Reproductive Sciences
1-26

DOI: 10.1177/1933719114533728
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Uterine Fibroids: Clinical Manifestations and Contemporary Management

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Abstract

Uterine fibroids (leiomyomata) are extremely common lesions that are associated with detrimental effects including infertility and abnormal uterine bleeding. Fibroids cause molecular changes at the level of endometrium. Abnormal regulation of growth factors and cytokines in fibroid cells may contribute to negative endometrial effects. Understanding of fibroid biology has greatly increased over the last decade. Although the current armamentarium of Food and Drug Administration-approved medical therapies is limited, there are medications approved for use in heavy menstrual bleeding that can be used for the medical management of fibroids. Emergence of the role of growth factors in pathophysiology of fibroids has led researchers to develop novel therapeutics. Despite advances in medical therapies, surgical management remains a mainstay of fibroid treatment. Destruction of fibroids by interventional radiological procedures provides other effective treatments. Further experimental studies and clinical trials are required to determine which therapies will provide the greatest benefits to patients with fibroids.

Keywords

leiomyoma, female infertility, growth factors, implantation

Introduction

Uterine leiomyomata, or fibroids, are the most common benign neoplasms in women of reproductive age, with a lifetime prevalence of 30% to 70%.[1,2] Approximately 30% of women with fibroids are symptomatic.[3] Black women have a 3-fold higher incidence of fibroids than white women.[4] Symptoms associated with these benign tumors include abnormal uterine bleeding (AUB), anemia, pelvic pressure and pain, dysmenorrhea, and reproductive dysfunction. Reproductive effects of fibroids include spontaneous abortions, impaired implantation, and infertility.[5] The total economic impact associated with fibroids in the United States (in 2010 dollars) was recently estimated to range between 6 and 34 billion dollars annually, including the direct costs (medical and surgical expenses) of 4 to 9 billion dollars and indirect costs (disability, lost wages, and costs due to obstetric complications related to fibroids) of 2 to 25 billion dollars.[6] The presence and severity of symptoms have traditionally been thought to be largely dependent on the size and location of the myomas (subserosal, intramural, or submucosal), although emerging evidence suggests that molecular mechanisms play an important role in the negative effects of fibroids.

Fibroids are hormonally responsive, and myoma growth is dependent on the ovarian steroid hormones estrogen and progesterone. They are rarely observed before puberty and are most prevalent during the reproductive years, then significantly diminish in volume after the menopause. Their growth pattern is influenced by endocrine and paracrine effects. Fibroid cells express estrogen receptor (ER) and progesterone receptor (PR) at levels greater than surrounding myometrial cells.[7,8] Fibroids also express aromatase that allows for endogenous production of estradiol.[9] The sensitivity of fibroids to estradiol is illustrated by the rapid decrease in fibroid size when patients are treated with gonadotropin-releasing hormone (GnRH) agonists, which induce a hypoestrogenic state. After discontinuation of GnRH agonist therapy, fibroids return to their pretreatment size, further demonstrating the growth response to estrogen. Progesterone also has a direct growth effect on fibroids. Peak mitotic activity in fibroids occurs in the luteal phase and in response to administration of progestational agents.[10-12] Administration of PR modulators such as the pure antagonist mifepristone (RU486) and the PR modulator ulipristal acetate results in a decrease in fibroid size.[13-16] Because of the hormonal regulation of fibroid growth, the majority of medical treatments have focused on manipulation of sex steroid activity.[17] Novel nonhormonal options are emerging for the medical management as we

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gain further understanding of the molecular signaling pathways involved in fibroid growth.[12,18-20]

Surgical management of fibroids is currently the mainstay of treatment. Between 2000 and 2004, of the approximately 600 000 hysterectomies performed in the United States annually, 41% were performed secondary to uterine fibroids (a hysterectomy rate for fibroids of 2.2 per 1000).[21] Although the definitive treatment is hysterectomy, conservative treatment options are available for women who wish to preserve their reproductive function. Conservative surgical management with myomectomy allows for surgical removal of fibroids without eliminating the possibility of pregnancy. Uterine fibroid embolization, in which polyvinyl alcohol particles are injected to selectively occlude the vessels feeding the fibroids, offers a nonsurgical treatment option in select patients.[22] Additional image-guided treatment modalities, including magnetic resonance imaging (MRI)-guided high-frequency focused ultrasound (MRgFUS), are promising techniques that offer minimally invasive management options for women with fibroids.[23] These minimally invasive procedures may effectively reduce the symptoms of excessive menstrual bleeding, pain, and pressure. Studies on reproductive outcomes after uterine fibroid embolization and MRgFUS are ongoing.[24,25]

Fibroids are benign tumors that originate from myometrial smooth muscle. They are composed of smooth muscle cells surrounded by an extracellular matrix (ECM) containing variable amounts of fibrous tissue and collagen. Unlike the quiescent myometrium, leiomyoma exhibits elevated rates of mitotic activity and S-phase fraction. Growth, proliferation, and differentiation of myometrial cells are regulated by complex interactions between ovarian steroids and growth factors produced locally.[26] These can be physiological, such as the growth and differentiation of myometrial cells in pregnancy that allow for expansion of the gravid uterus and increased contractility necessary for parturition. However, abnormal signaling within these pathways can lead to tumor formation. Fibroid tumorigenesis and enlargement are therefore due to signaling errors that cause increased proliferation in response to sex steroids and other growth factors.[27] A number of growth factors, including epidermal growth factor (EGF), platelet-derived growth factor (PDGF), insulin-like growth factor (IGF), heparin-binding EGF (HB-EGF), transforming growth factor (TGF) β, TGF-α, vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), and acidic FGF, are implicated in the development and proliferation of fibroids.[26,28-30] Aberrant regulation of these factors increases ECM components, including collagens, proteoglycans, and fibronectin, in a disorganized fashion.[31-33] These factors are differentially regulated by sex steroids and interact with each other to contribute to fibroid tumorigenesis.[34] Recently, these growth factors have been implicated in defective endometrial signaling with adverse effects on embryo implantation and regulation of endometrial hemostasis.[35]

Fibroids are associated with AUB, most commonly presenting with heavy menstrual bleeding (HMB).[36] Normal menstruation can be thought of as a ''controlled hemorrhage'' that requires a coordinated response to progesterone withdrawal.[37] The classic theory for the etiology of abnormal menstrual bleeding due to fibroids is that vascular structures in the uterus are altered, leading to dysfunction of normal hemostasis mechanisms.[38] These vascular changes were initially thought to be due to vascular compression; however, recent evidence shows that they are caused by the action of vasoactive growth factors released from fibroids.[39]

This article will review clinical manifestations of fibroids, specifically the impact of fibroids on fertility and AUB. Particular emphasis will be placed on the impact of growth factors, abnormally regulated in women with fibroids, on these processes. Current and future treatment options for fibroids will then be explored.

Methods

PubMed (National Center for Biotechnology Information) was searched for relevant English language clinical, epidemiological, and biological studies using relevant key words and hierarchical Medical Subject headings. The results of these searches were examined and key topics were explored. Highlighted topics include the endometrial effects of fibroids, their impact on fertility, current clinical management of fibroids, and emerging medical therapies.

Clinical Manifestations of Fibroids

Infertility. The association between uterine fibroids and infertility has long been a controversial issue for clinicians. Before transvaginal ultrasonography was widely utilized to increase the detection of uterine fibroids, fibroids were estimated to be present in up to 10% of women with infertility, and were identified as the sole factor for infertility in only 2% to 3% of patients.[3] A more recent prospective cohort study showed that, in women with unexplained infertility, only 11% of women with fibroids conceived spontaneously, while women without fibroids conceived spontaneously 25% of the time.[40] Removal of fibroids via myomectomy improves reproductive outcomes in selected patients.[41]

Effect of fibroid location. The location of fibroids within the uterus plays an important role in their fertility effects. Intramural and submucosal fibroids may impact fertility by distorting the endometrial cavity, obstructing the cervical canal, or obstructing the tubal ostia. Women with endometrial cavities distorted by fibroids have lower in vitro fertilization (IVF) pregnancy rates than women with normal cavities.[42] Submucosal fibroids are known to decrease implantation and clinical pregnancy rates.[41,43,44] Compared to infertile women without fibroids, women with submucosal myomas had significantly lower clinical pregnancy rates (relative risk [RR] 0.36), implantation rates (RR 0.28), ongoing pregnancy/live birth rates (RR 0.32), and significantly higher spontaneous abortion rates (RR 1.68).[41]

The impact of intramural fibroids on implantation is less clear. Studies examining assisted reproductive technology (ART) cycle outcomes in women with intramural fibroids have shown decreased fertility rates compared to women without fibroids and those with subserosal myomas.[45] A subgroup analysis, limited to 2 prospective studies examining 125 women, from a recent meta-analysis examining the impact of intramural myomas on fertility showed significant reduction in implantation rates, live birth rates, and a significant increase in spontaneous abortion in women with intramural fibroids, with RRs of 0.55, 0.46, and 2.38, respectively.[41] On the contrary, no differences in pregnancy outcomes were seen in patients undergoing IVF with solitary intramural fibroids causing no distortion of the endometrial cavity (confirmed by diagnostic hysteroscopy) when compared to age-matched controls with no fibroids.[46] The size and number of intramural fibroids may also play a role in the degree to which fertility is impacted. Patients undergoing IVF with intramural fibroids greater than 4 cm and no distortion of the endometrial cavity had lower pregnancy rates (29%) than patients with intramural fibroids less than 4 cm (51% with fibroids < 2 cm and 53% with fibroids 2-4 cm).[47] A large study comparing IVF outcomes in recipients in donor-oocyte cycles found no differences in cycle outcomes in recipients with or without intramural fibroids, regardless of size or number.[48] These findings suggest that high-quality oocytes (and resulting embryos) may be able to implant, despite less favorable endometrial conditions.

