Is ulipristal acetate the new drug of choice for the medical management of uterine fibroids? Res ipsa loquitur?

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Abstract
Ulipristal acetate (Esmya©) has been hailed the new wonder drug with regard to the medical management of uterine fibroids, and many postulate that it will remove the need for surgical treatment in the future. While the results from the PEARL studies are certainly promising and its amenorrhoeic rates and reduction in fibroid size are unquestionable, there is still a paucity of data with regard to its long-term effects, the effects on its usage prior to surgery and its variable efficacy in different ethnic populations. To facilitate our knowledge further, independent studies with clear outcome measures evaluating the long-term effects of the drug in a wider, more representative, ethnic minority population as well as assessing its true cost-effectiveness compared to surgery are needed. The aim of this article is to review the historical aspects with regard to the management of uterine fibroids to gain an understanding of where we are now and to evaluate the wider use of ulipristal acetate, both its benefits and limitations and postulate where to go in the future in order to allow our women to make safe and informed choices regarding their treatment options.

Keywords
Esmya, fibroids, myoma, PEARL, ulipristal acetate

Introduction
The use of ulipristal acetate (UPA), a drug initially licensed for and still used as an emergency contraceptive pill, in the medical management of fibroids has increased considerably in line with National Institute of Clinical Excellence (NICE) UK guidelines, and many hypothesise that it will herald a large shift away from the standard medical and particularly invasive surgical treatments that we currently offer for fibroids. The data from the landmark studies are indeed encouraging; however, many questions regarding its use still exist, particularly with regard to its long-term safety and cost-effectiveness, especially in the ethnic minority populations who carry the largest burden from this disease. The aim of this article is to review the medical management of uterine fibroids through the ages to gain an idea of where we currently stand and to evaluate in detail the use of UPA, both its benefits and limitations, and postulate what the future holds to ensure that we have all the information required to allow our patients to make safe and informed choices regarding their treatment options.

Historical perspective
Fibroids have been reported since antiquity with the ancient Greeks referring to them as ‘uterine stones’ (Hippocrates – 460–375 BC). They are also not a modern disease attested by the fact that they have been identified in 4000-year-old Egyptian mummies. Rokitansky in 1860 and Klob in 1863 first introduced the term ‘fibroid’, and
Virchow, the German pathologist, demonstrated that they originated from uterine smooth muscle leading to the conception of the word ‘myoma’, which remains in clinical use today.

They are the commonest benign tumour found in women; however, quoted prevalence rates in the literature vary between 15% and 80% and are largely dependent on patient ethnicity, age and the method of detection used. The majority of women remain largely asymptomatic; however, they can cause debilitating symptoms in up to 30%. Clinical features range from heavy menstrual bleeding to pain, pressure and subfertility, with symptom severity often depending on the number and position of the fibroids. Fibroids can have a significant impact on quality of life, with many women having to wait an average of 3.6 years before seeking medical help and often having to be seen by more than two medical practitioners before an intervention decision is reached. Fibroids also contribute significantly to both personal and social financial burden with an annual cost to the US economy estimated at approximately 4 billion dollars.

Pathophysiology of fibroids

Fibroids are benign monoclonal tumours that originate from single myometrial smooth muscle cells. The pathogenesis is not clearly understood, but risk factors include race, with fibroids being more prevalent in Blacks than in Caucasian and Hispanic populations, low-serum 25-(OH) vitamin D levels, obesity, early menarche and a family history. Increasingly, the genetic component appears to be particularly important in the development of fibroids with cytogenetic surveys revealing chromosomal alterations and anomalies in 40% of uterine fibroids. Fibroids contain a large amount of extracellular matrix (ECM) (collagen, proteoglycan, fibronectin), and studies have shown the mechanical properties of the ECM to be key to fibroid growth. Epigenetic changes in microRNA have also been implicated in fibroid formation.

