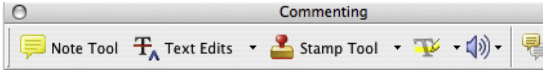
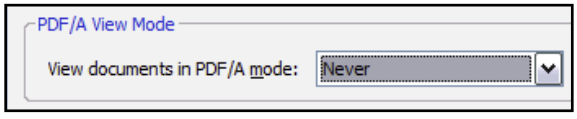
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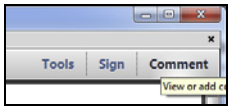
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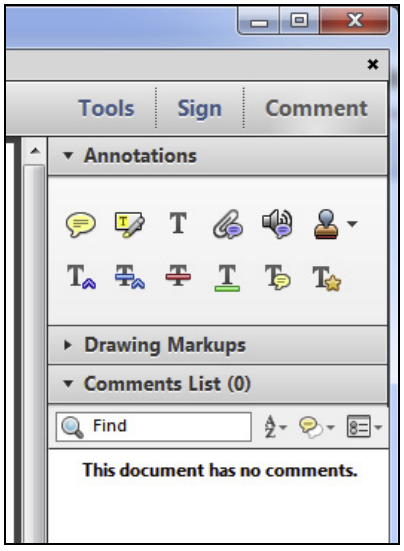
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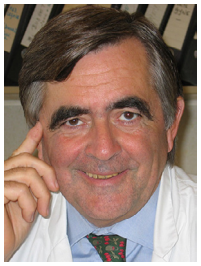
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REVIEW

Hormone therapy for intramural myoma-related infertility from ulipristal acetate to GnRH antagonist: a review



BIOGRAPHY

Jacques Donnez is Professor Emeritus at the Catholic University of Louvain and has been Director of Society of Research on Infertility in Brussels since 2012. His research interests are tubal infertility, endometriosis and ovarian cryopreservation and transplantation. He has published over 700 original articles in peer-review journals.

Donnez Jacques[1,*], Dolmans Marie-Madeleine[2]

KEY MESSAGE

The mechanisms linking uterine fibroids and infertility are numerous: uterine cavity distortion, impaired endometrial and myometrial blood supply, increased uterine contractility, molecular changes, impaired endometrial receptivity and a thicker capsule. The place of new molecules such as gonadotrophin releasing hormone antagonist in the case of intramural-related infertility is discussed.

ABSTRACT

Uterine fibroids may cause infertility, depending on their size and location according to the International Federation of Gynecology and Obstetrics classification. In this review, infertility relating to intramural myomas is evaluated. The mechanisms linking uterine fibroids and infertility are numerous: uterine cavity distortion (fibroids types 0, 1, 2, 2–5); impaired endometrial and myometrial blood supply; increased uterine contractility; hormonal, paracrine and molecular changes; impaired endometrial receptivity in gene expression (decrease in homeobox 10 [HOXA-10] expression); and thicker capsule. The negative effect of intramural myoma is related to myoma size and proximity of the uterine cavity. Therefore, a medical approach could be proposed to reduce the size of the myoma and push it back deep into the myometrium. The relevant medical treatments, including selective progesterone receptor modulator and gonadotrophin releasing hormone antagonist are reviewed. Even if the mystery surrounding intramural myomas remains, the development of new algorithms for intramural myoma-related infertility, and evaluation of the place of medical treatment as a primary approach are urgently needed. An algorithm, taking into account the mechanisms linking uterine fibroids and infertility, is proposed.

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KEYWORDS

Fibroids
GnRH antagonist
Infertility
Intramural fibroids
Medical therapy
Ulipristal acetate

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INTRODUCTION

Uterine fibroids are the most common form of benign uterine tumours, composed of large amounts of extracellular matrix containing collagen, fibronectin and proteoglycans (*Kim and Sefton, 2012*; *Bulun et al., 2013*; *Islam et al., 2013*; *Lumsden et al., 2015*; *Stewart et al., 2015*; *Donnez and Dolmans, 2016*; *Courtoy et al., 2015*; *2018*). Uterine fibroids occur in 50–60% of women, can cause morbidity because of the abnormal uterine bleeding and pelvic pressure, and may be responsible for pelvic pain, infertility and obstetrical complications (*Lumsden et al., 2015*; *Stewart et al., 2015*; *Donnez and Dolmans, 2016*).