Although submucosal fibroids clearly impair fertility, subserosal and pedunculated fibroids do not affect implantation rates or clinical pregnancy rates.[49] Although the role of intramural fibroids in infertility is controversial, there is substantial evidence that intramural fibroids with intracavitary component decrease fertility and increase miscarriage risk.[50]

Effect of myomectomy on fibroid-associated infertility. Hysteroscopic myomectomy (transcervical removal of submucosal fibroids) improves pregnancy rates and live birth rates in patients with infertility.[49,51,52] Improvements in pregnancy outcomes in patients with submucosal fibroids occur regardless of whether pregnancies are conceived spontaneously or via ARTs. A randomized trial in which patients with primary infertility and submucosal fibroids were randomized to hysteroscopic myomectomy or diagnostic hysteroscopy showed that patients who had undergone myomectomy had significantly greater spontaneous pregnancy rates than the patients who had diagnostic hysteroscopy.[53] In patients with submucosal fibroids undergoing IVF, hysteroscopic myomectomy prior to IVF improved pregnancy rates to a degree comparable to rates seen in patients undergoing IVF with normal uterine cavities.[52]

Although it is clear that surgical removal of submucosal fibroids improves pregnancy rates, the data on fertility outcomes after myomectomy in patients with intramural fibroids are less convincing. In a clinical trial by Casini et al, patients with intramural fibroids were randomized to myomectomy versus expected management. Intramural fibroids were subclassified based on whether there was a submucosal component (cavity impingement) or not. There was a significant improvement in pregnancy rate after myomectomy in patients with intramural fibroids having a submucosal component (36.4% in the myomectomy group and 15% in the expectant group, $P < .05$).[49] There was no statistically significant reduction in pregnancy rate after myomectomy in patients with intramural fibroids lacking a submucosal component (56.5% in the myomectomy group and 40.9% in the expectant group, $P =$ not significant). This study provided strong evidence that removal of any fibroid that distorts the cavity will improve pregnancy rates but did not show a statistically significant benefit after myomectomy in patients with intramural fibroids lacking cavity distortion.[49] Unfortunately, there was no report of the size or number of fibroids included in this trial. A systematic review by Metwally et al showed no statistically significant effect of intramural fibroids on clinical pregnancy rate (odds ratio [OR] 0.74, 95% confidence interval [CI] 0.50-1.09).[54] However, other studies have demonstrated a detrimental effect of intramural fibroids on implantation rate and pregnancy outcomes (OR 0.8, 95% CI 0.6-0.9) albeit the effect size being less than submucosal fibroids (OR 0.3, 95% CI 0.1-0.7).[41,55,56] These findings suggested that the previous studies may be underpowered to detect the effect of intramural fibroids on fertility and pregnancy outcomes.[56] Further studies with sufficient power will further delineate the effects of intramural fibroids on fertility and the impact of myomectomy in patients with infertility.

Endometrial effects of fibroids: Pathogenesis of fibroid-associated infertility. Embryo implantation and early development, dependent on endometrial receptivity, are impaired by fibroids. A short ''window of implantation'' occurs in which the endometrium is able to support blastocyst apposition, adhesion, and invasion. This window begins approximately 4 days after ovulation and continues for 6 days.[57-59] Timely expression of genes during the window of implantation mediates the changes necessary to allow implantation to occur. Endometrial receptivity is defective when key regulators of implantation, such as HOXA10, HOXA11, and leukemia inhibitory factor (LIF), are altered. The targeted disruption of these genes in mice results in infertility due to failed endometrial receptivity.[60-63] *HOX* genes regulate a number of molecular and morphological markers that function during the window of implantation including pinopodes, β3 integrin, tryptophan dioxygenase, and IGF-binding protein I).[64-67] There are no known human mutations of the *HOXA10* or *HOXA11* genes; however, women affected by conditions known to be associated with implantation defects, including submucosal myomas, have diminished expression of these genes.[68-71] Bone morphogenetic protein 2 (BMP-2), a multifunctional growth factor, is also critical to endometrial implantation. Conditional ablation of BMP-2 in the murine endometrium results in failed decidualization and the inability to support embryo implantation.[72,73]

It has been hypothesized that anatomic distortion of the endometrial cavity impairs embryo implantation in the endometrium directly overlying the leiomyoma. Fibroids are also thought to alter uterine peristalsis, which may interfere with

gamete and embryo transport.[74] Cavity distortion due to obstruction by large leiomyoma is also thought to hinder sperm migration through the cervix and to hinder the ostiae of the fallopian tubes. However, impaired reproduction is seen in women with smaller submucosal fibroids, which cannot be explained by tubal obstruction. The possibility of a biochemical factor is supported by studies examining endometrial changes in women with submucosal and intramural fibroids. Expression of *HOXA10* and *HOXA11*, factors known to be necessary for endometrial receptivity, was decreased in the endometrium of women with submucosal myomas.[68] Interestingly the decreased expression of these genes was seen globally throughout the endometrial cavity, rather than only in the endometrium directly overlying the myomas. Growth factors, known to be dysregulated in fibroids, are plausible candidates for the mediators of these endometrial effects. Transforming growth factor β, a growth factor known to be overexpressed and secreted by fibroids, has detrimental effects on signaling pathways necessary for endometrial receptivity to occur.[35,75]

Transforming growth factor β is a dimeric polypeptide growth factor that functions in many cell types to regulate proliferation and differentiation. Three isoforms exist (TGF-β1 to TGF-β3). In reproductive tissues, TGF-β3 is the most abundant isoform and is known to be produced in excess quantities in fibroids.[75] Recently, TGF-β3 was shown to decrease the receptivity of human endometrium to BMP-2 by decreasing the expression of BMP receptors.[35] Expression of *HOXA10* and *LIF* did not increase in endometrial cells from women with fibroids when treated with recombinant human BMP-2, while similar treatment increased *HOXA10* and *LIF* in cells from women without fibroids.[35] These findings suggest that TGF-β3, secreted from fibroids, impairs the BMP-2 signaling in the endometrium necessary for implantation. However, the exact molecular mechanisms of fibroid-induced endometrial changes are incompletely understood and remain to be elucidated.

The deleterious effects of fibroids on fertility are therefore mediated by multiple mechanisms. Anatomical distortion likely interferes with gamete and embryo transport, causes vascular alterations, and alters uterine peristalsis. The secretion of paracrine factors from fibroids alters the expression of factors critical to normal embryo implantation. The improvement in reproductive outcomes seen after myomectomy is therefore likely due to a combination of restoration of normal anatomy and removal of the source of the growth factors known to impair the normal mechanisms that regulate endometrial receptivity. Further research on the molecular mechanisms within the endometrium impacted by fibroid-secreted growth factors may lead to potential nonsurgical therapies to improve fertility in patients with fibroids.

Abnormal Uterine Bleeding. Abnormal menstrual bleeding due to fibroids is the leading cause of hysterectomy in the United States. Approximately 30% of women with fibroids experience menstrual abnormalities, and HMB is the most common symptom.[3] The size and location of fibroids have classically been thought to play a role in the incidence and severity of AUB, with submucosal fibroids being the most likely to cause abnormal bleeding.[76] This theory has been disputed by those who have shown that fibroids of any size or location can cause significant AUB.[77,78]

Etiology of Fibroid-Related AUB. Many theories exist for the menstrual dysfunction seen in women with fibroids. One classic theory was that increased endometrial surface area and endometrial cavity size contributed to increased menstrual blood flow.[79] A better-supported theory is that changes in the venous structures in the myometrium and endometrium, caused by the presence of fibroids, lead to venule ectasia.[80] With venule ectasia, the normal hemostatic actions of platelets and other coagulation factors are overwhelmed by the increase in vessel caliber.[39] The dilation in these blood vessels was historically thought to be due to compression of the veins by fibroids, as they course through the myometrium to drain into the larger veins of the uterus.[3] Although vascular compression may contribute to these vascular changes, more recent evidence suggests that vasoactive growth factors released from fibroids are sufficient to cause vascular ectasia biochemically. These vasoactive growth factors, known to be abnormally regulated within fibroids, enter the endometrium and result in proliferation and growth of blood vessels. The following growth factors: bFGF, EGF, HB-EGF, VEGF, PDGF, IGF-1,TGF-β, parathyroid hormone-related protein (PTHrP), and prolactin are abnormally expressed in fibroids.[34,39] Of these factors, VEGF, bFGF, PTHrP, and PDGF have known effects on uterine vasculature.[30,81-88] These vasoactive growth factors are summarized in Table 1. The aberrant expression of these factors in fibroids and their action on the blood vessels supplying the endometrium likely contribute to the menstrual dysfunction commonly seen in women with symptomatic fibroids.

Basic fibroblast growth factor is of particular interest because, in addition to abnormal regulation in fibroid cells, it is known to have abnormal signaling in the endometrium of women with fibroids. Basic fibroblast growth factor is overexpressed in fibroids, relative to normal myometrium, and promotes angiogenesis and smooth muscle proliferation.[89] The receptor for bFGF (FGF receptor 1) is also abnormally regulated in the endometrium of women with fibroids. This receptor is normally suppressed in the luteal phase; however this suppression does not occur in women with fibroid-associated HMB.[90] These findings illustrate that aberrant regulation of growth factors in women with fibroids can occur in adjacent tissues (ie, endometrium) and suggest that there may be important paracrine signaling between fibroid cells and the endometrium.

Although the number and caliber of blood vessels are important regulators of hemostasis, other hormonally sensitive factors are critical to normal endometrial bleeding. Endometrial stromal cells begin the process of decidualization in the luteal phase in response to the secretion of progesterone from the corpus luteum. Vascular changes in the luteal phase include proliferation of endothelial cells and coiling of the spiral arteries. Progesterone also induces the expression of tissue factor (TF)

Table 1. Vasoactive growth factors with increased expression in fibroid tissue, relative to myometrium.