Fibroids are highly hormone dependent, especially with regard to oestrogen and progesterone, and this has been well described in the wider literature. According to the ‘oestrogen hypothesis’, oestrogens exert a growth-stimulatory effect on fibroids mediated by cytokines, growth factors, and apoptosis factors. The ‘progesterone hypothesis’ suggests that progesterone plays a fundamental role in the development of fibroids by reducing apoptosis and increasing mitosis in the smooth muscle cells. Oestrogen is thought to have a further stimulatory effect by increasing the expression of progesterone receptors in fibroid cells.

Leiomyomas are benign lesions; however, a heterogeneous group of lesions have some characteristics of malignant disease and they are termed leiomyoma variants. Variants are classified as benign or malignant based on histologic features.

Modern management of fibroids

The modern management of fibroids should be patient-centric with a holistic approach taking into account the age of the patient, the severity and type of symptoms, the size, number and position of the fibroids, fertility aspirations and the desire to retain the uterus. In a national survey in the United States, 79% of women preferred a uterine-saving procedure irrespective of fertility desires. Currently, depending on symptoms, the treatment options are medical, surgical or radiological. Surgical treatments include myomectomy, hysteroscopic, laparoscopic or open, and ultimately hysterectomy. Radiological treatment options include uterine artery embolisation and magnetic resonance imaging (MRI)/ultrasound-guided radiofrequency thermal ablation; however, in the case of the latter, limited evidence is available and it is not widely used in the United Kingdom.

Current medical management

For women with symptomatic fibroids, a number of medical options are available. Medical interventions depend on whether fertility is an immediate desire. If women are currently seeking to conceive, hormonal treatment is contraindicated.

For some women, the use of non-steroidal anti-inflammatory agents has been shown to reduce menstrual flow by up to 30% and this can be further augmented by the concomitant use of tranexamic acid. Tranexamic acid, an anti-fibrinolytic agent, has been shown to reduce blood loss in women with heavy menstrual bleeding by up to 50%, although when used in women with fibroids, efficacy may be reduced. Furthermore, a small retrospective study found no difference in women with fibroids taking tranexamic acid. These options are appropriate for women who are actively seeking to conceive and have no large intracavity fibroids.

For women not actively seeking to conceive, the levonorgestrel intrauterine system has been shown to be effective. However, in women with uterine fibroids, there is an increase in expulsion rates. Expulsion rates are directly proportional to uterine volume and can be as high as 20%, 24, 25

Gonadotrophin-releasing hormone (GnRH) analogues have also been used in the medical management of uterine fibroids and have been shown to reduce the size of fibroids and ameliorate symptoms particularly before surgery. However, due to their side effects, which include menopausal symptoms and osteoporosis, their use is limited.

Selective progesterone receptor modulators and UPA

Selective progesterone receptor modulators (SPRMs), of which UPA is one, are not new. They were first developed in the 1980s, and the first to be introduced into clinical use...
was mifepristone, which has been shown to be effective in reducing fibroid symptoms but has no effect on fibroid volume. The results of a meta-analysis limit the recommendation for the use of mifepristone for the management of uterine fibroids.26 Since then, other SPRMs have been developed with differing effects and bioavailability, and currently, the only SPRM approved for medical management of fibroids is UPA.

UPA, acting as a progesterone receptor antagonist, inhibits the proliferation of myoma cells and induces apoptosis by increasing cleaved caspase-3 expression and decreasing Bcl-2 expression.27,28 It also downregulates the expression of angiogenic growth factors such as vascular endothelial growth factor (VEGF) and their receptors. This results in a suppression of neo-vascularisation, cell proliferation and cell survival in myoma cells, but not in the surrounding healthy myometrial cells.29

