Strategies for Relief: **New Approaches to Uterine Fibroids**

Clinical Highlights from a live CME/CE symposium in San Antonio, Texas October 2017

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This independent CME/CE activity is supported by an educational grant from **Allergan, Inc.**

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Introduction: Impact of Uterine Fibroids

William H. Catherino, MD, PhD

Uterine fibroids, or leiomyomas, are very common and are often associated with specific symptoms, including menorrhagia, pelvic pain, infertility, and a wide array of adverse pregnancy outcomes.[1] Despite their high prevalence and substantial symptomatology, uterine fibroids are not as well studied as other disease states that occur in women during the reproductive years, and as a result, standard treatment options have been fairly rudimentary.

Prevalence of Uterine Fibroids

The prevalence of uterine fibroids among women in the reproductive years is approximately 10%, overall.[2] The prevalence among black women is greater compared with white women: 16% vs 9%.[2] Among women undergoing hysterectomy, more than one third had fibroids identified.[3] The cumulative incidence of uterine fibroids tends to increase with age such that among postmenopausal women, 74% of black women and 42% of white women have had uterine fibroids.[4]

Factors Associated With Increased Risk of Uterine Fibroids

One of the key risk factors for uterine fibroids is age, with the incidence increasing from 0.31 per thousand woman-years at age 25 to 30 years to 6.20 by age 45 to 50 years, as shown in Table 1.[5-8] The rate declines sharply after age 50 or essentially at the time of menopause.[5]

Table 1. Key Risk Factors for Uterine Fibroids[5-8]

Risk Factor	Incidence
Age	Incidence among women aged: • 25-30 years: incidence = 0.31/1000 woman-years • 45-50 years: incidence = 6.20/1000 woman-years Declines sharply after age 50 years
Race	Incidence is approximately 3-fold greater among black women vs white women
Weight	Incidence is approximately 3-fold greater among women weighing ≥70 kg vs <50 kg
Infection	Incidence is approximately 3-fold greater among women having history of chlamydial infection vs no history

Race is an important risk factor, with black women having an approximate 3-fold greater risk compared with white women.[6] The difference in incidence is maintained after adjusting for marital status, body mass index (BMI), age at first birth, years since last birth, history of infertility, age at first oral contraceptive use, and current alcohol consumption.[6] Not only is the incidence of uterine fibroids higher among black women compared with white women, but black women typically have a higher incidence of fibroids, worse symptoms, and larger tumors.[6,9,10] The median age at diagnosis is also younger in black women compared with white women: 31 years vs 37 years.[11]

Weight is also associated with an increased likelihood of uterine fibroids. Women whose weight exceeds 70 kg have a 3-fold greater risk of having fibroids compared with women whose weight is less than 50 kg.[7] Importantly, chlamydial infection has been associated with a 3-fold greater risk of uterine fibroids.[8]

Factors Associated With Reduced Risk of Uterine Fibroids

Hormonal contraception, including progestin oral contraceptive pills, medroxyprogesterone injection, and progestin implants, is associated with a reduced risk of uterine fibroids, although it is difficult to ascertain whether the risk is actually reduced or whether the associated symptoms are reduced, thereby decreasing the likelihood that the patient will present for follow-up.[12-14]

Smoking may dramatically reduce the risk of fibroids by 20% to 50%.[15] However, this reduction is likely due to damage to the ovaries, resulting in more rapid movement towards decreased estrogen and menopause.[15-17]

Obstetric Complications Associated With Uterine Fibroids

Obstetric complications associated with uterine fibroids are fairly common as shown in a retrospective cohort study conducted from 1990 to 2007.[18] Of the 64,047 patients who were studied in their second trimester, 2058 had uterine fibroids.[18] Among the women with fibroids, the risk of complications—including cesarean section, preterm delivery, breech position, intrauterine fetal death in women with fetal growth restriction, preterm premature rupture of membranes, placenta abruption, and placenta previa—increased from 20% to more than double compared with those women without fibroids as shown in Table 2.[18]

Table 2. Obstetric Complications of Fibroids[18]

Complication	Fibroid	No Fibroid	Odds Ratio
Cesarean section	33.1%	24.2%	1.2
Preterm delivery (<37 weeks)	15.1%	10.5%	1.5
Breech position	5.3%	3.1%	1.5
Intrauterine fetal death (in women with fetal growth restriction)	3.9%	1.5%	2.5
Preterm premature rupture of membranes	3.3%	2.4%	1.3
Placenta abruption	1.4%	0.7%	2.1
Placenta previa	1.4%	0.5%	2.2

With permission from Stout MJ, Odibo AO, Graseck AS, Macones GA, Crane JP, Cahill AG. Leiomyomas at routine second-trimester ultrasound examination and adverse obstetric outcomes. *Obstet Gynecol*. 2010;116:1056-1063.