Factor	Receptor	Expression in Fibroids Relative to Myometrium	Fibroid-Associated Endometrial Changes	Angiogenic Effects
Basic fibroblast growth factor (bFGF)	FGFR-1 and FGFR-2	Increased expression in fibroids. ECM acts as a reservoir (Mangrulkar et al[89])	Increased FGFR-1 expression in luteal phase (Anania et al[90])	Endothelial cell proliferation and chemotaxis (Anania et al[90])
Vascular endothelial growth factor (VEGF)	*flt* (VEGFR-1) and KDR (VEGFR-2)	Increased expression in leiomyoma (Okolo et al[29] and Lewicka et al[82])	Unknown	Endothelial cell growth, proliferation, and maturation (Ferrara et al[88])
Platelet-derived growth factor (PDGF)	PDGFR-α and PDGFR-β	Increased expression of PDGF-CC isoform (Hwu et al[84]). Increased ratio of PDGF/TGF-β in fibroids (Wolanska et al[30])	Unknown	Stimulates VEGF expression (Taniguchi et al[87])
Parathyroid hormone-related protein	PTH1R	Increased expression in fibroid (Weir et al[85])	Unknown	Relaxes vascular smooth muscle (Botella et al[86])

Abbreviations: FGFR, fibroblast growth factor receptor; VEGFR, vascular endothelial growth factor receptor; KDR, kinase insert domain receptor PDGFR, platelet-derived growth factor receptor; PTH1R, parathyroid receptor 1; TGF, transforming growth factor. These vasoactive growth factors have increased expression in fibroid tissue, relative to the surrounding myometrium. They likely play an important role in the vascular changes that contribute to fibroid-related abnormal menstrual bleeding. The endometrial expression of the receptor for bFGF is abnormally regulated in endometrium from women with fibroids, suggesting a paracrine effect. There are no known fibroid-associated changes in endometrial VEGF, PDGF, or parathryoid hormone-related protein (see references Mangrulkar et al[89], Anania et al[90], Okolo et al[29], Lewicka et al[82], Wolanska et al[30], Hwu et al[84], Ferrara et al[88], Taniguchi et al[87], Weir et al[85], and Botella et al[86])

and plasminogen-activator inhibitor 1 (PAI-1).[91,92] Both TF and PAI-1 are mediators of endometrial hemostasis, acting to prevent hemorrhage within the endometrium by facilitating the formation of fibrin clots and preventing thrombolysis, respectively.[37] In nonfertile cycles, the withdrawal of progesterone causes a prehemorrhagic environment, due to reduction in TF and PAI-1, and leads to menstrual bleeding. The withdrawal of progesterone also increases the expression of matrix metalloproteinases (MMPs) which function in proteolysis and facilitate menstruation and tissue sloughing.[93] Interleukin-8 and macrophage chemoattractant protein 1 are also increased after progesterone withdrawal and act as chemoattractants for neutrophils and macrophages, respectively.[94] Estradiol, increasing at the start of the subsequent menstrual cycle, inhibits MMPs and stimulates vascular repair and angiogenesis. These actions stop menstrual blood loss and begin the regeneration of a new endometrium.[95] Estrogen-independent mechanisms, such as the increase in VEGF in the early proliferative phase, also contribute to the vascular repair necessary to stop menstrual bleeding.[96]

Transforming growth factor β3 functions by increasing cell proliferation and ECM deposition. Treatment of endometrial stromal cells with TGF-β3 decreases the expression of factors in the hemostatic pathway, specifically PAI-1, thrombomodulin (TM), and antithrombin III (ATIII).[35] Examination of endometrium in women with fibroids showed decreased expression of PAI-1 and TM, compared with endometrium from women without fibroids.[35] Decreased PAI-1, which acts as an antifibrinolytic, predisposes the endometrium to breakdown of fibrin clots and may contribute to fibroid-associated HMB. Although PAI-1 acts as a procoagulant, ATIII and TM function as anticoagulants; ATIII neutralizes thrombin and TM interacts with thrombin and reduces its prothrombotic effects. Interestingly TM, when bound to thrombin, also has an antifibrinolytic effect by cleaving thrombin-activatable fibrinolysis inhibitor into its active form.[97] Increased endometrial TGF-β3 in women with fibroids may alter expression of key mediators of the coagulation/anticoagulation mechanisms in the endometrium. Such altered regulation has implications in fibroid-associated HMB; therefore, further research is needed to completely understand the interactions between TGF-β3 and these factors. Once a better understanding of these mechanisms exists, therapeutic targets may become feasible.

Treatment Options for Fibroids

Fibroid management is largely dependent on the patient's symptoms, desire for childbearing, and age. Expectant management, medical management, surgical management, and interventional radiological approaches are all reasonable approaches; each having pros and cons. Medical management consists of hormonal and nonhormonal medications aimed to improve symptoms. Only GnRH agonists are approved for medical management of fibroids and only in the short term. Off-label usage of Food and Drug Administration (FDA)-approved medications for treatment of HMB also provides options for nonsurgical management. Additional medical therapies are currently being evaluated in clinical trials to determine their utility in fibroid therapy. Surgical management includes hysterectomy, myomectomy, and myolysis. Interventional radiological approaches include uterine artery embolization (UAE; also referred to as uterine fibroid embolization) and MRgFUS. This review will focus on the contemporary management of fibroids. Table 2 summarizes the current options available for medical fibroid therapy. Although the current armamentarium of FDA-approved medical therapies is limited,

Table 2. Current medical agents for the treatment of uterine fibroids.

Drug	Improvement in Abnormal Menstrual Bleeding	Reduction in Fibroid Volume	Bone Loss	Vasomotor Symptoms	Risks	Monthly Cost (USD)
Current medical treatments for fibroids approved by the US FDA						
Steroid synthesis inhibitors						
GnRH agonist	Yes (amenorrhea or marked reduction in menstrual blood loss)	Yes (35%-65% reduction at 3-4 mo)	Yes	Yes	Bone loss	800-1300
GnRH agonist + estrogen and progestin	Yes (92% resolved, 8% improved at 24 mo)	Yes (46% reduction at 24 mo)	No	No		810-1400
GnRH agonist + progestin alone	Yes (38% resolved, 50% improved at 24 mo)	Yes (14% reduction at 24 mo)	No	No		890-1560
GnRH agonist + raloxifene	Yes (95% amenorrhea at 18 mo)	Yes (80% reduction at 18 mo)	No	Yes		980-1580
GnRH agonist + tibolone	Yes (80% amenorrhea at 24 mo)	Yes (46% reduction at 24 mo)	Yes	Yes	Bone loss	N/A
Medical therapies approved for treatment of heavy menstrual bleeding						
Estrogen and progestin therapy						
Combined oral contraceptive pill (E + P)	Yes (reduction in days of menstrual flow from 5.8 to 4.4)	No	No	No	Venous thromboembolism	10-100
Progestin alone	Yes	Yes (7%-33% reduction)	No	Yes (17% with lynestrenol)		90-260
Levonorgestrel-releasing intrauterine system (IUS)						
Levonorgestrel-releasing intrauterine system (LNG-IUS)	Yes (up to 45% amenorrhea at 3 years, reduced PBAC score)	Variable	No	No	Expulsion	15-35
Antifibrinolytic therapy						
Tranexamic acid	Yes (up to 58% reduction in menstrual blood loss)	No	No	No	May cause fibroid infarction	210
Medical therapies currently being evaluated in clinical trials						
GnRH antagonists	Yes (100% amenorrhea)	Yes (25%-40% reduction at 3 weeks)	Yes	Yes	Bone loss	15000-25000
Aromatase inhibitors	Yes (48% reduction in blood loss at 3 months)	Yes (47% reduction at 3 months)	No (at 3 mo)	No	Ovarian cysts (when used as monotherapy)	380-1200
Selective estrogen receptor modulators (SERMs)						
Tamoxifen	Yes (40%-50% reduction in blood loss at 6 mo)	No	No	Yes	Endometrial hyperplasia	50-150
Raloxifene	No	No (9% reduction at 3 mo, NS)	No	Rare		180

(continued)

Table 2. (continued)

Drug	Improvement in Abnormal Menstrual Bleeding	Reduction in Fibroid Volume	Bone Loss	Vasomotor Symptoms	Risks	Monthly Cost (USD)
Progesterone receptor modulators						
Mifepristone (RU486)	Yes (63%-100% amenorrhea at 3-6 mo)	Yes (26% -74% reduction after 3-6 mo)	No	Yes	Endometrial hyperplasia **PAEC	N/A
Asoprisnil (J-867)	Yes (up to 70% amenorrhea at 12 wk, dose dependent)	Yes (up to 35% reduction at 12 wks)	No	Rare	PAEC	N/A
Ulipristal acetate (CDB-2914, ellaOne)	Yes (90%-98% with normal PBAC score at 13 wk)	Yes (36%-42 % reduction at 13 wks)	No	No	PAEC	200-400
Androgen therapy						
Danazol	Yes (increased hemoglobin and hemotocrit at 4 mo)	Yes (24% reduction at 4 mo)	No	Rare	Androgenic side effects (including voice change, acne, and hirsutism)	60-170
Gestrinone	Yes (amenorrhea at 6 mo)	Yes (35% reduction at 6 mo)	No	Rare	Androgenic side effects (including voice change, acne, and hirsutism)	N/A

Abbreviations: E, Estrogen; P, progestin; PAEC, progesterone receptor modulator associated endometrial change; PBAC, pictorial blood assessment chart; mo, month; wk, week; NS, not significant; FDA, Food and Drug Administration; GnRH, gonadotropin-releasing hormone; N/A, not applicable. Agents were compared based on their ability to treat abnormal uterine bleeding, ability to reduce fibroid volume, their effects on bone, and whether vasomotor symptoms are associated with their use. Clinical effects including improvements in bleeding and reduction in fibroid volume were quantified from referenced studies. Specific risks associated with therapeutic agents are highlighted. ** PAEC stands for PRM associated endometrial changes. PAEC may be erroneously diagnosed as endometrial hyperplasia. Low-dose mifepristone therapy has not been associated with endometrial hyperplasia. Monthly costs in USD were obtained using www.goodrx.com.

there are medications approved for use in HMB which can be used to treat fibroids and a number of agents currently being evaluated in clinical trials.

Expectant Management

Asymptomatic women with fibroids, or those who decline medical or surgical management, can be managed expectantly. Currently, there is no uterine size at which surgical management should be recommended. In the past, hysterectomy was recommended for women with fibroid uteri greater than 12 weeks size; however, these recommendations have been reevaluated and found to be unnecessary.[98] Similarly, the rate at which a fibroid grows was historically used to guide management decisions. The median rate of fibroid growth in a recent prospective study of 72 premenopausal women was 9% increase in 6 months, and most fibroids do not increase in volume more than 20% every 6 months.[99] Racial differences in fibroid growth exist. Fibroid growth rates in premenopausal white women decrease in women older than 45 years, while growth rates in black women do not decrease until menopause.[99] Women with rapidly enlarging uterine fibroids (uteri growing more than 6 weeks gestational size within 12 months) were thought to be at high risk of leiomyosarcoma and therefore recommended to undergo hysterectomy. More contemporary evidence suggests that the rate at which a fibroid enlarges does not influence the risk of leiomyosarcoma.[100] Fibroids are hormonally responsive and therefore regress after menopause due to cessation of ovarian steroid hormone production. Any growth in fibroids after menopause requires careful evaluation.

Women with fibroids who are being expectantly managed should undergo imaging to confirm the diagnosis of fibroids and avoid misdiagnosis of another pelvic mass. Although no consensus guidelines exist for the monitoring of fibroid growth, regular pelvic examinations with or without ultrasound imaging are recommended (the authors monitor fibroid growth every 6-12 months). The addition of ultrasound also allows for assessment of the ovaries that are often impossible to palpate reliably when large fibroids distort pelvic anatomy. Ultrasound is a widely used imaging modality due to its availability and cost-effectiveness. However, the use of ultrasound is limited in large (>375 mL) and multiple fibroid (>4)-containing uterus.[101] Magnetic resonance imaging is the best imaging modality for detection of size and localization of fibroids, but its high cost requires careful patient selection that would benefit most from it. Periodic laboratory assessments should also be performed to screen for

anemia and iron deficiency, especially in women with HMB. Women being expectantly managed should be aware that growth during this period may increase uterine/fibroid volume to a point that she may no longer be a candidate for a minimally invasive surgery when and if the need for surgery should arise.