It has been hypothesised that the potent anti-progesterone effect of UPA can have deleterious effects on the endometrium due to the resultant unopposed oestrogen with a consequential increased risk of endometrial hyperplasia and cancer. These concerns resulted in a workshop held in Bethesda, USA, in April 2006, where expert pathologists introduced recommendations for the interpretation of endometrial histology from patients treated with UPA. Most endometrial samples resembled those seen during a normal menstrual cycle; however, some were unclassifiable based on the standard criteria and were termed progesterone receptor modulators–associated endometrial changes (PAECs).29,30 About 10%–15% of women were found to have a thickened endometrium on ultrasound or MRI following a 3-month course of UPA; however, reassuringly these changes disappear after the cessation of treatment and do not appear to have any long-term implications. Current advice from the manufacturer for those using UPA longer term involves monitoring the endometrial thickness by undertaking an annual ultrasound scan during the treatment-free period. Irregular/abnormal bleeding while on UPA should be treated as per normal clinical practice and may require hysteroscopic assessment.

Other common side effects of UPA include hot flushes, headaches, nausea and fatigue. Less common and rare side effects include dizziness, constipation, breast tenderness and ovarian cysts.

It is advised that UPA should be avoided in patients with severe renal or hepatic impairment and severe asthma and it is also not recommended in patients taking p-glycoprotein substrates (e.g. digoxin), moderate or potent CYP3A4 inhibitors (e.g. erythromycin) and CYP3A4 inducers (e.g. rifampicin).

UPA was initially approved for the management of symptomatic uterine fibroids in women awaiting surgery based on the PEARL I and PEARL II studies.31,32 PEARL I (UPA vs placebo) used the inclusion criteria of symptomatic premenopausal women between the age group of 18 and 50 years, with a uterine size equivalent to or less than 16 weeks gestation and fibroids measuring between 3 and 10 cm. The results showed that UPA was better than placebo in reducing menstrual loss and the size of the dominant fibroid by 25%, establishing successfully that it was safe and effective in the management of fibroids.

In PEARL 2 (inclusion criteria was the same as PEARL I), UPA was compared to leuprolide and showed a similar reduction in pain and improvement of quality of life and haemoglobin levels. Leuprolide showed a greater reduction in fibroid volume 47% compared to UPA 20%–22%; however, UPA showed a better patient side effect profile and a more sustained effect of reduction in myoma volume during the 6-month follow-up period. The median time to amenorrhoea was 7 days with UPA compared to 21 days with leuprolide, and on stopping treatment, menstrual bleeding returned within 30 days with UPA compared to 90 days with leuprolide.

A subsequent study of women who did not go on to have surgery (PEARL 3) showed efficacy for long-term use.33 About 83.5% of women became amenorrhoeic after their first treatment course and most women were amenorrhoeic within 3.5 days of starting the medication. For subsequent courses, 88.5%, 88.2% and 88.8% for courses 2, 3 and 4, respectively, became amenorrhoeic within 3 days, and the 25% fibroid size (equivalent to a 45% volume reduction) was maintained through the treatment courses with an improved quality of life.

In Europe, following the results of PEARL 3, UPA was approved for longer-term intermittent use of up to four courses of 3 months with intervals depending on response and the development of endometrial abnormality. In line with European approval, usage in United Kingdom has been approved by NICE,34 on the basis that UPA may decrease the need for surgical intervention thus potentially addressing the need to decrease surgical morbidity and cost as well as social burden.

The first large study undertaken in the United States assessing the use of UPA in the management of fibroids has also recently been published: VENUS I.35,36 VENUS II is yet unpublished; however, promising results in keeping with those described in VENUS I were recently released by the pharmaceutical company.