In a previous review on the topic (*Donnez and Dolmans, 2016*), risk factors for uterine fibroid development were investigated, with race and age emerging as the most important. African–American women, as well as women of African origin living in Europe, stand a greater chance of being affected by uterine fibroids at an earlier age (*Baird et al., 2003*; *Wise et al., 2004*; ~~*2005*~~; *Wise and Laughlin-Tommaso, 2016*). Genetic factors may explain this disparity between white women and women of African origin (*Stewart et al., 2013*). Early menarche, delayed first pregnancy, low parity (*Baird et al., 2003*), obesity, high blood pressure, caffeine and alcohol intake (*Wise et al. 2004*), and some specific genetic alterations (~~*Mäkinen et al., 2011*~~; *Mehine et al., 2013*; *2014*), are also linked to fibroid growth.

RELEVANCE OF UTERINE FIBROIDS AND INFERTILITY

Uterine fibroids may cause infertility, depending on their size and their location (*Donnez and Dolmans, 2017*).

Myoma classifications are numerous and all of them take into account the degree of intramural extension and uterine cavity distortion (*Lasmar et al., 2005*; *Stamatelos and Bontis, 2007*). Since 2011, the International Federation of Gynecology and Obstetrics (FIGO) classification, published by *Munro et al. (2011)*, has identified eight types of fibroids, as well as a hybrid class (FIGURE 1A). As the focus of this paper is infertility, it is crucial that the mechanisms by which fibroids cause infertility are determined.

Uterine distortion is one of the most critical mechanisms involved (*Pritts et al., 2009*; *Sunkara et al., 2010*; *Yan et al., 2014*), and it is important to clearly differentiate submucosal myomas and intramural myomas distorting the uterine cavity (types 0, 1, 2, 2–5) from those that are purely intramural (types 3, 4) and intramural fibromas with some serosal

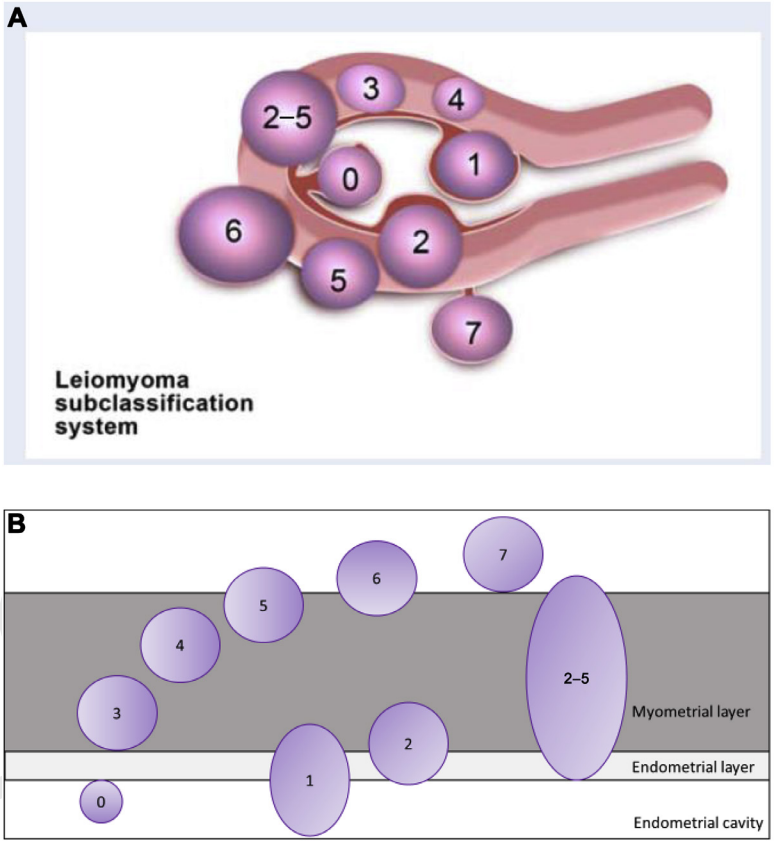


FIGURE 1 (A) Leiomyoma subclassification according to International Federation of Gynecology and Obstetrics classification of uterine fibroids according to *Munro et al. (2011)*. Fibroid types ranges are as follows: from 0 to 8: 0 = pedunculated (intracavitary); 1 = submucosal (<50% intramural); 2 = submucosal (≥50% intramural); 3 = contact with endometrium (100% intramural); 4 = intramural; 5 = subserosal (≥50% intramural); 6 = subserosal (<50% intramural); 7 = subserosal (pedunculated); and 8 = other (cervical, parasitic). Where two numbers are given (e.g. 2–5), the first number refers to the relationship with the endometrium, whereas the second number refers to the relationship with the serosa; e.g. 2–5 = submucosal and subserosal, each with less than half the diameter in the endometrial and peritoneal cavities, respectively. Fibroid classification cartoon republished with permission from *Munro et al. (2011)*; (B) relationship between myomas and myometrium adapted by Donnez and Dolmans from the Munro classification.