Effective Communication With Patients

It is vital that clinicians discuss with their patients key points regarding the extent of the disease and the impact of the disease on quality of life and plans related to pregnancy (Table 3). Not only does such discussion address patient concerns but also helps to guide treatment decisions. For example, certain therapies are unacceptable for patients interested in future childbirth.

Barriers to treatment should also be discussed with patients. These barriers include lack of social acceptance of fibroid-related symptoms and mistrust of the medical community, misunderstanding by the patient as to what is an acceptable menstrual burden, lack of insurance coverage, and difficulty getting to a care center, among others.

Table 3. Effective Communication With Patients

Clarify the impact of fibroids on quality of life
Clarify how fibroid-related symptoms may impact future plans, including those regarding pregnancy and delivery
Discuss the need for intervention
Clarify misconceptions about various interventions
Determine availability of interventions

Current Surgical and Minimally Invasive Treatment Options for Uterine Fibroids

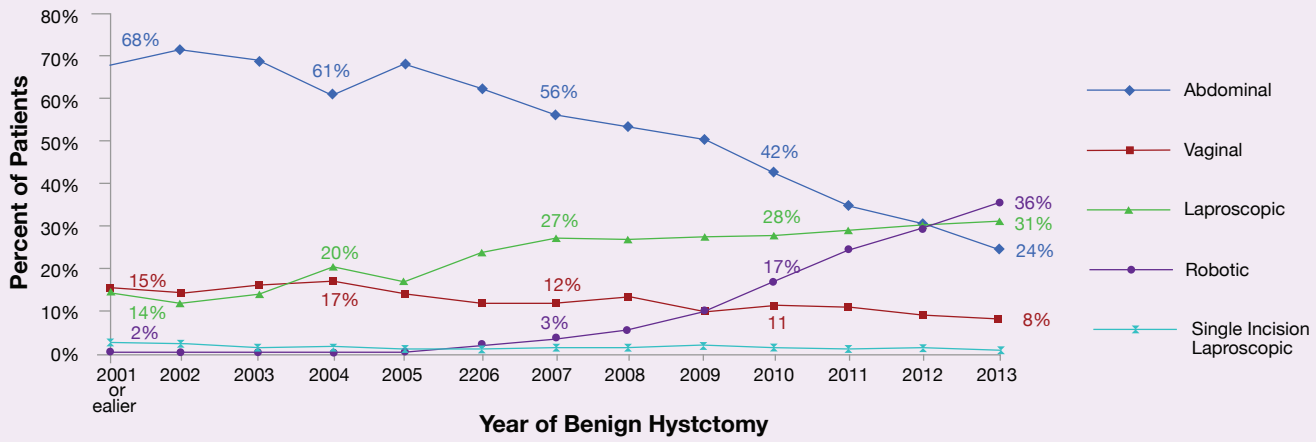
William H. Catherino, MD, PhD

More than 100 years of study are available from which to evaluate both the benefits anddrawbacks of surgical interventions. In turn, the strengths and weaknesses of newer procedures, particularly minimally invasiveprocedures and novel radiologic and medical therapies, can be compared with traditional approaches.

Hysterectomy

In 2001 abdominal hysterectomy accounted for nearly 70% of all hysterectomy modalities, but its use has decreased substantially since then as minimally invasive options have become more prevalent and more acceptable among patients and providers, as shown in Figure 1.[19] As a result, by 2013 the prevalence of robotic and laparoscopic surgeries accounted for 36% and 31% of procedures, respectively, compared with 24% for abdominal hysterectomy.[19]

Figure 1. Trends in Hysterectomy Use Over Time[19]



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Laparoscopic Myomectomy

It is important for clinicians to recognize how laparoscopic myomectomy compares with other surgical options. Compared with a mini-laparotomy, there is a shorter associated inpatient stay with laparoscopic myomectomy.[20] Compared with an open myomectomy, the laparoscopic procedure results in less postoperative pain and similar operative times and recurrence rates.[21-24] However, there is a 1.4% risk of conversion to laparotomy.[25] When using data from specific studies to select patients for laparoscopic myomectomy, clinicians should consider the degree to which a patient matches the inclusion criteria for those studies.

