduce uterine bleeding, GnRH analogues, and, more recently, selective progesterone receptor modulators to control uterine bleeding and reduce fibroid volume. (Fertil Steril® 2014;102: 630–9. ©2014 by American Society for Reproductive Medicine.)

Key Words: Fibroids, sex steroids, fibroids treatment, progestins, selective progesterone receptor modulators, selective estrogen receptor modulators

Discuss: You can discuss this article with its authors and other ASRM members at http://fertstertforum.com/chabbertbuffetn-fibroids-growth-medical-treatment/

Use your smartphone to scan this QR code and connect to the discussion forum for this article now.*

* Download a free QR code scanner by searching for "QR scanner" in your smartphone's app store or app marketplace.

Fibroids are the most common gynecologic tumors, occurring in ~70% of women over 30 years of age (1). They are benign tumors developing in the myometrium. Despite the high incidence of the disease and its impact on women's quality of life, there has been relatively little research on fibroids until recently (2).

Fibroids develop from a single myometrial smooth muscle cell and are therefore classified as a clonal disease (3, 4). Risk factors for developing fibroids, apart from ethnic origin and heredity, include situations causing prolonged high exposure to estrogens and/or progesterone, such as early age of menarche (5, 6), polycystic ovary syndrome (7), obesity (8), and late pregnancy (9). Consistent with these epidemiologic data, the best known stimulator of tumor growth is the combined action of estrogens and progesterone. Growth factors, cytokines, and chemokines (1) have also been described as playing a role. Several animal and in vitro models (5) developed over the past decade have contributed to a better understanding of the disease.

Fibroids are mostly asymptomatic (80%) but can induce symptoms with a high impact on women's health (10) depending on their size and location. Until recently, they were largely classified as being either subserosal or interstitial. However, the International Federation of Gynecology and Obstetrics now recognizse eight subtypes: types 0–2, submucosal; 3–5, interstitial; 5–7, subserosal; and 8, extrauterine (e.g., parametrium; Fig. 1) (11). Heavy menstrual bleeding is the most frequent fibroid-related symptom, resulting in reduced quality of life and anemia (5), and it can be related either to the location of the fibroid (submucosal) or to fibroid-related endometrial dysfunction (11). In addition, associated endometrial lesions may be present in up to 20% women with abnormal uterine bleeding, particularly adenomyosis (12–15). Pretherapeutic workup should, of course, aim to identify these associated conditions, because they may require specific care.

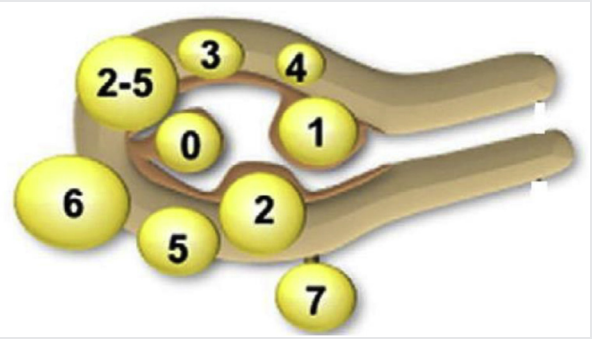
Symptoms related to tumor volume are less frequent and include pelvic pain, dyspareunia, and urinary symptoms, such as pollakiuria and dysuria. Fibroid volume can also occasionally result in urinary tract compression and ureteral dilation, which can lead to renal dysfunction. The role of fibroids in infertility is limited and mostly related to submucosal lesions resulting in implantation defects (16). Whether large interstitial fibroids can cause infertility through deformation of the uterine cavity is still under discussion (16). However, although African women have a high incidence of fibroids and more severe lesions, their rate of fertility remains high even

Received June 9, 2014; revised and accepted July 15, 2014.
N.C.-B. is a member of the French Gedeon Richter's scientific advisory board. N.E. is funded by HRA Pharma for her Ph.D. P.B. is a member of Preglem's scientific advisory board.
Reprint requests: Nathalie Chabbert-Buffet, M.D., Ph.D., Obstetrics Gynecology and Reproductive Medicine Department, Tenon Hospital, 4 rue de la Chine, 75 020 Paris, France (E-mail: nathalie.chabbert-buffet@tnn.aphp.fr).

Fertility and Sterility® Vol. 102, No. 3, September 2014 0015-0282/$36.00

http://dx.doi.org/10.1016/j.fertnstert.2014.07.1238

FIGURE 1



The 2011 FIGO classification of fibroids (reproduced from Munro et al. [11] with permission).

Chabbert-Buffet. Fibroids growth and treatment. Fertil Steril 2014.

though pregnancy usually occurs at an age where the rate of fibroids is already high: 25–35 years (17).