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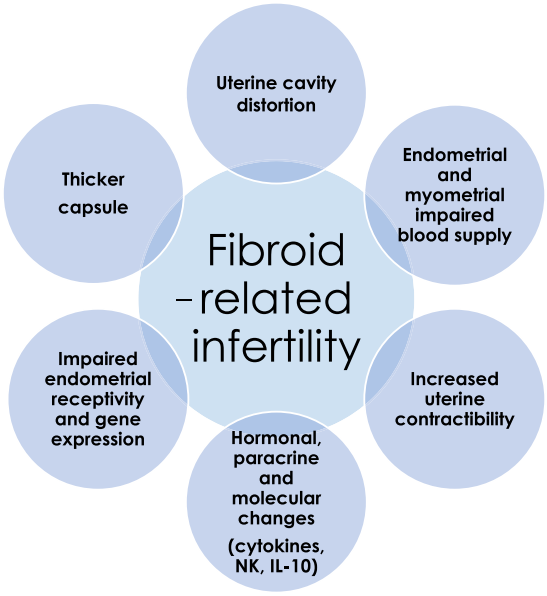


FIGURE 2 Mechanisms linking uterine fibroids and infertility.

deformation (types 5, 6) (FIGURE 1A and FIGURE 1B). Indeed, the mechanisms linking uterine fibroids and infertility are numerous (FIGURE 2): uterine cavity distortion (fibroids types 0, 1, 2, 2–5) (FIGURE 1B); impaired endometrial and myometrial blood supply; increased uterine contractility; hormonal, paracrine and molecular changes; impaired endometrial receptivity and gene expression (decrease in homeobox 10 [HOXA-10] expression); and thicker capsule.

Uterine cavity distortion

This first mechanism is self-evident and has been widely documented (*Pritts et al., 2009*; *Donnez and Dolmans, 2016*). As our review focuses on intramural myomas, we will concentrate on intramural myoma-related infertility. In the case of non-distorting uterine cavity fibroids, the mechanisms detailed below are implicated.

Impaired endometrial and myometrial blood supply

The presence of fibroids close to the uterine cavity (type 3) interferes with endometrial blood flow. Several studies using contrast magnetic resonance imaging have reported reduced blood flow in fibroids and their surrounding myometrium (*Forssman et al., 1976*). In a study using transvaginal ultrasound (*Sladkevicius et al., 1996*), uterine fibroids displayed increased blood velocity, a decreased resistance index and diminished pulsatility in their uterine arteries. A low uterine artery pulsatility index, suggests greater blood flow to myomas, facilitating growth.

In a prospective study (*Niewenhuis et al., 2018*), baseline fibroid vascularization measured with three-dimensional power Doppler was significantly related to fibroid volume at 12 months and fibroid growth rate as a percentage of volume at baseline over the course of 1 year. These investigators also demonstrated that the increase in myoma volume was greater in highly vascularized myomas. Czuczwar *et al.* (2015) reported that treatment with ulipristal acetate (UPA) for 3 months decreased fibroid volume and the vascular index, but Chia *et al.* (2016) demonstrated that gonadotrophin-releasing hormone (GnRH) agonists reduced fibroid size whereas vascular indices were not modified.

The study by *Niewenhuis et al. (2018)* underscores the hypothesis that highly vascularized fibroids tend to grow faster than poorly vascularized fibroids, which strongly supports the premise that blood supply modifications could interfere with blastocyst implantation, as suggested by *Schild et al. (2000)* and Kim *et al.* ~~(2015)~~.

Increased uterine contractility

One of the mechanisms by which non-cavitary intramural myomas may impair fertility is that these fibroids alter uterine peristalsis and, subsequently, blastocyst implantation (*Miura et al., 2006*; *Orisaka et al., 2007*). One study using magnetic resonance imaging (*Yoshino et al., 2010*) reported that intramural myomas caused abnormal uterine peristalsis, which resulted in lower implantation and pregnancy rates. As stressed by *Fanchin et al. (2002)*, contractile activity plays an important role in the human reproduction process, and its regulation depends on the menstrual cycle phase. Contractility decreases in response to progesterone, probably to favour embryo implantation (*Fanchin et al., 2001*). If the presence of intramural myomas alters uterine peristalsis, it may also interfere with the surrounding myometrium, leading to impaired uterine contractility.