VENUS I is a multicentre, randomised, double-blind, placebo-controlled trial, comparing UPA to placebo with inclusion criteria similar to the PEARL studies. Results highlighted a significant benefit in the UPA group with regard to cessation of bleeding, the time taken to cessation of bleeding and quality of life scores. A good safety profile was noted with minimal side effects. VENUS II was subsequently undertaken to assess the use of UPA versus placebo over two 12-week treatment courses. The data are yet unpublished; however, the initial results released by the pharmaceutical company are promising with high efficacy and reassuring safety profiles.
More recently, there have also been further developments in newer types of SPRMs and one such development is the use of vilaprisan. ASTEROID II is a phase 2 randomised, placebo-controlled study assessing the efficacy and safety of vilaprisan in patients with uterine fibroids and comparing its effects to UPA.37

**Pregnancy after UPA**

Luyckx et al.38 reported a retrospective study of 52 women from the PEARL I and II studies – 21 of which wanted to conceive. 15 women (71%) became pregnant resulting in 18 pregnancies and 12 live births, the majority of which were by caesarean section. There was no increase in size of the fibroids during pregnancy. There was one reported congenital abnormality, an ectopic kidney, but this was not thought to be related to UPA treatment.

**The ethnic diversity challenge**

Fibroids are more common in women of African descent; they tend to appear at an earlier age and present a greater burden in terms of symptoms.5 In women of African origin, the fibroid recurrence rate may be as high as 59% 4–5 years after primary intervention.39 In the fibroid growth study, Peddada et al.40 showed that the rate of fibroid growth in African American women did not slow down with the approach of the menopause as it does in other ethnic groups.

Unfortunately, 90% of the study population in PEARL I and II were Caucasian and only 10% were ethnic minorities. This recruitment bias was present despite the well-known fact that women of African origin have their fibroids diagnosed at an earlier age, have more severe disease and have different disease patterns when compared to Caucasian women. Hence, the question needs to be asked whether the findings are generalisable to all women with uterine fibroids. In a study of 101 Korean women with symptomatic uterine fibroids, Lee et al.41 demonstrated that there was a lesser reduction in fibroid size with UPA compared to GnRH analogues, and 37% of patients in the UPA arm of the study did not show any fibroid shrinkage after 3 months of UPA treatment. Murji et al.42 looked at the role of ethnicity in treating fibroids with UPA and concluded that Black women were more likely to be dissatisfied with UPA treatment which may be related to the greater fibroid burden and the low amenorrhoea rates achieved with UPA in this ethnic subgroup. Differences in circulating oestrogen levels, low-serum 25-(OH) vitamin D levels and disordered ECM production and cell proliferation have all been implicated in the differing disease pattern in Black women. However, the recent VENUS study by Simon et al. reported on a subset analysis of Black women, which encompassed 68% of the 157 patients, included in the study. They found no difference in response rates in obese Black women compared to others and concluded that efficacy of UPA was observed irrespective of race or body mass index (BMI).33 However, due to the overall paucity of data on this topic, further studies are required to elucidate this issue.

**Ambiguity in approach to management**

The economic and social burden of uterine fibroids is well known,7 and what women want as the outcome for their uterine fibroids has also been documented.6 Additionally, we now have a potential drug that could revolutionise our approach to uterine fibroids. Despite all the above knowledge, there are no national repositories that record, collate and analyse what is known and what the outcome would be if UPA is used for the right indication, on the right patients and for the right desired outcome. The Pre-operative Treatment of Moderate to Severe Symptoms of Uterine Fibroids (PREMYA) trial looked at the use of UPA beyond the PEARL studies with the aim of looking at outcomes for women who were treated in a routine clinical setting. The trial demonstrated improved quality of life, but unfortunately, there were no other statistically significant outcome measures.43

**UPA and surgery**

In the presence of uterine fibroids, there are a number of clinical situations where pre-operative medical treatment can be useful:

1. Optimisation of anaemic patients prior to surgery as this has been shown to improve clinical outcomes for women who have menorrhagia particularly coupled with anaemia.44
2. Women who have large submucous fibroids.
3. In women who are having a hysterectomy in order to reduce the size of fibroids, which may allow for a more beneficial minimal access route thus decreasing morbidity.