In an Italian study following more than 2000 patients, approximately 70% of those who wished to become pregnant achieved pregnancy within 42 months after laparoscopic myomectomy, with a delivery rate of 80%.[26] Although uterine rupture is always a concern with laparoscopic interventions, this same study found only a single rupture, occurring at week 33 and due to an adenomyoma, among the women who delivered.[26]

A Japanese group evaluated the feasibility of vaginal deliveries on patients who became pregnant following laparoscopic myomectomy.[27] Of the 74 attempted vaginal deliveries, 80% had vaginal birth and 20% had cesarean section.[27] No uterine ruptures were reported.[27] These findings suggest that attempted vaginal delivery is not an unreasonable choice for women following laparoscopic myomectomy, yet the final decision should rest with the obstetrician based upon clinical assessment.

Robotic vs Traditional Laparoscopic Myomectomy

The typical hospital stay following robotic myomectomy is generally comparable with laparoscopic myomectomy as shown in Table 4.[28-35] As is also shown, the hospital stay following robotic myomectomy is generally shorter compared with that seen following abdominal myomectomy.[30-32,35]

Table 4. Robotic vs Traditional Laparoscopic Myomectomy—Hospital Stay Across Studies[28-35]

Study	Comparison	Mean Hospital Stay
Hsiao 2013	RM (n = 20) vs LM (n = 22)	4 days vs 4 days (*P* = .21)
Gargiulo 2012	RM (n = 174) vs LM (n = 115)	>1 day: 29 for RM vs 4 for LM (OR 5.73, 95% CI 1.58-20.81)
Nash 2012	RM (n = 27) vs AM (n = 220)	0.70 days vs 2.3 days (*P* = .001)
Barakat 2011	RM (n = 89) vs LM (n = 93) vs AM (n = 393)	1 day vs 1 day vs 3 days (*P* <.001)
Ascher-Walsh 2010	RM (n = 75) vs AM (n = 50)	0.51 days vs 3.28 days (*P* = .000)
Bedient 2009	RM (n = 40) vs LM (n = 41)	>2 days: 12% vs 23% (*P* = .22)
Nezhat 2009	RM (n = 15) vs LM (n = 35)	1 day vs 1.05 days (*P* = .12)
Advincula 2007	RM (n = 29) vs AM (n = 29)	1.48 days vs 3.62 days (*P* <.0001)

Abbreviations: AM, abdominal myomectomy; CI, confidence interval; LM, traditional laparoscopic myomectomy; OR, odds ratio; RM, robotic laparoscopic myomectomy.

With regard to operative time, robotic surgery is typically substantially longer than either laparoscopic or abdominal myomectomy as shown in Table 5.[28-35]

Table 5. Robotic vs Traditional Laparoscopic Myomectomy—Operating Time Across Studies[28-35]

Study	Comparison	Mean Operating Time (min)
Hsiao 2013	RM (n = 20) vs LM (n = 22)	210 vs 145 (*P* = .006)
Gargiulo 2012	RM (n = 174) vs LM (n = 115)	195.1 vs 118.3 (*P* <.001)
Nash 2012	RM (n = 27) vs AM (n = 220)	226.41 vs 114.54 (*P* <.0001)
Barakat 2011	RM (n = 89) vs LM (n = 93) vs AM (n = 393)	181 vs 155 vs 126 (*P* <.001)
Ascher-Walsh 2010	RM (n = 75) vs AM (n = 50)	192.32 vs 138.56 (*P* = .010)
Bedient 2009	RM (n = 40) vs LM (n = 41)	141 vs 166 (*P* = .06)
Nezhat 2009	RM (n = 15) vs LM (n = 35)	234 vs 203 (*P* = .03)
Advincula 2007	RM (n = 29) vs AM (n = 29)	231.38 vs 154.41 (*P* <.0001)

Abbreviations: AM, abdominal myomectomy; LM, traditional laparoscopic myomectomy; RM, robotic laparoscopic myomectomy.