Medical Management

Current medical treatments for fibroid-related symptoms approved by the US FDA

Gonadotropin-releasing hormone agonists. GnRH agonists are currently the most successful medical therapy for fibroids. They are FDA approved for short-term therapy (3-6 months) prior to fibroid-related surgery along with iron supplementation to facilitate surgery and to reduce anemia-related sypmtoms.[102] They effectively downregulate pituitary GnRH receptors and cause profound reductions in the production of ovarian steroid hormones by decreasing follicle-stimulating hormone (FSH) and luteinizing hormone (LH). The clinical outcome is a state of amenorrhea and a reduction in uterine and fibroid volumes by 35% to 65%.[103,104] This effect is maximal within 3 months of treatment.[105] Gonadotropin-releasing hormone agonists decrease the production of aromatase in fibroid cells, which decreases in situ estrogen production and may contribute to myoma shrinkage.[106] Clinical improvements in both abnormal menstrual bleeding and bulk symptoms are seen with GnRH agonist therapy.[107] Preoperative GnRH agonist therapy for 3 to 6 months in patients who are planning surgical management with hysterectomy or myomectomy is beneficial for a number of reasons. The correction of HMB improves iron deficiency anemia.[108,109] Reduction in fibroid volume can decrease intraoperative blood loss and allow surgeries to be performed via less invasive incisions.[109-112] Although statistically significant reductions in surgical blood loss occur with preoperative GnRH agonist therapy, they are clinically insignificant and the major hematological benefit comes from improvements in iron deficiency anemia prior to surgery.[109] Reductions in fibroid volume after GnRH agonist therapy are temporary, as fibroids return to their pretreatment size within several cycles.[113] Drawbacks to GnRH agonist use for long-term treatment of fibroids are related to decreased bone mineral density (BMD) as a result of prolonged hypoestrogenism; therefore, the American Congress of Obstetricians and Gynecologists recommends limiting use of these agents to 6 months or less without the addition of add-back therapy.[114]

Although clinically effective in correcting abnormal menstrual bleeding and reducing fibroid volume, the hypoestrogenic side effects of GnRH agonists—hot flashes, vaginal dryness, and headaches—often temper benefits. Bone demineralization is another major risk associated with GnRH therapy, especially with prolonged treatment. Reductions in BMD in treatment courses shorter than 6 months in duration are reversible with discontinuation of therapy.[115] However, prolonged therapy greater than 6 months in duration is associated with progressive and irreversible decreases in BMD.[116] In patients who are being treated during the perioperative period for a period less than 6 months, GnRH agonists can be safely used with little risk of long-term detrimental effects on BMD.

Prolonged use of GnRH agonists for more than 3 to 6 months, the duration approved by the FDA, should be considered off-label usage, and the hypoestrogenic side effects of these agents must be minimized or eliminated.[117] Add-back therapy is the addition of pharmacologic agents to a GnRH agonist treatment regimen with the goal of reducing the hypoestrogenic side effects of the GnRH agonist while preserving its therapeutic efficacy. Add-back regimens used in the treatment of fibroids have included progestins alone, estrogens alone, estrogen plus progestin, tibolone, and raloxifene. Add-back therapy is necessary for any patient with fibroids who is going to be treated with a GnRH agonist for greater than 6 months to prevent bone loss; however, any patient who is treated with GnRH agonists and seeks alleviation of hypoestrogenic symptoms should be offered add-back. Data have been published on the clinical utility of GnRH agonists for treatment of fibroids for up to 2 years.[117] Although add-back therapy is used in other gynecologic conditions treated with GnRH agonists, such as endometriosis, the unique molecular characteristics of fibroids require additional thought when selecting a particular add-back pharmacologic agent.

Because fibroids are sensitive to the effects of both estrogen and progesterone, the selection of add-back therapy for treatment of fibroids requires special consideration. A randomized controlled trial (RCT) by Friedman et al examined the effects of estrogen and progestin versus progestin alone, starting after 3 months of GnRH agonist therapy without add-back and continuing for 2 years.[117,118] Both add-back regimens were successful in treating symptoms of HMB and preventing hypoestrogenic side effects such as bone loss and vasomotor symptoms. However, while add-back with estrogen and progestin preserved reductions in uterine volume until the discontinuation of therapy, add-back with progestin alone allowed for regrowth of fibroids to near pretreatment size.[117] More women in the progestin-only group dropped out of the study due to fibroid regrowth than in the estrogen and progestin groups. This study demonstrates that add-back with a combination of estrogen and progestin is superior to add-back progestin alone for preservation of reduction in fibroid size. Patients with bulk symptoms due to fibroids who desire long-term GnRH agonist therapy should therefore be offered a combined estrogen and progestin add-back regimen.

Additional agents have been used for add-back therapy with GnRH agonists to prevent bone loss. Selective ER modulators (SERMs) are nonsteroidal agents that bind to the ER and act as either an agonist or an antagonist, depending on the tissue in which they are expressed. Raloxifene is an SERM that is used to prevent postmenopausal bone loss. It has been studied as an add-back agent in conjunction with GnRH agonists in women with fibroids and found to prevent bone loss and preserve (and possibly increase) reductions in fibroid volume compared to women treated with GnRH agonists alone.[119,120] Although other add-back agents have favorable effects on hypoestrogenic side effects, raloxifene does not improve symptoms of hot flushes or vaginal dryness. Tibolone is a synthetic steroid with

estrogenic, androgenic, and progestogenic effects. It is widely used in Europe for relief of menopausal symptoms, but is not currently approved by the FDA in the United States. Tibolone has been used as an add-back agent in conjunction with GnRH agonists and reduces hypoestrogenic side effects while preserving efficacy in terms of fibroid volume reduction and reduction in menstrual blood loss.[121,122] Although these effects are favorable, the lack of FDA approval of tibolone limits its use in the United States.

Medical Therapies Approved for Treatment of HMB

Estrogen and progestin therapy. Estrogens and progestins, usually combined in the form of the oral contraceptive pill, are commonly used as the first-line therapy for patients with fibroids in an attempt to resolve excessive menstrual bleeding. Although this may temporarily alleviate these symptoms by causing endometrial atrophy and stabilization, they do not reduce myoma size.[17] In fact, these hormones can stimulate myoma growth in vitro and therefore should be used with caution in women with symptoms related to fibroid size (bulk symptoms). Fibroid cells proliferate in response to both estradiol and progesterone in vitro and demonstrate increases in mitotic activity, growth factor expression, and B-cell lymphoma 2 (Bcl-2; an antiapoptotic peptide) expression.[10,123,124]

Many studies involving the effect of combined oral contraceptives on fibroids growth have been done in conjunction with GnRH agonists. Clinical data from several studies treating women with GnRH agonists have shown that progestin add-back therapy eliminated some of the reductions in fibroid volume seen with GnRH agonist therapy alone.[125,126] In contrast, combined estrogen–progestin add-back therapy, when used in conjunction with GnRH agonists, caused no change in myoma growth. Although data on the use of estrogens and progestins without the concomitant use of GnRH agonists are limited, some conclusions can be drawn. Estrogen plus progestin therapy may improve HMB and have minimal effect on myoma growth.[127,128] Therefore, while combined OCP's will not improve bulk symptoms related to fibroid size, they are inexpensive agents that may be used as a first-line therapy in patients with fibroids and abnormal menstrual bleeding. Progestin-only treatment of fibroids with depot medroxyprogesterone acetate (DMPA) and lynestrenol may improve bleeding parameters and increase hemoglobin with a modest reduction in fibroid volume.[129-131] Reductions in fibroid volume seen in women treated with DMPA and lynestrenol are in contrast to in vitro data showing increase in fibroid growth after progestin exposure[127]

Levonorgestrel-releasing intrauterine system. The levonorgestrel-releasing intrauterine system (LNG-IUS) is a safe and effective treatment option for HMB. It induces endometrial atrophy, and clinical data show a significant reduction in menstrual loss exceeding 90% after 3 to 12 months of use.[132] Its safety profile and efficacy have resulted in high patient satisfaction, and it has successfully been used for the management of women with idiopathic HMB.[133] Fibroids that enlarge or distort the uterine cavity are listed as contraindications to the use of the LNG-IUS due to an increased risk of expulsion. Despite this contraindication, LNG-IUS has been studied as potential treatment for women with fibroids and HMB.[134,135]

Premenopausal women with fibroids measuring a maximum of a 12-week size and without uterine cavity distortion, who desired the LNG-IUS for contraception, were evaluated in an RCT (1 group received LNG-IUS, the other did not).[136] Of these women, 39% had HMB. Women using the LNG-IUS had significant reduction in menstrual blood loss by 3 months with increases in hemoglobin and ferritin levels. The amenorrhea rate was 40% after 12 months LNG-IUS use, and there was also a significant reduction in fibroid volume.[136] However, some women may experience unscheduled bleeding episodes during the course of treatment and removal of the LNG-IUS may be necessary.[137]

Additional trials have treated women with fibroid uteri less than 12 weeks size with the LNG-IUS. All trials have shown improvements in abnormal menstrual bleeding.[138-142] The effects of LNG-IUS on uterine and fibroid volumes were variable in these trials, however. Uterine and fibroid volumes decreased after LNG-IUS treatment in a subset of studies.[136,138,139,142] Other trials found that uterine and fibroid volumes were unchanged after treatment.[140,141] Treatment failure, defined as IUS expulsion or the need for an additional medical or surgical therapy, occurred in 23% of women.[142] Women with idiopathic HMB (not due to fibroids), treated with LNG-IUS by the same group of authors, experienced treatment failure 11% of the time.[143]

These findings suggest that LNG-IUS can lead to significant improvements in abnormal menstrual bleeding in women with fibroids. There may be a benefit in terms of reduction in uterine and fibroid volumes; however, this is more controversial. Although LNG-IUS therapy fails more in women with fibroids and HMB than in women with HMB without fibroids, the overall success rates in women with fibroids remain excellent. Additional studies are needed to determine whether the LNG-IUS would benefit women with uterine size greater than 12 weeks.