In a Cochrane systematic review, the authors concluded that the use of GnRH analogues reduced the size of fibroids, corrected anaemia and had the potential to reduce intra-operative blood loss.45 For patients needing a hysterectomy, this reduction in size resulted in an increased use of vaginal hysterectomy or the use of a low transverse incision rather than a midline approach reducing morbidity. However, caution must also be applied as the use of GnRH analogues is associated with an increased risk of fibroid recurrence.46 Furthermore, although the data are limited and based mainly on surgical experience, many surgeons avoid the pre-operative use of GnRH analogues as there are concerns that they may distort the fibroid capsule with a resultant loss of surgical planes between the
fibroid and myometrium potentially making the surgery more difficult and time-consuming. In a randomised study comparing premenopausal women with or without pre-operative use of GnRH analogues, Campo and Garcea found that laparoscopic myomectomy took longer in women with pre-operative treatment and they concluded that the use of GnRH analogues did not offer any advantages. In a more recent systematic review and meta-analysis, Chen et al. concluded that there was no difference in operating times or blood loss with or without pre-operative treatment. Kamath et al. in a systematic review and meta-analysis of GnRH analogues prior to hysteroscopic surgery demonstrated that there was a decrease in women needing re-operation, decrease in fluid deficit and decrease in operating times, but these were not found to be statistically significant.

UPA may be able to replace GnRH analogues in the pre-operative treatment of fibroids, particularly as they are as efficient in reducing the size of fibroids, are able to achieve amenorrhoea quicker and have a better side effect profile.

To date, there have been a number of studies looking at the effect of UPA on surgery. In a prospective non-randomised trial, Bizzari et al. showed that letrozole, triptorelin and UPA decreased the size of fibroids when given for 3 months prior to hysteroscopic resection of fibroids, but there was no difference in operating time between patients given UPA and those who were not given any pre-treatment. In a retrospective analysis, Ferrero et al. reported an increased ability to perform complicated hysteroscopic myomectomy after pre-treatment with UPA for 3 months. The same group also reported on the use of UPA 3 months prior to laparoscopic myomectomy. In a non-randomised study of 77 women, 34 were given a 3-month course of UPA. There was a decrease in overall operating time, but suturing time was not different between the 2 groups. Aref-Adib et al. reported on the lack of surgical planes when UPA was used prior to laparoscopic myomectomy and this finding was echoed by Wais et al. in a multicentre prospective trial where they found a significant difference in the difficulty of separation of fibroids from the myometrium and denucleation in patients pre-treated with UPA compared to no pre-treatment, but apart from the nuances, there was no significant difference in operation outcome. Although theoretically possible to alter the route of hysterectomy with a decrease in uterine size following the administration of UPA, there have been reports of increase in size of fibroids and cystic degeneration following UPA use.

**UPA and uterine artery embolisation**

Czuczwar et al. in a case–control study compared 17 pre-menopausal women who had a 3-month course of UPA with 17 patients who underwent uterine artery embolisation (UAE). They found a reduction in the size of fibroids in both groups. UPA also decreased fibroid vascularity, but to a lesser degree than UAE. The participants in this study were not ethnically diverse and there are no studies that compare long-term outcome comparing UPA and UAE.

**UPA and leiomyosarcoma**

In recent times, there has been controversy surrounding morcellation and the management of uterine fibroids. However, because of the diversity of options needed for the management of uterine fibroids, it is not feasible to abandon all conservative management of uterine fibroids.

In keeping with the findings of leiomyosarcoma after medical treatment of uterine fibroids, to date, there is one report of leiomyosarcoma in a laparoscopic hysterectomy specimen in a woman who was treated with UPA. This was managed with contained morcellation.

**The future**

The efficacy in terms of reduction in size of fibroids and improvement of symptoms is no longer in dispute as evidenced by a recent Cochrane review. Furthermore, the use of UPA as postulated would potentially open a new frontier for the medical management of uterine fibroids. This will be in line with other gynaecological disorders, for example, ectopic pregnancy where management has gone from a purely surgical intervention to 30% of women being managed medically.