Hormonal, paracrine and molecular changes

In a recent review, *Ikhena and Bulun (2018)* stressed the importance of the complex series of interactions that allow successful implantation of the embryo during the window of implantation, which includes apposition, adhesion and invasion. Fibroids can alter expression of genes that are important for implantation, such as glycodelin and bone morphogenetic protein receptor type 2 (BMPR2). *Horcajadas et al. (2008)* identified three genes that are dysregulated in women with intramural myomas, one of them being glycodelin. In a study by *Ben-Nagi et al. (2010)*, decreased levels of glycodelin and interleukin-10 were found in uterine flushing fluid from mid-luteal phase endometrium of women with fibroids. Myomas may also be responsible for diminished release of cytokines critical to implantation, such as leukemia inhibitory factor and cell adhesion molecules. Interleukin-11 plays a role in the regulation of trophoblast invasion and, if myomas are present, its production declines during the window of implantation. Decreased expression of the cell adhesion molecule E-cadherin was also described in the endometrium of women with non-cavity-distorting intramural myomas (*Casini et al., 2006*; *Ikhena and Bulun, 2018*). As stressed by *Ikhena and Bulun (2018)*, uterine fibroids significantly affected the functioning and gene expression of endometrium, but further studies are needed to provide firm evidence. Indeed, all these factors possibly interfere with endometrial receptivity.

Impaired endometrial receptivity and gene expression: the role of transforming growth factor beta-3 and *HOXA-10*

In their first study, *Rackow and Taylor (2010)* found that endometrial mRNA expression of *HOXA-10* (an important

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gene regulating endometrial receptivity) was globally decreased in the presence of submucosal myomas, rather than focally changed in the endometrium overlying the myoma. *HOXA* mRNA expression and stromal protein expression were also affected in the intramural group compared with the control group. In 2010, these investigators suggested that endometrial receptivity was altered through a specific or selective molecular mechanism of action, mediated by a diffusible molecule originating from the myoma. It is possible that the same signalling pathway proceeds from intramural myomas to the endometrium but has a less pronounced effect on endometrial receptivity (than seen with submucosal myomas) owing to the greater distance and therefore lower concentration in the endometrium.

Later, the same group showed that growth factor beta-3 (*TGF-β3*) is elevated in leiomyoma-conditioned media, leading to repression of BMP receptor types 1B and 2 and eventually a lack of response to BMP (*Doherty and Taylor, 2015*). As *HOXA-10* expression is regulated by BMP-2, they found that *TGF-β* acts as a diffusible signalling molecule to alter BMP-2, reducing *HOXA-10* expression throughout the endometrium and, subsequently, interfering with implantation. In a recent editorial, *Taylor (2018)* focused on size and distance, suggesting that larger fibroids produce more *TGF-β3* and those closest to the uterine cavity allow more TGF-β to reach endometrial cells. The amount of *TGF-β3* reaching the uterine cavity would vary by the square of the distance from the cavity ($1/x^2$, where X is the distance between the endometrium and the fibroid) (*Taylor, 2018*). Indirect proof that myomas impair endometrial receptivity is that, after intramural myomectomy, expression of endometrial receptivity genes increases significantly (*Unlu et al., 2016*).

Thicker capsule

A capsule surrounds the fibroid and can be considered a different entity (*Tinelli et al., 2018*; *2019*). This pseudocapsule consists of compressed myometrium and contains nerves. It is not clear whether an increase in pseudocapsule thickness also increases the number of neuroendocrine fibres, but their presence may influence muscle contractility and uterine peristalsis (*Tinelli et al., 2018*; *2019*).

EFFECT OF NON-CAVITY-DISTORTING UTERINE FIBROIDS

The effect of non-cavity-distorting uterine fibroids is still an ongoing debate. Since publication of the review by *Pritts et al. (2009)*, and the clear message that women with submucosal myomas experience significantly lower implantation, clinical pregnancy, ongoing pregnancy and live birth rates, as well as significantly higher miscarriage rates, the need to treat submucosal fibroids is widely accepted. With the development of hysteroscopic techniques, resection of type 0 and 1 myomas is the primary approach (*Betocchi et al., 2003*; *2004*; *Di Spiezio et al. 2008*; *2010*; *2015*). In case of type 2 myomas, distortion of the uterine cavity occurs, so resection is indicated and may be facilitated by preoperative medical treatment (GnRH agonist or selective progesterone receptor modulators [SPRM]) (*Donnez and Dolmans, 2016*). Fibroids in other locations (types 3, 4, 5, 6, 2–5), however, continue to present a clinical conundrum (*Donnez and Dolmans, 2016*).