There are no clinical data demonstrating a significant increase in fibroid volume in response to the LNG-IUS. This significantly contrasts with in vitro data, which suggest that progestins stimulate fibroid growth.[10,125] The reason for this discrepancy is currently unknown and further investigation is needed. The LNG-IUS is therefore an excellent option for women with fibroids and HMB who desire nonsurgical management. It should not be used as a first-line therapy for women with significant bulk symptoms as the effects on reduction in uterine and fibroid size remain unclear.

Tranexamic acid. Tranexamic acid was approved by the US FDA in 2009 for the treatment of excessive menstrual blood loss in women with fibroids. It acts to stabilize fibrin clots by inhibiting plasminogen activity. It is a nonsteroidal antifibrinolytic agent that has been successfully used to treat women with HMB worldwide.[144] It effectively reduces the volume of

menstrual blood loss in women with and without uterine fibroids.[145] Women having fibroids treated with tranexamic acid experienced 75 mL reduction in menstrual blood loss from their baseline.[145] Moreover, other studies demonstrated 44% and 58% reductions in menstrual blood loss after tranexamic acid treatment in women with HMB.[146,147] The drug is well tolerated, and despite fears that its antifibrinolytic activity would lead to formation of venous thromboses, the risk of blood clots in treated women is not elevated. Infarct-type necrosis and thrombosis of leiomyoma were seen in 15% of pathological sections from women with fibroids taking tranexamic acid, compared to 5% in women not taking the drug.[18] These findings suggest that women with fibroids taking tranexamic acid for the treatment of HMB are at risk of thrombosis of the feeding vessels of their fibroids and subsequent necrosis. The clinical manifestations of thrombosed and necrotic fibroids include pelvic pain, nausea, malaise, and low-grade fevers. These symptoms are similar to those commonly seen after UAE, an interventional radiology-guided procedure in which the vessels feeding fibroids are selectively occluded.[148] Although the ultimate result of this thrombosis and necrosis is regression of the fibroid, the pain associated can be severe. Clinicians treating women having fibroids with tranexamic acid for HMB should therefore be aware that these patients may be at risk of fibroid necrosis.

Tranexamic acid may have additional benefits in patients with fibroids. Expression of the coagulation factors PAI-1 and TM is significantly reduced in endometrial stromal cells in women with fibroids.[35] Expression of these factors is regulated by TGF-β3, which is overexpressed in uterine leiomyoma. Tranexamic acid may exhibits its hemostatic properties in women with fibroids by counteracting these TGF-β3 mediated changes in endogenous coagulation regulation in the endometrium. Further investigation is required to test this hypothesis.

Medical Therapies Currently Being Evaluated in Clinical Trials

Gonadotropin-releasing hormone antagonists. Fibroid and uterine volumes are reduced in women with symptomatic leiomyomas treated with GnRH antagonists.[149-151] Unlike GnRH agonists, which cause an initial surge of FSH and LH (flare effect) followed by the prolonged suppression in FSH and LH, GnRH antagonists block pituitary GnRH receptors and cause an immediate decline in FSH and LH. This rapid effect enables a shorter duration of treatment and a reduction in the duration of side effects. Although the maximal effect in fibroid volume reduction requires 3 months of therapy with GnRH agonists, maximal fibroid volume reduction (25%-40% volume reduction) takes only 3 weeks with GnRH antagonist therapy and can be seen as early as 16 days after treatment.[149,150] Pituitary function also rapidly normalizes upon the discontinuation of treatment. Clinical effects of GNRH antagonists are comparable to those achieved with GnRH agonist therapy, with a significant reduction in the treatment duration.[151] Vasomotor symptoms were the most common side effects, and these resolved after discontinuation of the medication.[152] Further investigations are needed to determine the safety of prolonged GnRH antagonist therapy and make recommendations for the timing of add-back therapy. The cost of GnRH antagonists, in the doses studied, would currently be prohibitive to mainstream use as a medical treatment for fibroids, as the estimated monthly cost of treatment ranges from US$15 000 to US$25 000 per month.

Aromatase inhibitors. Aromatase inhibitors directly inhibit ovarian estrogen synthesis and rapidly produce a hypoestrogenic state. Serum estrogen levels decrease after 1 day of treatment.[153] This contrasts with the mechanism of GnRH agonists, which initially upregulates pituitary receptors, causing an initial flare-up period with resulting hyperestrogenism, followed by downregulation of the receptors, and consequent hypoestrogenism. Fibroids are known to express high levels of aromatase, which suggests that elevated tissue levels of estradiol within fibroids are at least partly due to endogenous synthesis.[9,154,155] Aromatase inhibitors, including letrozole, anastrozole, and fadrozole, have successfully been used for treatment of fibroids.[153,156-158] Successful treatment of fibroids with aromatase inhibitors in a postmenopausal woman (therefore having no ovarian estrogen production) demonstrated that inhibition of estrogen synthesis locally within fibroid tissue was sufficient to decrease fibroid size.[158] Premenopausal women with fibroids treated with letrozole at a dose of 5 mg daily (standard dose) for 3 months were found to have improvements in menstrual blood loss, reduction in fibroid volume, and no change in BMD.[156] A potential drawback of aromatase inhibitor therapy is that gonadotropin levels are increased in patients, given these agents at standard doses due to the lack of estrogen negative feedback in pituitary cells. Elevated gonadotropin levels in premenopausal women increase the formation of follicular ovarian cysts. Indeed, in the trial of women receiving letrozole at a dose of 5 mg daily, 56% of treated patients formed ovarian cysts.[156] Patients treated with aromatase inhibitors at standard doses require pituitary suppression with a GNRH agonist (or antagonist), estrogen, or progesterone to prevent increase in gonadotropins or face the risk of ovarian cyst formation due to FSH stimulation. Because these hormones have additional risks and benefits in the management of fibroids, more data on the effects of aromatase inhibitors in combination with these agents for treatment of fibroids are needed. Patients with fibroids treated with low-dose letrozole (2.5 mg daily) for 3 months showed reduction in fibroid volume without changes in serum estradiol, FSH, or LH.[159] No ovarian cysts or hot flushes developed in patients treated with low-dose letrazole.[159] These findings suggest that low-dose aromatase inhibitors may be sufficient to treat fibroids without alterations in gonadotropin levels, thus reducing the risk of ovarian cyst formation. The effects of long-term aromatase inhibitor therapy on bone health are not known at this time, and therefore surveillance of BMD is necessary if long-term therapy is considered.

Steroid receptor modulators. Knowing that fibroids proliferate in response to sex steroids, compounds that influence cellular

responses to estrogen and progesterone have been investigated for the treatment of fibroids. The goal of this research was to identify therapies with clinical effects equivalent to GnRH agonists without hypoestrogenic side effects. Selective ER modulators and selective PR modulators (SPRMs) have been investigated as candidate drug classes.

Selective ER modulators. Tamoxifen and raloxifene are the 2 SERMs that have been best studied as treatments for fibroids. Although other SERMs, such as bazedoxifene, have shown beneficial effects on endometrial tissue, there are no data on their role in the management of fibroids.

Tamoxifen acts as a partial ER agonist in bone, cardiovascular tissue, and the endometrium. The agonist action in the endometrium increases the risk of endometrial hyperplasia and cancer.[160] It has an antagonistic effect on the ER in the breast and within the central nervous system. A small prospective trial was performed to determine the effect of tamoxifen on symptomatic fibroids over a 6-month period. Although there was no reduction in fibroid size or uterine volume, there was improvement in menstrual blood loss and pelvic pain.[161] The side effects in the study group included hot flushes, dizziness, and benign endometrial thickening. The impact of the negative side effects outweighed the marginal benefits of this therapy, making its value less effective for the therapeutic management of fibroids.

Raloxifene, a second-generation SERM, has no agonist effect on endometrium and subtle antiestrogenic effects.[17,162] Postmenopausal women with fibroids who were treated with raloxifene demonstrated significantly decreased uterine and fibroid volumes.[163] A pilot study examining the effects of raloxifene on premenopausal women with fibroids noted a nonsignificant decrease in fibroid size in the raloxifene-treated group compared with the control group.[164] A second study on the effects of raloxifene on 25 asymptomatic premenopausal women with fibroids showed a nonsignificant reduction in fibroid volume in the treatment group.[165] Only 1 of the 12 women receiving raloxifene in this study complained of hot flushes, suggesting that vasomotor symptoms are not as commonly seen in premenopausal women as they are in postmenopausal women.[165] Raloxifene, when used as add-back therapy in conjunction with GnRH agonists, prevents bone loss while preserving reductions in uterine and fibroid volumes (see previous section on GNRH agonist therapy).[120] Raloxifene may therefore be a potentially useful agent in premenopausal women with bulk symptoms; however, larger studies are necessary to study the true incidence of vasomotor symptoms in these women.

Selective PR modulators. Fibroids express high levels of PRs compared to surrounding normal myometrium and proliferate in vitro when treated with progestins.[10,11,14,123,124] Progesterone receptor ligands can exert pure agonism, pure antagonism, or mixed agonist/antagonist activity.[163] The progestin effect of PR ligands can be assayed by the standard McPhail test (endometrial changes assessed after treatment of estrogen-primed rabbits) or more contemporary methods that assess in vitro transcriptional activity[167,168]

Mifepristone is a PR ligand with pure antagonist activity that also has antiglucocorticoid activity.[169] Animal models of fibroids exist and confirm that fibroid growth is inhibited when animals are treated with mifepristone.[170] Clinical studies of mifepristone for the treatment of fibroids have demonstrated reductions in uterine volume by 27% to 49% and fibroid volume by 26% to 74%.[13,171-174] A systematic review of the effects of mifepristone on women with fibroids showed that 75% of women showed improvement in or resolution of pelvic pain or dysmenorrhea and 91% were amenorrheic.[174] There was no decrease in BMD in treated women. Hot flushes were reported in 38% of women and elevations in liver transaminases were seen in 4% of women.[174]

Although fibroid volume is reduced and abnormal bleeding is improved with mifepristone therapy, studies before 2009 raised safety concerns with regard to endometrial effects. In a study published in 2003, patients treated with 10 mg daily of mifepristone were found to have a 28% incidence of simple endometrial hyperplasia without atypia within 6 months of treatment.[171] The risk of endometrial hyperplasia with mifepristone appears dose dependent, as women treated with lower doses of mifepristone (2.5 mg daily) for 6 months did not have any endometrial hyperplasia but did show cystic glandular dilation. Cystic glandular changes seem to be a dose-independent effect of mifepristone, and the absence of cellular atypia and endometrial hyperplasia with lower doses of mifepristone is thought to be reassuring.[175] Moreover, these endometrial changes seen after 6 months of ultra-low dose mifepristone (2.5 mg) likely represent PR modulator associated endometrial changes (PAECs). As shown by Mutter et al in 2009, PAEC is a unique presentation of multicystic endometrium, in which the glands are lined by incongruous epithelial type, a mixed pattern of moderately dilated glands. These glands show low or absent mitotic activity, varying levels of epithelial secretory change, occasional pseudodecidual change, and they lack fibrin thrombi or stromal breakdown.[176] Short-term follow-up studies indicate that the PAEC is reversible.[16] However, additional long-term safety studies involving the use of low-dose mifepristone are needed before reevaluating the utility of these agents for treatment of fibroids.[177] Mifepristone is currently not approved by the US FDA for the treatment of fibroids.