Morcellation Risk Associated With Gynecologic Surgery

In 2014, the FDA issued a safety communication that warned "against the use of laparoscopic power morcellators in the majority of women undergoing myomectomy or hysterectomy for treatment of fibroids."[36] The warning was based on the assessment that 1 in 350 women (0.29%) undergoing hysterectomy or myomectomy for the treatment of fibroids have unsuspected uterine sarcoma, which could spread within the abdomen and pelvis with use of laparoscopic power morcellation.[36]

As shown in a 2011 retrospective study, morcellation worsens cumulative disease-free and overall survival in women with uterine leiomyosarcoma.[37] Another study showed that regardless of the type of intervention that injures the tumor—open myomectomy, hysteroscopic myomectomy, laparoscopic hysterectomy with morcellation, or total abdominal hysterectomy—any injury risks the upstaging of a leiomyosarcoma.[38]

A population-based analysis, published in 2015, retrospectively analyzed data from more than 41,000 women and found the risk of unsuspected uterine sarcoma was substantially lower than assessed by the FDA, however.[39] The analysis found the prevalence of sarcoma in women younger than 40 years was 0.04%, increasing to 0.14% in women between 40 and 49 years and 0.65% in women aged 50 to 59 years.[39]

Uterine Artery Embolization

Compared with hysterectomy, uterine artery embolization is associated with a more rapid return to work, and health-related quality of life is comparable between the two procedures for 2 years.40 By 2 years, however, approximately one in four patients who had undergone uterine artery embolization went on to have a hysterectomy.41 Predictors of failure include more fibroids and fibroids of larger size.[42]

Substantial pregnancy complications related to uterine artery embolization exist, including increased risk of cesarean section, spontaneous miscarriage, preterm delivery, malpresentation and postpartum hemorrhage, as shown in Table 6.[43] Furthermore, the risk of placenta previa is increased in patients who undergo uterine artery embolization compared with patients with untreated fibroids or without fibroids.[18,44]

Table 6. Pregnancy Complications After Uterine Artery Embolization[43]

Complication	Data From 51 Pregnancies (France, Italy, US)
Cesarean delivery	63% (22/35)*
Spontaneous miscarriage	24% (12/51)
Preterm delivery	16% (5/32)*
Malpresentation	11% (4/35)*
Postpartum hemorrhage	6% (2/35)*

*Calculations based on number of singleton pregnancies that continued past 20 weeks gestation.

Compared with myomectomy, uterine artery embolization is associated with a lower pregnancy rate and a longer time to pregnancy, a higher miscarriage rate, and a lower delivery rate.[45] In addition, endometrial defects, which create a hostile environment for embryo implantation, are noted in nearly two thirds of women who undergo uterine artery embolization.[46] Due to these risks, uterine artery embolization is typically not recommended for patients who have an intention of becoming pregnant in the future.

Magnetic Resonance-Guided Focused Ultrasound Surgery

Magnetic resonance-guided focused ultrasound surgery (MRgFUS) produces symptom reduction by 1 year in approximately 50% of patients, yet 4% to 17% of patients who receive MRgFUS have been shown to undergo additional surgery within that same 1-year time frame.[47-50] Although better outcomes are associated with a larger treatment area, spreading the heat to surrounding tissues can potentially traumatize normal endometrium or damage normal myometrium or blood vessels.[47]

In a randomized, placebo-controlled trial among women who underwent pretreatment MRI measurement followed by either MRgFUS or a sham procedure, a comparable difference was observed between the groups at 12 weeks in the Uterine Fibroid Symptom Quality of Life Questionnaire for symptom severity as well as quality of life.[51] MRgFUS showed improvement, in the Short Form Health Survey (SF)-36 Physical Component Summary, but the improvement was not statistically significant.[51] No difference between the groups was observed in the SF-36 Mental Health Summary.[51]

Ablation Procedures

Ultrasound-Guided Percutaneous Microwave Ablation

Ultrasound-guided percutaneous microwave ablation has shown a mean uterine fibroid reduction rate of 87% at 12 months, with adverse effects, including vaginal secretion and abdominal pain, occurring at a rate of approximately 11%.[52,53] Although viable, full-term pregnancies are possible after treatment, data are insufficient to recommend this procedure for women who want future pregnancy.[54]

Radiofrequency Ablation

The goal for clinicians performing radiofrequency ablation is to address the fibroid while not damaging surrounding healthy tissue. This goal is challenging given that the temperature of the electrode tip exceeds 90° C and remains as high as 75° C within 1 to 2 cm, and 60° just beyond 2 cm.[55] With apoptosis occuring at 44° C and necrosis at 46° C, these temperatures are sufficient to damage surrounding tissue.[56]

Endometrial Ablation

Endometrial ablation produces severe damage to the endometrium resulting in very limited, if any, remaining tissue with the purpose to eliminate menorrhagia symptoms.[57] The procedure does not treat fibroids and is not meant to address the pelvic pressure or pain symptoms associated with a leiomyoma bulk.