In 2010, a systematic review by *Sunkara et al. (2010)*, including 19 observational studies and involving 6087 IVF cycles, showed a significant decrease in clinical pregnancy rates ($P = 0.002$) in women with non-cavity-distorting fibroids compared with women without fibroids. Nevertheless, a number of limitations were identified. The most notable weakness was related to the heterogeneity between studies and diverse diagnostic methods used to assess the normality of the uterine cavity. Mean size and number of fibroids varied considerably across the studies. The conclusion reached by the investigators was indeed rather curious. They concluded that the presence of non-cavity-distorting myomas reduces the chances of a live birth through IVF; they also stated that this evidence does not justify advocating myomectomy for these women. On the basis of a single-centre study, *Yan et al. (2014)* reported that non-cavity-distorting fibroids (types 3, 4, 5) do not affect IVF and intracytoplasmic sperm injection (ICSI) outcomes, but that intramural myomas over 2.85 cm in size significantly impair the delivery rate of patients undergoing IVF/ICSI.

Marqueta et al. (2016) described the detrimental effect of non-cavity-distorting intramural myomas. In an observational study, *Christopoulos et al. (2017)* found that the deleterious effect of non-cavity-distorting myomas on live birth rates was significant in women with two or more fibroids, and those with fibroids 30 mm or wider in diameter. Later, *Yan et al. (2018)* evaluated the specific influence of type 3 intramural fibroids on IVF outcomes in a retrospective cohort study (151 women with type 3 fibroids compared with 453 matched control patients). Their results strongly suggest that type 3 fibroids have a negative effect on clinical pregnancy and live birth rates, particularly if the single-fibroid diameter or total reported fibroid diameter is wider than 2 cm. As acknowledged by the investigators themselves, this study also had limitations, such as inevitable selection bias in data analysis in a retrospective study.

Following this study, *Taylor (2018)* wrote an editorial stating that large intramural myomas near the endometrial cavity warrant removal before IVF, as they affect endometrial haemostasis and endometrial receptivity through molecular signalling.

A retrospective cohort study by *Behbehani et al. (2018)* analysing a total of 929 fresh single-blastocyst transfer cycles (94 with only non-cavity-distorting intramural myomas versus 764 without myomas) revealed that relatively small (from >1.5 cm) intramural myomas may affect clinical pregnancy and live birth rates, even in the presence of only one myoma.

In a meta-analysis totalling 28 studies involving 9189 patients, Wang *et al.* (2018) conducted an updated systematic review and reported that non-cavity-distorting intramural myomas significantly reduce implantation ($P = 0.04$), clinical pregnancy and live birth rates. Recently, *Rikhraj et al. (2019)* reviewed 15 quantitative studies out of a total of 139 records identified. Among the 15 studies, eight reported live birth rates and five were prospective in nature (with a total of 5029 patients). Their systematic review concluded that patients with non-cavity-distorting intramural fibroids undergoing IVF had 44% lower odds of a live birth and 32% lower odds of a clinical pregnancy than women without fibroids. By excluding those with both intramural and subserosal myomas, and focusing solely

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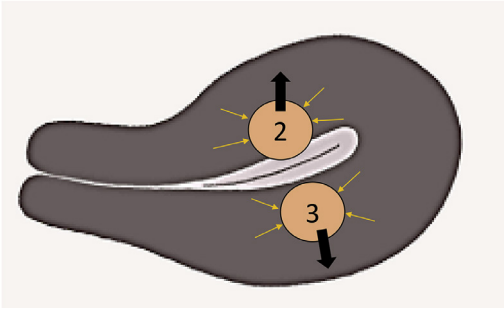


FIGURE 3 Migration effect (thick arrows) associated with a reduction in size (thin arrows) may favour blastocyst implantation. This should be the goal of medical treatment.

on patients with intramural fibroids, they removed the potentially confounding effect of subserosal myomas, and also observed lower odds of a live birth and clinical pregnancy in this subgroup. Subgroup analysis of prospective studies demonstrated significantly reduced live birth odds in women with intramural myomas too, providing a more robust conclusion on the subject. Some limitations were nevertheless reported, as assisted reproduction methods used, diagnostic tools and the lack of exact assessment of the size and location of myomas differed in each study.