Selective PR modulators exhibit agonist and antagonist activities with a high degree of PR specificity and tissue selectivity.[178,179] Asoprisnil (J-867), ulipristal acetate (CDB2914, VA2914, or ellaOne), and telapristone (CDB4124 or Proellex) are SPRMs that exert antiproliferative, proapoptotic, and antifibrotic actions on leiomyoma cells in a cell-type specific manner.[180-184] Asoprisnil modulates the ratio of PR isoforms (PR-A and PR-B), suppresses expression of growth factors, angiogenic factors, and their receptors in fibroid cells, and induces apoptosis by activating the mitochondrial and tumor necrosis factor-related apoptosis-inducing ligand pathways.[12] Asoprisnil also suppresses types I and III collagen synthesis by modulating ECM-remodeling enzymes in cultured leiomyoma cells

without affecting myometrial cell ECM.[12] These molecular findings parallel the clinical effects of asoprisnil identified in several studies. Women with fibroids treated with asoprisnil had significant reduction in fibroid size and pressure symptoms, diminished menstrual bleeding, increased hemoglobin levels, and an amenorrhea rate of 80%.[179] Bone metabolism, assessed by urine and serum markers of bone turnover, was unchanged after treatment.[179] In addition to their favorable effects on uterine bleeding profiles, fibroid size, bone metabolism, and endometrial histology, SPRMs are well tolerated. Treatment with asoprisnil also decreased uterine artery blood flow.[185] Vasomotor symptoms were seen in up to 10% of women treated with asoprisnil, while no women in the placebo-treated group complained of these symptoms. Simple ovarian cysts were seen in 8% of women treated with asoprisnil. All cysts resolved spontaneously.[179]

Ulipristal acetate has also been used clinically for the treatment of fibroids with excellent results. Small RCTs comparing ulipristal acetate to placebo have shown reduction in fibroid volume and decrease in menstrual blood loss in women treated with ulipristal acetate.[186,187] In a recent noninferiority trial comparing the effects of ulipristal acetate to the GnRH agonist leuprolide acetate in more than 300 women with fibroids, women receiving ulipristal acetate for 13 weeks had reductions in uterine bleeding who were similar to those women receiving leuprolide with a more rapid time to amenorrhea and lower incidence of hot flushes.[15] In a separate RCT including more than 200 women with fibroid-related anemia, Donnez et al showed that ulipristal acetate also reduced uterine bleeding, improved hemoglobin values, and reduced fibroid volume, and improved self-report pain scores when compared to placebo.[16] Treatment with ulipristal acetate did not affect serum estradiol values and the incidence of hot flushes was similar in ulipristal acetate and placebo-treated women (<3% overall).[16]

Although endometrial hyperplasia can occur in women treated with the antiprogesterone mifepristone (in a dose-dependent fashion), endometrial proliferation was not increased by asoprisnil in human trials.[179] In fact, SPRMs may have an inhibitory effect on endometrial growth, as in vitro studies show decreased proliferation in cultured endometrial cells following treatment.[188] Clinically, the endometrial thickness, assessed by transvaginal ultrasound in women treated with SPRMs, is unchanged or decreased.[16,179] Histologically, the effects of SPRMs on the endometrium are unique and it is critical for gynecological pathologists to be aware of these. Treatment with asoprisnil for 3 months results in weakly secretory endometrial glands with little to no mitotic activity and stromal changes varying from compaction to focal predecidualization. As discussed earlier, these endometrial changes are now classified as nonphysiologic secretory effects associated with the PAEC.[166,189] PR modulator associated endometrial changes were seen after 13 weeks in women treated with ulipristal acetate; however, when endometrial sampling was repeated 6 months after completion of treatment the endometrial changes had resolved, showing that these changes are reversible.[16,190]

Treatment of SPRM seems to offer safe and well-tolerated most effective conservative measure for symptomatic uterine myoma. There are no studies to date evaluating its effect on fertility outcomes in women with uterine myoma. Larger, long-term studies assessing the safety and efficacy of SPRMs for the treatment of fibroids are ongoing. As more women are treated with these promising agents, gynecological pathologists need to become familiar with PAEC to avoid mislabeling these changes for endometrial hyperplasia.

Androgen therapy. Danazol is a testosterone derivative that acts in the pituitary, ovary, and endometrium to cause a hypoestrogenic state. It inhibits pituitary gonadotropin secretion and ovarian steroid production, with suppression of endometrial growth and suppresses the production of sex hormone-binding globulin. Although the effects are primarily androgenic, it has moderate progestogenic, antiprogestogenic, and antiestrogenic properties. Danazol therapy in women with fibroids effectively decreased myoma volume by 24% to 38% and increased hemoglobin concentrations within 4 to 6 months of therapy.[191] The effect was not dose dependent, as doses of 100 to 400 mg/d produced similar results of symptomatic improvement. There is a paucity of data to explain the molecular mechanism responsible for the reduction in fibroid volume and menstrual bleeding. Further studies may help to explain the molecular pathways that likely regulate the hormonal and vascular effects responsible for the efficacy of danazol therapy on symptomatic leiomyoma.

Gestrinone is a synthetic steroid, a derivative of ethinylnortestosterone, which has antiestrogenic and antiprogestogenic properties similar to danazol. Treatment of women with fibroids with gestrinone results in a hypoestrogenic state due to feedback in the pituitary and reduction in gonadotropin secretion. The clinical effects of gestrinone treatment on fibroids are reduction in myoma volume and amenorrhea.[192-194] It may be administered orally or vaginally in doses of 2.5 to 5 mg 2 to 3 times weekly for 4 to 24 months. In contrast to danazol, its efficacy is maintained for 18 months in patients who discontinued therapy after 6 months.[192] Although a distinct advantage over danazol, this therapy is not available in the United States.

The androgenic side effects of danazol and gestrinone often preclude their use. These include weight gain, edema, decreased breast size, acne, oily skin, hirsutism, hepatocellular changes, hot flushes, headache, and muscle cramps. The most significant side effect, which may limit their use to a maximum of 6 months, is an irreversible deepening of the voice.

Growth Factor Modulators: Emerging Treatments

Growth factors, in conjunction with hormonal stimuli, cause proliferation and result in a variety of negative clinical symptoms of fibroids. Understanding of the molecular interactions between these growth factors and surrounding normal uterine tissue has increased greatly in the last decade. Novel medical therapies targeting specific growth factors are being investigated for the

treatment of fibroids. These therapies, if shown to be safe and effective, may revolutionize the treatment of fibroids.

Because fibroids contain an abundance of ECM and proliferate more than adjacent myometrium, regulators of ECM proliferation are attractive targets for fibroid therapy. Transforming growth factor β3 increases the expression of many individual components of ECM, including fibronectin, versican variants, collagen, connective tissue growth factor, and fibromodulin.[32,33,75,195,196] Transforming growth factor β3 also decreases the expression of MMPs that degrade ECM.[32,197] Treatment of cultured fibroid cells with TGF-β induces the production of ECM, and blockade of TGF-β activity decreases ECM production.[75,198] Therapies that target TGF-β or counteract its activity are being developed for the treatment of fibroids. Pirfenidone is an antifibrotic agent that has been used clinically for the treatment of pulmonary fibrosis.[199] When studied for its potential use in pulmonary fibrosis, pirfenidone was found to decrease TGF-β production in response to stimuli that increase its expression.[200] It also decreases the expression of procollagen genes, known to function in ECM production.[201] In vitro treatment of cultured fibroid cells with pirfenidone inhibits the production of collagen types I and III and decreases cell proliferation.[195] Although these effects are promising, human clinical trials examining the effects of pirfenidone on pulmonary fibrosis showed significant amounts of adverse effects such as nausea, photosensitive rash, and fatigue.[202] These side effects may prevent the routine use of pirfenidone for the treatment of fibroids.

Additional agents that modulate TGF-β signaling in fibroids have been studied. SB-525334 is a synthetic molecule that inhibits the type I TGF-β receptor kinase.[203] Eker rats are predisposed to formation of fibroids due to mutations in the tuberous sclerosis gene TSC-2.[204] Treatment of Eker rats with SB-525334 significantly decreased the incidence, multiplicity, and size of fibroids in these animals.[203] Unfortunately, treatment with SB-525334 results in proliferation and decreases apoptosis in renal epithelial cells and therefore stimulated the growth of renal cell carcinomas in these rats.[203] The effects of SB-525334 provide an excellent example of the risks associated with the systemic administration of therapies targeting growth factors with expression in multiple organs. Therapeutic targeting of additional factors that target TGF-β signaling may result in reduction in fibroid size without adverse systemic risks. Local, rather than systemic, administration of growth factor modulators may also improve safety profiles.

Because it acts as a proangiogenic factor and a growth factor, bFGF is particularly appealing target for the treatment of both fibroid-related bleeding abnormalities and bulk symptoms. Interferons (IFNs) are a family of proteins that are known to block the synthesis and action of fibroblast growth factors.[205] Treatment of myometrial and fibroid cells with IFN-α inhibited proliferation in response to bFGF[206]. Interferons are also potent antifibrotic agents and inhibit TGF-β and collagen synthesis in fibroblasts.[207] Interestingly, a patient treated with IFN-α to treat hepatitis for 6 months showed persistent reduction in fibroid volume by 50%.[208] Interferon α is approved in the United States for the treatment of hepatitis C, melanoma, condyloma, and Kaposi sarcoma.[20] Although it is appealing for the medical management of fibroids, side effects may preclude its use. Common side effects include fever, headache, myalgias, arthralgias, and fatigue. Less common, but severe, side effects include bone marrow suppression, induction of autoimmune disorders (ie, thyroiditis), and pulmonary fibrosis.[209] The side effects of IFN are time limited; however, clinical reduction in fibroid volume may be long lasting. The safety of IFN-α therapy in pregnancy is unclear (US FDA pregnancy category C) due to a lack of large prospective studies.[210] Animal studies do not show evidence of teratogenicity; however, concerns exist regarding the potential for intrauterine growth restriction. Data on the safety of IFNs in pregnancy are limited to case reports and small case series.[210,211] Although no major adverse events have occurred in offspring inadvertently exposed to IFN in utero, IFN therapy should not be offered to pregnant women or those planning to become pregnant. Additional studies of this agent for its use in the treatment of fibroids are ongoing.