Data from a retrospective population-based cohort showed the vast majority of women older than age 45 years were satisfied with this procedure and did not require additional therapy within 5 years. In contrast, nearly one third of women aged 35 years or younger were not satisfied and had additional surgery within the 5-year timeframe.[58]

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Current and Investigational Medical Management for Uterine Fibroids

Ayman A. Al-Hendy, MD, PhD

The management of uterine fibroids typically depends on many factors, including factors related to the fibroids themselves, such as the number, size, and location of the tumors, as well as factors related to the patient herself, most particularly as related to fertility potential and plans. Women who want to preserve their future fertility potential are very interested in minimally invasive or noninvasive therapy for their disease.

Oral and Intrauterine Device Contraceptives

Oral contraceptives have been used for many years as a first-line treatment for uterine fibroids. They provide, however, only symptomatic relief by controlling the bleeding associated with uterine fibroids through their suppressive effect on endometrial proliferation.[59] Similarly, the levonorgesterel-releasing intrauterine device is used for the same purpose of controlling uterine bleeding.[60]

Tranexamic Acid

Tranexamic acid is an oral, nonhormonal, antifibrinolytic that is approved for the treatment of cyclic heavy menstrual bleeding.[61] Its use results in a 50% reduction in bleeding in women with menorrhagia.[62] An analysis of five studies, performed from 1998 to 2013, found tranexamic acid "may reduce blood loss perioperatively in myomectomies, and may reduce menorrhagia in patients with fibroids."[63] Data are limited, however, regarding the effectiveness of tranexamic acid on bleeding as stratified by uterine size and location.[63]

Selective Progesterone Receptor Modulators

Selective progesterone receptor modulators (SPRMs) are a relatively new class of synthetic steroid ligands that bind to the progesterone receptor competitively and with tissue-selective agonist and antagonist effects.[59] They are being investigated for use in patients with uterine fibroids due to their potential direct effects on fibroid and endometrial cells.[59] With minimal effect on serum estrogen levels, it is not anticipated they would induce menopausal-like symptoms or bone loss.[59]

Several SPRMs are in phase II or phase III testing: ulipristal acetate, vilaprisan, and telapristone acetate. Ulipristal acetate is already approved for the treatment of uterine fibroids in Canada and in Europe based on four international phase III trials.[64,65] In the United States, two phase III studies have been completed and are pending publication with an FDA application also pending.[66-68] Vilaprisan is currently in phase III testing, and telapristone is currently in phase II testing.[69-71]