In conclusion, all published studies and meta-analyses concur that non-cavity-distorting intramural fibroids do have a deleterious effect on IVF outcomes. Two factors seem to be key, namely the size of myomas (if larger, there is greater secretion of TGF-β3), and the close proximity of the uterine cavity. Close to the endometrial lining, a type 3 myoma of 2 cm or more will have a detrimental effect. If a myoma is intramural but not in contact with the underlying endometrium (type 4, 5), a diameter of 3 cm is considered the cut-off depending on the study or meta-analysis.

Several investigators have recommended surgical removal of these intramural fibroids (*Taylor, 2018*). The crucial question (*Donnez and Dolmans, 2016*), however, should be that, if the negative effect is related to myoma size and proximity of the uterine cavity, why not try a medical approach to reduce the size of the myoma, and to push it back deeper into the myometrium (FIGURE 3).

Relevant medical treatment

Medical treatments for intramural myomas are discussed below and presented in TABLE 1.

Oral contraceptives

Although oral contraceptives may reduce abnormal uterine bleeding likely by stabilization of the endometrium, they fail to decrease the fibroid volume, so have limited benefits for women with fibroid-related infertility (*De la Cruz and Buchanan, 2017*; *Donnez et al., 2018*).

Levonorgestrel-releasing intrauterine system

The levonorgestrel-releasing intrauterine system (LNG-IUS Mirena^{R}) yield a significantly greater reduction in menstrual blood loss at 12 months then do oral contraceptives, but reported expulsion rates of the LNG-IUS are 5–20% (Zapata *et al.*, 2010) in women with uterine fibroids. Hence, the benefits of LNG-IUS for fibroid volume reduction remain limited (*De la Cruz and Buchanam, 2017*; *Donnez et al., 2018*).

Tranexamic acid

Tranexamic acid is a non-hormonal oral antifibrinolytic agent that significantly curtails blood loss compared with a placebo but has no effect on fibroid volume reduction (*Lethaby et al., 2000*; *Lukes et al., 2010*).

GnRH agonists

Preoperative administration of GnRH agonists (leuprolide, goserelin, triptorelin) boosts haemoglobin levels and significantly reduces fibroid volume, but long-term treatment is contraindicated because of bone mineral density (BMD) loss (*Donnez et al., 1989*; *2018*; *Lethaby et al., 2002*). Moreover, menopausal symptoms (hot flushes, vaginal dryness, sweating, changes in breast size, loss of libido) result from this hypoestrogenic status. For more than 3 decades now (*Donnez et al., 1989*), GnRH agonist has been widely used to reduce type 1 and 2 myoma size before hysteroscopic resection. Indeed, significant volume reduction and decreased endometrial thickness and vascularization facilitate surgical fibroid removal by hysteroscopy and lower the risk of fluid overload (*Donnez et al., 1989*).

Selective progesterone receptor modulators

The advantage of SPRMs over GnRH agonists is their absence of hypoestrogenic adverse effects and the fact that they do not cause BMD loss (*Bouchard et al., 2011*; *Donnez et al., 2012a*; *2012b*). They induce progesterone receptor modulator-associated endometrial changes, which are benign and reversible if intermittent therapy is proposed (3-month UPA courses with an off-treatment period of 2 months in between) (*Donnez et al., 2014*; *2015a*; *2015b*; *Williams et al., 2007*; *2012*; *Kolanska et al., 2019*). Two cases of adenocarcinoma were recently reported in women taking asoprisnil continuously for more than 2 years without any off-treatment period (*Diamond et al., 2019*), which is not recommended. The advantages of UPA have been clearly demonstrated in various studies (*Donnez et al., 2012a*; *2012b*; *2014*; 2015) showing a reduction in fibroid volume of more than 50% after two courses of 3 months; restoration of haemoglobin levels; and significant and swift control of bleeding. All these advantages should be taken into account when different therapeutic options are discussed with patients. *Ciarmela et al. (2014)* found that UPA modulates expression of activin in leiomyomas, whereas *Courtoy et al. (2015*; 2016; *2018a*; *2018b*) elucidated some of the in-vivo mechanisms explaining its effect at the molecular level. Matrix metalloproteinase activity and expression of genes related to apoptosis or the extracellular matrix are modified by UPA, but gene expression was shown to be different in poor and good responders (*Courtoy et al., 2015*; *2018a*; *2018b*). *Lewis et al. (2019)* reported that UPA decreases active TGF-β3 levels, which are directly responsible for the fibrotic phenotype. An in-vitro study (*Del Bello et al., 2019*) suggested that autophagy upregulation induced by UPA may also contribute to leiomyoma shrinkage.