Theoretic postulations on how UPA may be used include the following:

1. Fertility sparing in women who have delayed childbearing;
2. Amelioration of symptoms in women who are nearing menopause;
3. Avert the need for surgery in women who have symptomatic fibroids as some of the fibroids will shrink, allowing for fertility treatment;
4. Avert treatment in some women negating the need for future surgery;
5. Control of symptoms in women who cannot have surgery;
6. Prevention of recurrence of fibroids after surgery in women who wish to defer starting a family.

But as stated above, the outcome of treatment with UPA in the general population remains unknown. A recent ‘Inklings’ article in the Fertility and Sterility suggests that ‘too many surgical procedures are performed for intramural fibroids distorting the uterine cavity’ and that UPA may reduce this as well as subsequent complications thereof. Unfortunately, at the present time, there is no evidence to
suggest that UPA may allow less invasive surgery or its complete avoidance – Are we just deferring surgery and potentially making such surgery more difficult with larger fibroids and potentially poorer fertility outcomes?

The best way forward would be to enrol all patients who present with uterine fibroids needing management into clinical trials, either into randomised or into well-designed observational studies. We would then be able to ascertain what the real short- and long-term outcomes are for women treated with UPA enabling us to have evidence-based conversations with women who will then be able to make choices based on realistic expectations.

**Conclusion**

There is a popular saying, ‘do not let evidence spoil a good story’. UPA could potentially revolutionise the medical management of uterine fibroids. Although the licence in the Europe has been extended for intermittent use of up to four doses, there is no outcome evidence for women to make informed choices for their individual circumstance. UPA may be the answer to the personal, economic and social burden of uterine fibroid management; however, the time has come for this evidence to be gathered, and the introduction of UPA into the armoury of options for the management of uterine fibroids presents a clear opportunity to advance our knowledge on the outcome of medical as well as surgical management of uterine fibroids. Patients who use UPA should be enrolled in studies with clear input and output measures, as it is well known that women who are involved in clinical trials have better outcomes. This will allow for the true evaluation of cost-effectiveness compared to surgery and evaluation of outcomes in the ethnic minority populations that probably need this medication most.