Although bleeding may have a marked impact on their quality of life, women often delay seeking medical advice. This may be because they underestimate the importance of the bleeding (18) or because of a fear of surgical treatment. It is therefore important that women are better informed about medical treatment options.

The only curative treatment to date is surgical removal either by myomectomy or hysterectomy. Although alternative surgical strategies have resulted in a reduction of the number of hysterectomies (19), 55,000 hysterectomies a year are still performed for fibroids in the United Kingdom and 600,000 in the United States (20), resulting in a heavy economic burden (21). Destruction techniques, by ultrasound or radiofrequency (22), are under evaluation as complementary or associated techniques. Endometrial ablation, either by surgical or physical means, such as thermablation (23), is an alternative option for women close to menopause who would like to avoid surgery (20). However, the current trend is for uterine-sparing therapeutic strategies, mainly because the age of a first pregnancy is on the increase. Because myomectomy can be detrimental on pregnancy outcome (24), medical options are frequently offered as a first-line option. Medical therapy is also required before surgery in women with fibroid-related anemia to reduce postoperative morbidity (25) or to facilitate endometrial ablation techniques (26).

Most medical treatments reduce bleeding. Modulators of estrogen signaling, such as aromatase inhibitors, and selective estrogen receptor modulators (SERMs) have been evaluated. Progestins are also used for this purpose but have limited efficacy and can induce tumor growth as discussed below. Finally GnRH analogues and selective progesterone receptor modulators (SPRMs) can be used to reduce both tumor volume and bleeding (Table 1).

FIBROID GROWTH

Although quite a lot is known about the factors contributing to fibroid growth, the pathophysiology of this disease remains largely unelucidated (1, 5).

Histology

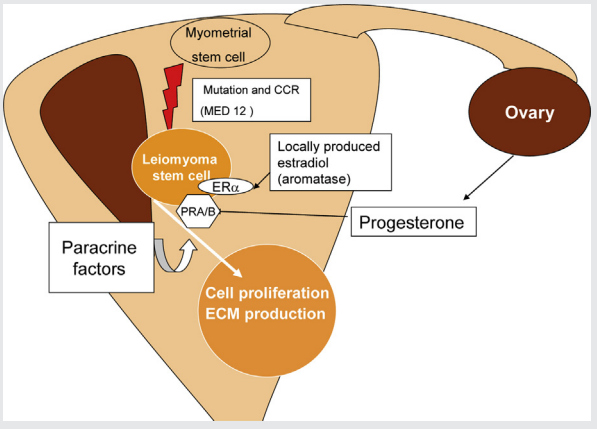
Fibroids are benign tumors developing in the myometrium (Fig. 2) and appear as a disordered organization of the myometrial cells forming spheres and nesting in abundant extracellular matrix (ECM) (9, 27). This results in the classic surgical description of fibroids as firm tumors with a clear dissection plane and easy to enucleate.

Other histologic presentations have been described, such as cellular fibroids with scarce ECM component or bizarre fibroids with unusual, but nonsuspect, tissue organization. Numerous other forms have also been described (9), including vascular fibroids, intravascular fibroids, and benign disseminating fibroids (leiomyomatosis) (28). These latter forms, though benign, can be life-threatening. Preoperative differential diagnosis with sarcoma is mostly based on the analysis of the tumor vascularization on Doppler-coupled ultrasound scan and magnetic resonance imaging (29). This differential diagnosis is important, especially in the case of a nonsurgical therapeutic option, even though sarcomas are extremely rare, occurring in ~10 out of 1 million women every year (30).

Stem cells may be involved in fibroid growth. Specific myometrial cellular subpopulations exhibiting myometrial stem cell characteristics have been identified (31) and found to be necessary for fibroid growth in an animal model (32). These cells appear to be pluripotent and may be tumor initiating (33). One single stem cell is thought to give birth to a specific fibroid (which is why it is called a clonal disease) (3, 4). Stem cells present in fibroids, compared with stem cells in normal myometrium, carry mutations of the *MED12* (mediator complex subunit 12) gene located on the X chromosome (32). This suggests a primary role of genetic events in the stem cells to allow tumor growth. *MED12* is one of the components involved in the control of transcription initiation in association with the preinitiation complex (34).

Finally, the role of the ECM in fibroid growth, as part of the tumor microenvironment, is also thought to be very

FIGURE 2



Fibroid growth. CCR = complex chromosomal rearrangement; ECM = extracellular matrix; ER = estrogen receptor; PR = progesterone receptor.

Chabbert-Buffet. Fibroids growth and treatment. Fertil Steril 2014.