Fertility after medical treatment with ulipristal acetate

Only a few papers documenting pregnancy and live birth rates after medical treatment for intramural myoma-

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TABLE 1 ADVANTAGES AND DISADVANTAGES OF DIFFERENT MEDICAL TREATMENTS FOR INTRAMURAL MYOMAS

Treatment type (medical treatment)	Advantages	Disadvantages
Tranexamic acid/mefenamic acid	Reduces heavy menstrual bleeding in women without uterine fibroids; improves health-related quality of life.	Efficacy in the presence of fibroids is unknown.
Levonorgestrel releasing intrauterine system	Treatment of choice for heavy menstrual bleeding in the absence of fibroids; provides contraception.	Cannot be used if the uterine cavity is distorted by fibroids; high expulsion rate with submucosal fibroids.
Selective progesterone receptor modulators	Reduces heavy menstrual bleeding and shrinks fibroids; does not cause menopausal side-effects or bone demineralization; licensed for preoperative use (ulipristal acetate) to 'manage moderate to severe symptoms' of uterine fibroids and for intermittent long-term use; correction of anaemia.	Associated with endometrial changes known as progesterone receptor modulator-associated endometrial changes; need for liver enzyme monitoring.
Mifepristone	Can reduce bleeding and pressure symptoms for up to 6 months.	Uncertain effect on fibroid volume.
Gonadotrophin-releasing hormone agonists	Can be used for 3–6 months before surgery to reduce uterine and fibroid size; helps correct iron deficiency anaemia.	Long-term treatment beyond 6 months can reduce bone density; vasomotor and other menopausal symptoms are common.
Gonadotrophin-releasing hormone antagonists	Now in phase 3 study evaluation; fast effect on heavy menstrual bleeding; reduces fibroid volume and corrects anaemia; efficacy and side-effects are dose dependent, low-dose causes limited bone mineral density loss.	At high-doses, can reduce bone mineral density requiring add-back therapy for long-term treatment; other menopausal symptoms are common at high doses.

related infertility have been published, and only three studies have reported pregnancies after medical treatment with SPRMs (UPA) (FIGURE 4). Since the first publication by our group in 2014 of a case series of 15 patients (*Luyckx et al., 2014*) who conceived after UPA treatment, six case reports have been published (Wdowiak *et al*., 2013; *Monleon et al., 2014*; *Romer 2015*; *Tikhomirov 2015*; *Murall 2016*; *Luyckx et al., 2016*). A second series of 40 women and third series of 53 women pregnant after UPA treatment were reported in multicentre studies in Canada and Portugal, respectively (*De Gasperis-Brigante et al., 2018*; *Costa et al., 2020*).

Among the six case reports, four women conceived without interval myomectomy. Looking at the Belgian, Canadian and Portuguese case series, the first (*Luyckx et al., 2014*; *2016*) reported 16 patients and 18 pregnancies, the second 40 patients and 47 pregnancies (*De Gasperis-Brigante et al., 2018*), and the third 53 patients and 55 pregnancies (*Costa et al., 2020*). From the three case series and six case reports, 126 pregnancies were reported in total. No differences were found in miscarriage rates between the groups, with the rate ranging from 23–30%.

In the Canadian series, two patients experienced delivery complications (obstructive myoma and shoulder dystocia). In the Belgian and Portuguese series, no obstetrical complications were reported. Among all the live births, only one fetal malformation (ectopic kidney) occurred (*Luyckx et al., 2014*; *2016*).

Maintaining fertility is an important goal in the management of symptomatic uterine fibroids. For women wishing to preserve their fertility, SPRMs have provided an alternative, and one drug in particular (UPA) is recommended in algorithms for patients with fibroids who would like to remain fertile (*Donnez and Dolmans, 2016*). In the present review, 126 pregnancies in six case reports and three case series are reported.

These case series, however, have some limitations. All were retrospective and only included women who had achieved pregnancy after UPA treatment. The exact interpretation and scientific value of the data are, therefore, uncertain, and no strict guidelines can be extrapolated. Indeed, in most cases, the size and location of the fibroids (according to the FIGO classification) are not clearly detailed. Nevertheless, according to the pathogenic mechanisms and cases we have reported, if the myoma is only slightly distorting the cavity or is intramural and close to the endometrium, it is logical to prescribe UPA with the goal of reducing its size to less than 2.5–3 cm and pushing it back into the myometrium (induced migration), as far as possible from the endometrium (FIGURE 3).