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**References**

1. Virchow R. Ueber Makroglossie und pathologische Neubildung quergestreifter Muskelfasern. Arch Pathol Anat Physio Klin Med 1854; 7(1): 126–138.
2. Murji A, Whitaker L, Chow TL, et al. Selective progesterone receptor modulators (SPRMs) for uterine fibroids. Cochrane Database Syst Rev 2017; 4: CD010770.
3. Baird DD, Dunson DB, Hill MC, et al. High cumulative incidence of uterine leiomyoma in black and white women: ultrasound evidence. Am J Obstet Gynecol 2003; 188(1): 100–107.
4. Marsh EE, Ekpo GE, Cardozo ER, et al. Racial differences in fibroid prevalence and ultrasound findings in asymptomatic young women (18-30-years old): a pilot study. Fertil Steril 2013; 99(7): 1951–1957.
5. Stewart EA, Nicholson WK, Bradley L, et al. The burden of uterine fibroids for African-American women: results of a national survey. J Womens Health (Larchmt) 2013; 22(10): 807–816.
6. Borah BJ, Nicholson WK, Bradley L, et al. The impact of uterine leiomyomas: a national survey of affected women. Am J Obstet Gynecol 2013; 209(4): 319.e1–319.e20.
7. Cardozo ER, Clark AD, Banks NK, et al. The estimated annual cost of uterine leiomyomata in the United States. Am J Obstet Gynecol 2012; 206(3): 211.e1–211.e9.
8. Kjerulff KH, Langenberg P, Seidman JD, et al. Uterine leiomyomas. Racial differences in severity, symptoms and age at diagnosis. J Reprod Med 1996; 41(7): 483–490.
9. Flake GP, Andersen J and Dixon D. Etiology and pathogenesis of uterine leiomyomas: a review. Environ Health Perspect 2003; 111(8): 1037–1054.
10. Baird DD, Hill MC, Schechtman JM, et al. Vitamin D and the risk of uterine fibroids. Epidemiology 2013; 24(3): 447–453.
11. Sabry M, Halder SK, Allah AS, et al. Serum vitamin D3 level inversely correlates with uterine fibroid volume in different ethnic groups: a cross-sectional observational study. Int J Womens Health 2013; 5: 93–100.
12. Ross RK, Pike MC, Vessey MP, et al. Risk factors for uterine fibroids: reduced risk associated with oral contraceptives. Br Med J (Clin Res Ed) 1986; 293(6543): 1027.
13. Shikora SA, Niloff JM, Bistrian BR, et al. Relationship between obesity and uterine leiomyomatosis. Nutrition 1991; 7(4): 251–255.
14. Tiltman AJ. The effect of progestins on the mitotic activity of uterine fibroblasts. Int J Gynecol Obstet 1985; 20(2): 89–96.
15. Vikhlyaeva EM, Khodzhahaeva ZS and Fanschenko ND. Familial predisposition to uterine leiomyomas. Int J Gynaecol Obstet 1995; 51(2): 127–131.
16. Gross KL and Morton CC. Genetics and the development of fibroids. Clin Obstet Gynecol 2001; 44(2): 335–349.
17. Norian JM, Owen CM, Taboas J, et al. Characterization of tissue biomechanics and mechanical signaling in uterine leiomyoma. Matrix Biol 2012; 31(1): 57–65.
18. Asada H, Yamagata Y, Taketani T, et al. Potential link between estrogen receptor-alpha gene hypomethylation and uterine fibroid formation. Mol Hum Reprod 2008; 14(9): 539–545.
19. Olmos Grings A, Lora V, Dias Ferreira G, et al. Protein expression of estrogen receptors α and β and aromatase in myometrium and uterine leiomyoma. Gynecol Obstet Invest 2012; 73(2): 113–117.
20. Bulun SE. Uterine fibroids. N Engl J Med 2013; 369(14): 1344–1355.
21. Ishikawa H, Ishi K, Serna VA, et al. Progestrone is essential for maintenance and growth of uterine leiomyoma. Endocrinology 2010; 151(6): 2433–2442.
22. Lakhani KP, Marsh MS, Purcell W, et al. Uterine artery blood flow parameters in women with dysfunctional uterine
bleeding and uterine fibroids: the effects of tranexamic acid. Ultrasound Obstet Gynecol 1998; 11(4): 283–285.

23. Ikomi A, Mansell E, Spence-Jones C, et al. Treatment of menorrhagia with the levonorgestrel intrauterine system: can we learn from our failures? J Obstet Gynaecol 2000; 20(6): 630–631.

24. Rosa e Silva JC, de Sá Rosa e Silva AC, Cândido dos Reis FJ, et al. Use of a levonorgestrel-releasing intrauterine device for the symptomatic treatment of uterine myomata. J Reprod Med 2005; 50(8): 613–617.

25. Zapata LB, Whiteman MK, Tepper NK, et al. Intrauterine device use among women with uterine fibroids: a systematic review. Contraception 2010; 82(1): 41–55.

26. Tristan M, Orozco LJ, Steed A, et al. Mifepristone for uterine fibroids. Cochrane Database Syst Rev 2012; 8: CD007687.

27. Maruo T, Matsuo H, Samoto T, et al. Effects of progesterone on uterine leiomyoma growth and apoptosis. Steroids 2000; 65(10–11): 585–592.

28. Horak P, Mara M, Durdír P, et al. Effect of a selective progesterone receptor modulator on induction of apoptosis in uterine fibroids in vivo. Int J Endocrinol 2012; 2012: 436174.

29. Biglia N, Carinelli S, Maiorana A, et al. Ulipristal acetate: a novel pharmacological approach for the treatment of uterine fibroids. Drug Des Devol Ther 2014; 8: 285–292.

30. Mutter GL, Bergeron C, Deligdisch L, et al. The spectrum of endometrial pathology induced by progesterone receptor modulators. Mod Pathol 2008; 21(5): 591–598.