Many growth factors, including those important in angiogenesis and cell proliferation, bind heparin. Heparin antagonizes the activity of heparin-binding growth factors by sequestration.[212,213] Heparin inhibits fibroid cell proliferation in cell culture.[214,215] Because it also acts as an anticoagulant, heparin is not an ideal candidate for fibroid therapy as it would exacerbate HMB. Heparin-like molecules, without anticoagulant effects, exist and can inhibit angiogenesis and cell proliferation.[216] These heparin analogs, such as RG-13577, inhibit proliferation of fibroid cells in vitro.[198] There are no human trials examining the effects of these heparin analogs on fibroids. The safety profile of these medications is unknown and therefore they are not currently available for use in fibroid treatment.

Thiazolidinediones act by binding the nuclear peroxisome proliferator-activated receptor γ (PPAR-γ). Rosiglitazone and pioglitazone are thiazolidinediones that are approved for the treatment of type 2 diabetes mellitus. Treatment results in increased insulin sensitivity and decreased circulating insulin levels. These compounds also inhibit angiogenesis by decreasing VEGF levels.[217] Fibroids express PPAR-γ at greater levels than normal myometrium.[218] Treatment of fibroids cells with PPAR-γ agonists resulted in decreased estradiol-induced cell proliferation.[219] Safety concerns have emerged regarding the thiazolidinediones. Troglitazone, another thiazolidinedione, was removed from the market in the United States due to concerns over hepatotoxicity. Fluid retention and edema are also commonly seen with thiazolidinedione treatment and these medications must therefore be used with caution in patients with congestive heart failure as they can worsen this condition.

A number of additional growth factor modulating therapies are currently being investigated for potential use in the treatment of fibroids. Halofuginone is an antiprotozoal agent that inhibits collagen production and angiogenesis.[220] It is currently being investigated for use in a number of fibrotic disorders.

Low doses of halofuginone significantly inhibited myometrial and fibroid cell proliferation in culture.[198] Human toxicity of this agent is currently unknown; however, skin fragility was seen in chickens treated with high doses of the drug.[198] Tranilast is a mast cell inhibitor used in the treatment of asthma that also has inhibitory effects on collagen production from fibroblasts and vascular smooth muscle cells.[221,222] When fibroid cells are treated with tranilast, proliferation decreases but there is no change in collagen deposition.[223] Side effects of Tranilast include elevations in liver function tests, fatigue, and eosinophilic cystitis. Additional studies are necessary before tranilast is recommended for treatment of fibroids.

Other Medical Treatments

Vitamin D. Vitamin D is a steroid hormone with diverse modulatory effects on bone metabolism, the cardiovascular system, the immune system, and the endocrine system. Within the last decade, numerous animal studies have evaluated the effect of vitamin D and its biologically active metabolite, 1,25-dihydroxyvitamin D3, on the reproductive system. In an in vitro study, 1,25-dihydroxyvitamin D3 treatment decreased the expression of proliferation and antiapoptosis markers PCNA (proliferating cell nuclear antigen), CDK1 (Cyclin-dependent kinase 1), ERK (extracellular-signal-related kinases), and Bcl-2 and reduced the growth rate of immortalized human fibroid cells.[224,225] Moreover, treatment of human fibroid cells with 1,25-dihydroxyvitamin D3 suppressed production of TGF-β3-induced fibronectin and collagen and regulated MMP expression, suggesting it has antifibrotic properties.[226,227] The beneficial effects of vitamin D were also demonstrated in a rat model of fibroid disease, in which 1,25-dihydroxyvitamin D3 treatment reduced fibroid size by 75% without significant side effects.[228]

Observational studies in women demonstrated the association of vitamin D deficiency with uterine fibroids. In a cross-sectional study in 154 premenopausal women, lower serum concentrations of 25-hydroxyvitamin D was found in women with fibroids compared to the control group without fibroids. Furthermore, the vitamin D concentrations were inversely correlated with the fibroid volume in women with the disease.[229] In a separate case–control study, 128 women with fibroids were more likely to have vitamin D deficiency compared with the 256 women in the control group. (OR 2.4, 95% CI 1.2-4.9)[230] Larger series showed that women with sufficient serum 25-hydroxyvitamin D levels had an estimated 32% lower odds of having fibroids compared with women with vitamin D insufficiency(OR 0.68, 95% CI 0.48-0.96).[231] Although vitamin D has the potential to be a safe, effective therapeutic agent, randomized controlled clinical trials are needed before it emerges as a clinically viable option.

Green tea extracts. Epigallocatechin gallate (EGCG), a major green tea ingredient, is a biologically active bioflavonoid with antioxidant and anti-inflammatory effects.[232,233] Treatment with EGCG has been shown to reduce the growth of immortalized human fibroid cells through the regulation of PCNA, CDK4, Bcl-2, and BAX. Similar effects have been observed in rat fibroid cells in vitro. Moreover, orally administered EGCG has been shown to shrink subcutaneous fibroid lesions in immune-compromised mice.[234,235] In a randomized controlled study, EGCG treatment reduced fibroid volume by 32.6%, reduced menstrual blood loss, and increased hemoglobin levels compared to pretreatment levels.[236] Epigallocatechin gallate may emerge as an innovative oral therapy with minimal side effects.[233,237] Further studies are needed to delineate the molecular mechanisms, safety, and clinical effectiveness of green tea extracts.

Gene therapy. Over the last decade, gene therapy using viral vectors have been extensively investigated for the treatment of cancers and other metabolic diseases. Adenoviral vectors have emerged as popular and potentially safe vectors for gene therapy. The localized nature of fibroids makes them attractive targets for delivery of genetic material.[238] The suppressive effect of adenoviral vectors carrying dominant negative ERs (Ad-DN-ERs) on the growth of human fibroid cells has been shown by Hassan et al. Dominant negative ERs form heterodimers with the wild-types ER-α and ER-β and suppress the transcriptional activity of these endogenous receptors. The suppression of ER receptors ultimately results in increased apoptosis, decreased cell growth, and fewer PRs.[239] In a separate study, transfection of rat and human fibroid cell lines with Ad-DN-ER substantially reduced cell proliferation and increased apoptosis in vitro. Upon transplantation into nude immunodeficient mice, Ad-DN-ER-transfected rat fibroid cells formed substantially smaller tumors compared with the control (Ad-LacZ-transfected) cells. Moreover, injection of Ad-DN-ER vectors arrested tumor growth and decreased fibroid size in the preexisting tumors.[240,241] Similarly, vectors utilizing the herpes simplex virus thymidine kinase (Ad-HSV1TK/GCV) vector followed by ganciclovir treatment resulted in substantially decreased fibroid volume in a rat model.[242] Fibroid cells transfected with Ad-HSV1TK/GCV express viral thymidine kinase, which converts ganciclovir to its toxic metabolite. Although only a fraction of fibroids cells were transfected with Ad-HSV1TK/GCV, the toxic metabolites of ganciclovir diffused to adjacent fibroid cells through gap junctions and arrested cell growth. The impact of transfection is significantly enhanced as a result of this so-called bystander effect.[243,244] Further studies demonstrated that adenoviral fiber proteins can be modified to increase transfection efficacy.[245-247]Gene therapy is promising and may emerge as a viable clinical option for the treatment of fibroids. Further studies will help to delineate its safety and efficacy in humans.

Surgical Management

Hysterectomy. The definitive treatment for symptomatic uterine fibroids is hysterectomy. Approximately 250 000 hysterectomies are performed in the United states each year for the treatment of fibroids.[248] Although the total number of hysterectomies has remained stable over the past decade, the proportion

of hysterectomies being performed for fibroids has decreased.[21] This is likely due to the emergence of alternatives to hysterectomy for the treatment of fibroids. Despite the increasing availability of alternative treatments, and after consideration of a patient's age, childbearing wishes, and associated symptoms, hysterectomy remains an excellent option for treatment of fibroids in select patients. Hysterectomy can be performed by a variety of surgical approaches, including abdominal, vaginal, laparoscopic (total laparoscopic- and laparoscopic-assisted vaginal hysterectomy), and robotic. Each of these approaches has advantages and disadvantages that must be weighed by the surgeon and patient when planning surgery. Factors that influence the route of hysterectomy include the size and shape of the uterus and vagina, accessibility to the uterus, presence of extrauterine disease, surgeon experience and training, hospital equipment, and, ultimately, the preference of the informed patient.[249] Clinical manifestations of fibroids such as HMB and dysmenorrhea and bulk symptoms such as pain, pressure, urinary, and gastrointestinal complaints are greatly improved following hysterectomy. Additional quality-of-life measures, such as depression and anxiety, are significantly improved following hysterectomy.[250,251] Hysterectomy carries a risk of injury to adjacent pelvic structures, such as the urinary tract and bowel, and postoperative vesicovaginal fistula formation. The risk of complications from hysterectomy varies depending on the route in which it is performed.

In general, vaginal hysterectomy is superior to other routes in terms of patient outcomes, cost, and risk of injury.[249,252,253] Compared with vaginal hysterectomy, abdominal hysterectomy is associated with increased risk of complications, febrile morbidity, and need for blood transfusions.[254] Even when comparing outcomes of abdominal versus vaginal hysterectomy in patients with enlarged uteri, the vaginal route was associated with decreased operative time, less febrile morbidity, reduced postoperative narcotic use, and shorter duration of hospital stay.[255] When uteri are enlarged, as is commonly seen in patients with fibroids, vaginal hysterectomy can often be completed successfully using uterine volume reducing techniques such as wedge morcellation, coring, and uterine bisection.

When a hysterectomy cannot be performed vaginally, the surgeon and patient must decide between abdominal and laparoscopic approaches. Laparoscopic hysterectomy has benefits over abdominal hysterectomy including reduced hospital stay, decreased intraoperative blood loss, faster recovery, and reduction in wound complications. These benefits must be weighed against the increased cost, operating time, and risk of urinary tract injury associated with laparoscopic hysterectomy when compared to abdominal hysterectomy.[252] Robotic assistance during laparoscopy is being utilized more frequently in surgery for benign gynecologic disease, such as hysterectomy. A recent review of robotic surgery for benign gynecologic conditions found that outcomes, complication rates, and duration of hospital stay were similar between conventional laparoscopic surgery and robot-assisted laparoscopy.[256] Robotic assistance, in the trials included in this review, did not improve clinical outcomes or safety.