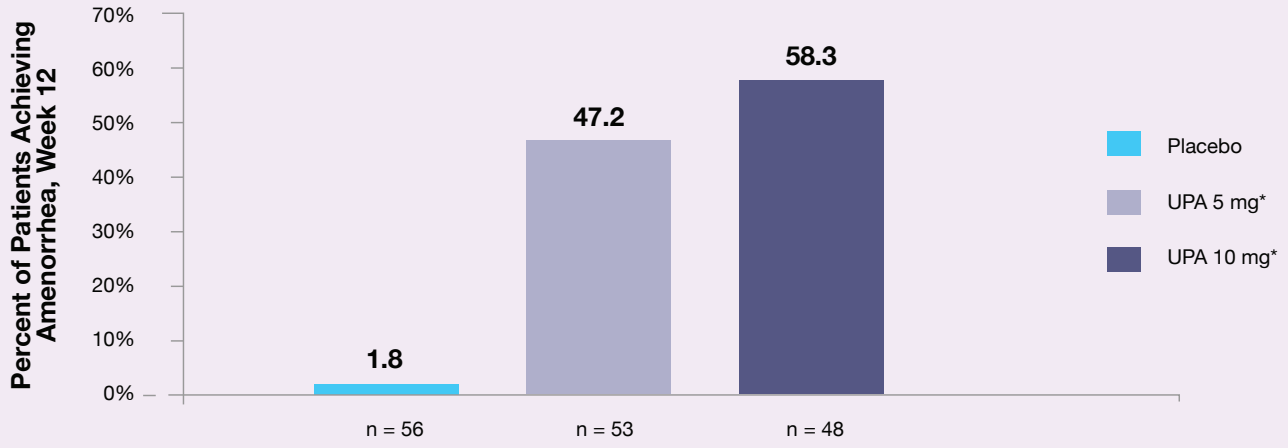
Ulipristal Acetate

Ulipristal acetate attacks the fibroid itself, killing fibroid cells rather than offering only symptomatic relief.[72] Binding to the progesterone receptor with high affinity, ulipristal acetate inhibits fibroid proliferation and activates apoptosis.[72] Furthermore, it inhibits the production of extracellular matrix, such as collagen, which gives the fibroid tumor its bulk of tumor mass.[72] Interestingly, the drug does not have the same effect on myometrial cells.[72] It has completed two US phase III studies (VENUS I and II), and four international phase III trials (PEARL I, II, III, and IV).[66,67,73-79]

VENUS I US-Based Phase III Ulipristal Trial—Preliminary Findings for Primary Endpoint

Venus I was a randomized, placebo-controlled, parallel-group, multicenter study that enrolled premenopausal women with cyclic heavy uterine bleeding (more than 80 mL over the first 8 days of menses) and at least one uterine fibroid lesion.[66] The study design included ulipristal acetate at two dose levels (5 mg and 10 mg) vs placebo for 12 weeks. The primary endpoints at week 12 were amenorrhea and time to achieve amenorrhea.[66] Among those patients who received ulipristal acetate, 58.3% of those who received the 10-mg dose and 47.2% of those who received the 5-mg dose achieved amenorrhea compared with only 1.8% of patients who received placebo (P <.0001 for both dose levels) according to preliminary data presented at the 2016 American Society for Reproductive Medicine (ASRM) annual meeting (Figure 2).[73] Importantly, ulripristal acetate-treated patients quickly achieved an absence of bleeding: 9.5 days for patients who received the 10-mg dose.[7]

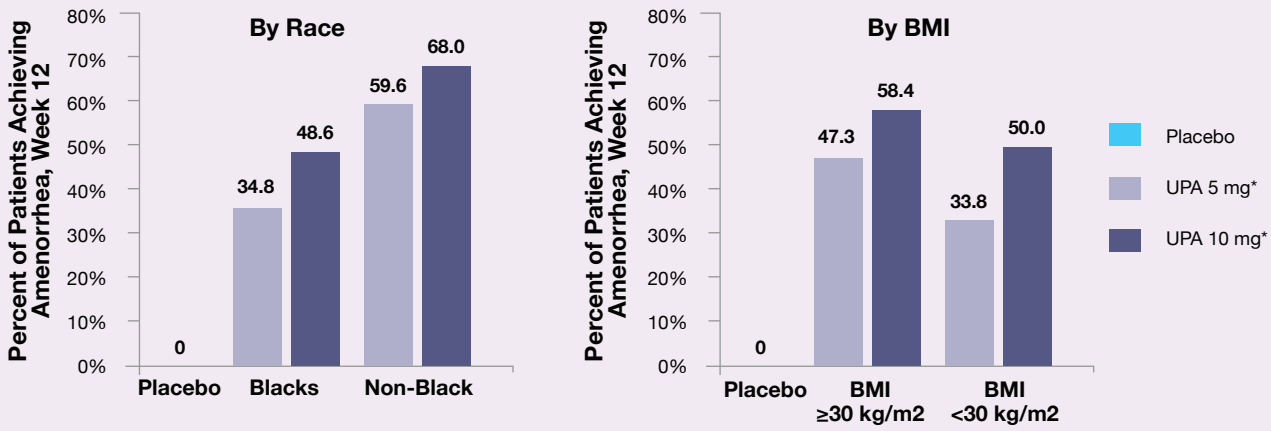
Figure 2. VENUS I US-Based Phase III Ulipristal Trial—Preliminary Findings for Primary Endpoint[73]



* P-value for both UPA 5 mg and 10 mg vs placebo: P <.0001.
Abbreviation: UPA, ulipristal acetate