31. Donnez J, Tatarchuk TF, Bouchard P, et al. Ulipristal acetate versus placebo for fibroid treatment before surgery. N Engl J Med 2012; 366(5): 409–420.

32. Donnez J, Tomaszewski J, Vazquez F, et al. Ulipristal acetate versus leuprolide acetate for uterine fibroids. N Engl J Med 2012; 366(5): 421–432.

33. Donnez J, Vazquez F, Tomaszewski J, et al. Long-term treatment of uterine fibroids with ulipristal acetate. Fertil Steril 2014; 101(6): 1565–1573.e18.

34. National Institute for Health and Care Excellence (NICE). Heavy menstrual bleeding: assessment and management. Clinical Guideline [CG44], August 2016. London: National Institute for Health and Care Excellence (NICE).

35. Simon JA, Catherino W, Blakesley R, et al. Ulipristal acetate treatment of uterine fibroids in black and obese women: venus 1 subgroup analyses [28G]. Obstet Gynecol 2017; 129: 785–795.

36. Simon J, Catherino WH, Segars J, et al. First US-based phase 3 study of ulipristal acetate (UPA) for symptomatic uterine fibroids (UF): results of VENUS-I. Fertil Steril 2016; 106(3): e376.

37. Seitz C, Bumbuliene Z, Costa AR, et al. Rationale and design of ASTEROID 2, a randomized, placebo- and active comparator-controlled study to assess the efficacy and safety of vilaprisan in patients with uterine fibroids. Contemp Clin Trials 2017; 55: 56–62.

38. Luyckx M, Squifflet JL, Jadoul P, et al. First series of 18 pregnancies after ulipristal acetate treatment for uterine fibroids. Fertil Steril 2014; 102(5): 1404–1409.

39. Malone LJ. Myometomy: recurrence after removal of solitary and multiple myomas. Obstet Gynecol 1969; 34(2): 200–203.
55. Wais M, Lee S, Liu G, et al. Surgical experience with ulipristal acetate or gonadotropin releasing hormone agonists for uterine fibroids. *J Minim Invasive Gynecol* 2016; 23(7): S1–S252.

56. Raga F, Pascual C, Boigues D, et al. Cystic degeneration of uterine leiomyoma during ulipristal acetate treatment. *Uterus Ovary* 2016; 2: e1077.

57. Czuczwar P, Wozniak S, Szkodziak P, et al. Influence of ulipristal acetate therapy compared with uterine artery embolization on fibroid volume and vascularity indices assessed by three-dimensional ultrasound: prospective observational study. *Ultrasound Obstet Gynecol* 2015; 45(6): 744–750.

58. FDA. UPDATED laparoscopic uterine power morcellation in hysterectomy and myomectomy: FDA safety communication. https://wayback.archive-it.org/7993/20161023125535/http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm393689.htm, 2016.

59. Odejinmi F, Agarwal N, Maclaran K, et al. Should we abandon all conservative treatments for uterine fibroids? The problem with leiomyosarcomas. *Womens Health* 2015; 11(2): 151–159.

60. Laursen JB and Istre O. Unexpected uterine leiomyosarcoma during laparoscopic hysterectomy. *J Gynecol Surg* 2016; 32(5): 280–285.

61. Odejinmi F, Huff KO and Oliver R. Individualisation of intervention for tubal ectopic pregnancy: historical perspectives and the modern evidence based management of ectopic pregnancy. *Eur J Obstet Gynecol Reprod Biol* 2017; 210: 69–75.

62. Donnez J, Donnez O and Dolmans MM. Rewriting the script: time to rethink the indications for myoma surgery. *Fertil Steril* 2017; 107(2): 334–335.

63. Nijjar SK, D’Amico MJ, Wimalaweera NA, et al. Participation in clinical trials improves outcomes in women’s health: a systematic review and meta-analysis. *BJOG* 2017; 124(6): 863–871.