Myomectomy. Uterine conserving options exist for women who have not completed childbearing or wish to retain their uterus. Myomectomy, via an abdominal, laparoscopic, or hysteroscopic approach, surgically removes fibroids from the surrounding myometrium. Myomectomy leads to clinical improvements in abnormal menstrual bleeding, pain, dysmenorrhea, and pressure symptoms. Myomectomy can serve a dual purpose in patients with HMB and infertility. Abnormal menstrual bleeding symptoms are improved after myomectomy and reproductive outcomes are improved in women undergoing ART after myomectomy.[5,49] The choice of route of myomectomy depends on the location of the fibroids within the myometrium. Fibroids can be classified according to the European Society of Hysteroscopy system. Type 0 fibroids are pedunculated submucosal myomas. Type I fibroids are submucosal myomas that extend less than 50% into the myometrium. Type II fibroids are submucosal myomas with greater than 50% extension into the myometrium.[257] Type 0 and Type I fibroids can be removed hysteroscopically. Type II fibroids should be removed abdominally or laparoscopically, depending on surgeon experience. Only hysteroscopic surgeons with advanced training should attempt removal of type II fibroids hysteroscopically.

Patients considering myomectomy should be counseled about the immediate (perioperative) and long-term risks of the procedure. Immediate risks of myomectomy include bleeding, anemia, need for blood transfusion, injury to adjacent pelvic organs, postoperative ileus, and conversion to hysterectomy related to intraoperative complications. Long-term complications must also be addressed. Fibroids have a recurrence rate of approximately 10% at 5 years and 27% at 10 years following abdominal myomectomy; up to 1/3 of those with recurrence will undergo hysterectomy.[258,259] The recurrence rate is higher after laparoscopic myomectomy than after abdominal myomectomy, presumably because smaller fibroids cannot be palpated intraoperatively and are left in situ.[260] Recurrence after laparoscopic myomectomy may be as high as 50%.[261] Recurrence rates are higher after multiple fibroids are removed than when a solitary fibroid is excised.[262] Adhesion formation is common after myomectomy, especially when multiple fibroids are excised. Scarring of the interstitial portion of the fallopian tube can impair postoperative fertility, thus extreme care must be taken to avoid anatomic distortion in this portion of the uterus. Patients who conceive after myomectomy are at an increased risk of spontaneous uterine rupture during gestation and intrapartum uterine rupture. The absolute risk of uterine rupture following myomectomy is low, with estimates as high as 0.24%.[263] The risk may be higher after laparoscopic myomectomy, compared with abdominal myomectomy as closure of myometrial defects is technically more challenging during laparoscopic myomectomy.[264] Because of the risk of uterine rupture following myomectomy and the catastrophic outcomes that can occur as a result, patients who have extensive myometrial dissection or a breach in the endometrial cavity during myomectomy are generally recommended to undergo cesarean delivery.

Myolysis is a laparoscopic approach in which fibroids are destroyed by electrocautery, cryotherapy, or laser.[265-267]

Outcomes after myolysis are sparse, and uterine ruptures have been seen during subsequent pregnancy.[268] At the current time, myolysis is not recommended for women who desire future childbearing.[269]

Uterine artery embolization. Uterine artery embolization is a process in which a transarterial catheter is introduced, under fluoroscopic guidance, into the uterine arteries where embolization material (such as polyvinyl alcohol particles) is injected to occlude the vessel. This technique is performed by interventional radiologists and has been used for the control of massive pelvic hemorrhage for many years. The procedure was first used for the treatment of fibroids in 1995.[270] The goal of treatment is to reduce fibroid blood flow, which results in infarction. It has since gained popularity for the treatment of symptomatic fibroids in women who do not desire surgery. When the procedure is performed by experienced radiologists, short-term outcomes are favorable. Abnormal menstrual bleeding, dysmenorrhea, and bulk symptoms are all improved following UAE.[271] Uterine volume also decreases 35% to 60% after UAE.[272] Although these clinical improvements are impressive, UAE is not free of side effects or complications. Most patients having UAE experience "postembolization syndrome" that consists of pelvic pain, cramping, low-grade fever, fatigue, leukocytosis, nausea, vomiting, and malaise.[273] These symptoms typically resolve within 48 hours. Patients are often admitted to the hospital after UFE for management of postembolization syndrome. More severe complications of UFE such as uterine necrosis and sepsis are less common, but potentially life threatening.[114]

The outcomes of UAE have been compared to outcomes after hysterectomy and myomectomy in a number of trials.[22,274] Compared to patients undergoing hysterectomy, patients having UAE had significantly shorter hospital stays and were able to return to work sooner.[22] However, readmission rates were higher in patients undergoing UAE. Long-term outcomes after UAE are notable for a significantly higher number of repeat interventions in patients who had undergone UAE compared to those who had undergone hysterectomy.[22,274] This is not unexpected since women who have undergone hysterectomy are no longer at risk of fibroid recurrence. Comparison of UAE and myomectomy outcomes offers a better result, as both treatments allow patients to retain their uteri. Reoperation for symptomatic fibroids after UAE is required approximately 30% of the time, compared to 3% to 6% of the time following myomectomy.[114] Hysterectomy, myomectomy, and repeat UAE are treatment options at the time of reoperation.

Uterine artery embolization is not recommended for women who wish to preserve fertility, as adverse pregnancy outcomes and diminished ovarian reserve have been reported following the procedure.[114] Case series of pregnancy outcomes after UAE are concerning for elevated rates of abnormal placentation, such as placenta previa and placenta accreta following UAE.[275] The impact of UAE on ovarian reserve is currently unclear. Because of the extensive collateral circulation networks that exist in the uterus, the passage of polyvinyl alcohol particles into the ovarian vasculature is possible. Ovarian failure is a theoretical risk of embolization of these vessels. Indeed, data exist showing a decrease in ovarian function and an increased risk of ovarian failure following UAE.[276] Rates of ovarian failure, defined as FSH levels greater than 40, in the 12 months following UAE were similar to rates of ovarian failure after hysterectomy with ovarian conservation (11% vs 18%, respectively).[277] Apart from the risk of ovarian failure, studies have shown detrimental effects of UAE on the endometrium. In a study by Mara et al, 59% of women in the group who had undergone UAE had endometrial abnormalities, such as tissue necrosis, intrauterine synechia, and fistula between the endometrium and the necrotic fibroids.[278] Additionally, myomectomy was associated with better pregnancy outcomes compared to UAE in women with fibroids.[279] In conclusion, women planning childbearing should not be counseled to undergo UAE because of the detrimental effects on ovarian function and on the endometrium and the increased incidence of adverse pregnancy outcomes associated with the procedure.

Laparoscopic UAE. Laparoscopic UAE (L-UAE) is a technique in which the uterine arteries are clamped with endoclips and the uteroovarial ligaments are coagulated bilaterally. The advantages of L-UEA are laparoscopic assessment of the pelvis and abdomen, avoiding the use of foreign bodies like polyvinyl alcohol particles and less postoperative pain.[280] Moreover, the risk of abnormal endometrial changes like necrosis of the uterine cavity was significantly less after L-UAE compared to UAE.[281] However, UAE was more successful in reducing the mean uterine volume and the rate of recurrent symptoms.[280] Additionally, L-UAE requires general anesthesia and an experienced surgical team. Laparoscopic UAE is not currently suggested as a routine treatment modality for the treatment of uterine fibroids.

Magnetic resonance imaging-guided high-frequency focused ultrasonography. Focused high-intensity ultrasound therapy results in protein denaturation, coagulative necrosis, and irreversible cell damage.[114] Focused high-intensity ultrasound has been used for the successful treatment of breast, prostate, and liver tumors. In 2004, the FDA-approved GE Exablate 2000 (Insightec, Dallas) for MRgFUS as a treatment option for fibroids. A series of 109 patients treated with MRgFUS for fibroids had modest reductions in fibroid volume but demonstrated significant quality-of-life improvements following treatment.[23] These improvements were temporary, however. Although 71% of women had symptom reduction 6 months after treatment, only 51% had symptom reduction at 12 months.[23] Because MRgFUS is a new technique, it is currently recommended only for women with symptomatic fibroids who have completed childbearing. However, a case series reporting pregnancy outcomes in 51 women who have conceived following MRgFUS showed no significant adverse pregnancy outcomes attributable to the procedure.[24] Side effects of the treatment included heavy menses, skin burns, nausea, and 1 case of transient sciatic nerve dysfunction.

Although this technique represents a novel and noninvasive treatment strategy for women with symptomatic fibroids, additional data are necessary before the technique is widely adopted.

Conclusion and Future Directions

Fibroids are highly prevalent in women of reproductive age, and many of these women experience symptoms. These hormonally responsive tumors cause AUB, anemia, pelvic pain, dysmenorrhea, and reproductive dysfunction. Classically, symptoms related to fibroids were thought to be related to increased endometrial surface area, vascular compression causing venule ectasia, and interference with gamete and embryo transport. Although these mechanisms likely contribute to fibroid-related symptoms, contemporary evidence shows that aberrantly regulated growth factors also play an important role in the pathogenesis of fibroid-related HMB and reproductive dysfunction. Many treatment options exist for medical management of fibroids, each with pros and cons. A number of agents are currently being evaluated in clinical trials and show great promise, especially the SPRMs. Increasing understanding of the risk factors, causes, and pathogenesis of fibroids may lead to development of new prevention and treatment strategies. The role of stem cells in the pathogenesis of fibroids has only recently been elucidated. Innovative medical treatments targeting the abnormal intracellular pathways within the fibroid stem cells may reduce the growth of fibroids before they become clinically significant. Medical therapies targeting the detrimental effects of fibroids on endometrium have the potential to decrease symptoms, greatly increase patient satisfaction, and increase the success of rate of infertility treatments. As further understanding of abnormal regulation of growth factors in fibroids is gained, pharmacologic manipulation of these factors will likely become a valuable tool in the nonsurgical treatment of this common public health problem. Finally, gene therapy emerges as a promising venue for fibroid research.

Authors' Note

LD, LM, DS, and HT (all authors) conceptualized the review. LD, LM, and DS performed the literature review and analysis. LD, LM, and DS contributed to the manuscript preparation. HT and LD revised the manuscript. All authors approved the final version of the manuscript.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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