A key component of the VENUS program in the United States is that it included a substantial proportion of black patients as well as patients with high BMI such that population-based subgroup analysis could be performed, as shown for VENUS II in Figure 3.[80] When analyzed by race, the percent of patients achieving amenorrhea showed no meaningful difference in preliminary data: 48.6% for blacks and 68.0% for whites with ulipristal acetate 10 mg.[80] In addition, ulipristal acetate was effective both in women with BMI at or above 30 kg/m^2 as well as in women with BMI less than 30 kg/m^2: 58.4% and 50.0%, respectively, with ulipristal acetate 10 mg.[80]

Figure 3. VENUS II US-Based Phase III Ulipristal Trial—Preliminary Data by Race and BMI, Course 1[80]

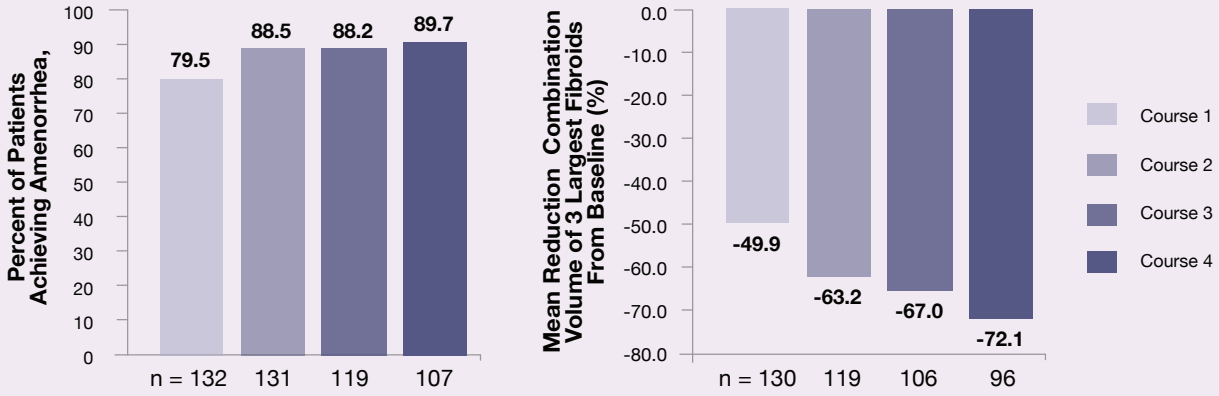


Abbreviations: Abbreviations: BMI, body mass index; UPA, ulipristal acetate.

PEARL III Extension Study—Bleeding Control With Ulipristal Acetate 10 mg

The phase III PEARL III clinical trial used ulipristal acetate 10 mg for four 3-month courses, each separated by an off-treatment period to include a full menstrual cycle, allowing for the patient to alternate betweenactive treatment and shedding of the endometrial lining with bleeding.[77] As shown in Figure 4, a high percentage of patients achieved amenorrhea following each of the four ulipristal acetate courses, from 79.5% following course 1 to 89.7% following course 4.[77] Furthermore, fibroid shrinkage data showed a 49.9% reduction from baseline in the combined volume of the three largest fibroids following course 1 and a 72.1% reduction following course 4.[77]

Figure 4. PEARL III Extension Study—Bleeding Control with UPA 10 mg[77]



Ulipristal Phase III Trials—Adverse Effects

In VENUS I there were no treatment-related serious adverse effects or deaths reported and no treatment discontinuations related to adverse effects in preliminary data.[73] No malignancies or endometrial atypical hyperplasia were reported, and there was no increased risk of progesterone receptor modulator-associated endometrial changes, a reversible benign histologic change, with ulipristal acetate vs placebo.[59,73] Preliminary safety data from VENUS II showed common adverse effects, including hot flush, headache, fatigue, and nausea, although for most the incidence was comparable to placebo.[74] One serious treatment-related adverse effect was reported, uterine hemorrhage, in a patient who received ulipristal acetate 5 mg.[74]

Vilaprisan

Vilaprisan is highly selective for and strongly antagonistic at the progesterone receptor.[81] In an animal model, the antiprogestagenic potency was five times that of ulipristal.[81] It has completed phase I and phase II testing and is now undergoing phase III trials in the ASTEROID clinical program.[82-87]

Preliminary phase II data from the ASTEROID 1 trial was reported at the 2016 ASRM annual meeting.[84] At 12 weeks, patients who received placebo continued to have heavy bleeding whereas patients who received vilaprisan, particularly at a dose above 0.5 mg, showed a dramatic reduction in the amount of bleeding.[84] Among the patients who received vilaprisan at a dose of 1 mg or higher, 97% to 100% achieved controlled bleeding.[84] Once treatment with vilaprisan was stopped, however, all patient groups returned to bleeding, although less than at baseline, suggesting the return of ovulation and also the return to bleeding is rapid.[84]

Telapristone Acetate

Telapristone acetate is another progesterone receptor modulator, although some consider it a "relatively pure" progesterone antagonist.[88] At the molecular level, it has been shown to also inhibit proliferation and induce apoptosis in uterine fibroids but not in normal myometrial cells.[89] After an earlier phase III trial was suspended by the FDA due to elevated liver enzymes, a new phase II approach was launched using a vaginal approach at a lower dose.[59,71]

Gonadotropin-Releasing Hormone Agonists/Antagonists

The release of gonadotropin-releasing hormone (GnRH) results in stimulation, synthesis, and secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the anterior pituitary.[88] Its half-life is 2 to 4 minutes.[88] Synthetic GnRH analogs are developed as agonists or antagonists and have the same initial mechanism of action as natural GnRH analogs but have increased potency and duration.[88] With GnRH agonists, an initial flare of FSH and LH secretion is triggered, leading to downregulation and inhibition of the pituitary-gonadal axis.[90] With GnRH antagonists, the GnRH receptor in the pituitary is blocked, thereby immediately downregulating FSH and LH release.[91]

Gonadotropin-Releasing Hormone Agonists

The classic GnRH agonist is leuprolide acetate, which has been widely used in the United States and worldwide for many years. It is approved for concurrent administration with iron for preoperative hematologic improvement of patients with iron deficiency anemia secondary to uterine fibroids.[92] Patients should first have a 1-month trial with iron alone before starting leuprolide.[92] The recommended duration of therapy is up to 3 months.[92] Leuprolide reduces fibroid size and symptoms by downregulating the pituitary GnRH receptor to induce a hypoestrogenic state.[59] Adverse effects include hot flushes, vaginal dryness, and mood swings, as well as bone demineralization and decreased bone mineral density.[59]

Gonadotropin-Releasing Hormone Receptor Antagonists

Three novel oral GnRH antagonists are currently in phase III testing: elagolix, relugolix, and OBE2109.[93-98]

Elagolix

Elagolix is a second-generation, nonpeptide GnRH antagonist that delivers dose-dependent suppression of LH, FSH, and estradiol.[88] Preliminary findings from a double-blind, randomized, placebo-controlled, parallel-group phase II study of elagolix vs placebo, with and without add-back therapy, in premenopausal women with fibroids and heavy menstrualbleeding showed reduced bleeding, with and without add-back therapy, and reduced flushing with add-back therapy.[99] Two phase III trials are currently underway.[93,94]

Relugolix

Relugolix is currently being evaluated in two phase III trials: LIBERTY 1 and LIBERTY 2.[95,96] Preliminary phase II data from a Japanese trial were reported at the 2017 American Congress of Obstetricians and Gynecologists annual meeting and showed significant dose-dependent improvement in bleeding compared with placebo as well as dose-dependent decrease in myoma and uterine volumes.[100]

OBE2109

No data are yet available for OBE2109. Two phase III trials—PRIMROSE 1 and PRIMROSE 2—are in progress.[97,98]

Conclusion

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Uterine fibroids are prevalent, and for many women, they are symptomatic. In particular, black women have a greater disease burden. Fibroid burden involves multiple variables, including menorrhagia and pelvic pain, which are dependent on the size, location, and number of fibroids present. Appropriate care requires understanding the disease burden, including specific patient challenges and goals, as well as the keys to optimizing care.

From a surgical and radiologic standpoint, current and future therapeutic options for leiomyomas have demonstrated a steady movement toward minimally invasive interventions. Yet current treatment approaches for uterine fibroids are far from optimal. Oral and levonorgestrel-releasing intrauterine device contraceptives may show short-term success, particularly for symptomatic decrease of the amount of bleeding, but they typically fail over time and, importantly, they do not shrink the fibroids. Two exciting groups of oral compounds—SPRMs and GnRH antagonists—have data that suggest effective, safe, and durable treatment of fibroids and, importantly, have the potential of being fertility friendly. Best practices should continue to be tailored to the individual patient's disease and their personal wishes as to the optimal outcome.

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