A frequent question is how long it takes to conceive after treatment cessation. From the PEARL studies, we know that progesterone receptor modulator-associated endometrial changes are reversible and disappear 2 months after discontinuation of UPA treatment (if two menstrual bleeds have taken place) (*Donnez et al., 2016*). A recent paper by the team of Chabbert-Buffet (*Kalonska et al., 2019*) clearly demonstrated the absence of any long-term effects on endometrial proliferation and maturation. It is generally accepted that assisted reproduction procedures may start after the second menstrual bleed after UPA cessation (*Donnez et al, 2016*).

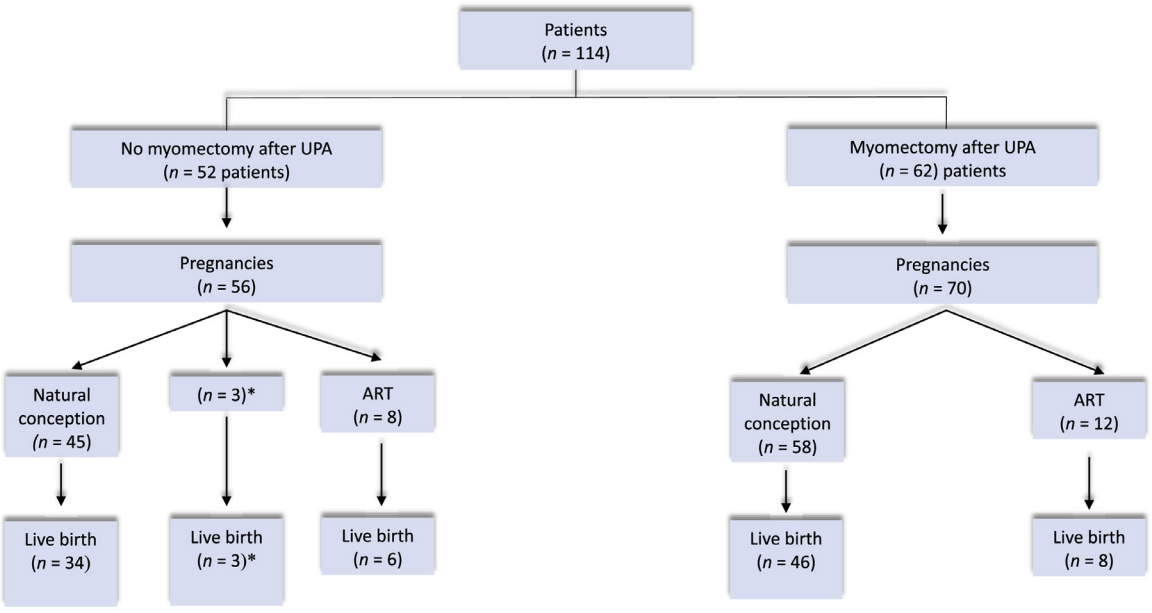
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Unfortunately, the Pharmacovigilance Risk Assessment Committee of the European Medicines Agency (EMA) has recommended that women stop taking 5 mg UPA (Esmya) for uterine fibroids while a safety review is ongoing. In the meantime, UPA use will be suspended temporarily throughout the European Union. This follows in the wake of a 2018 EMA review of five cases of liver injury that led to transplantation (*Donnez, 2018*; *Donnez et al, 2018*).

Five out of over 900,000 patients who had been treated with UPA since its authorization in 2012 required transplantation, so the EMA concluded that there is a risk of rare but serious liver injury with UPA, and measures were implemented to minimize the risk. Despite adherence to these measures, however, a new case of serious liver injury occurred, and the EMA is now starting another review.

It is unfortunate for gynaecologists, but it is even more unfortunate for patients. Many of them have been successfully treated with this drug, which is able to stop heavy menstrual bleeding caused by ~~to~~ fibroids, reduce fibroid volume and improve quality of life. We had a good drug in our hands, but safety is the primary objective, and efforts to

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*, Method of conception unknown
ART, assisted reproductive technology.

FIGURE 4 Pregnancies (reported from three case series and six case reports) after ulipristal acetate treatment (Wdowiak *et al.*, 2013; *Luckx et al, 2014*; *2016*; *Monleón et al., 2014*; *Römer, 2015*; *Tikhomirov, 2015*; *Murad, 2016*; *De Gasperis-Brigante et al., 2018*; *Costa et al., 2020*).

minimize rates of drug-induced liver injury could not prevent a new case of liver transplantation. Six out of over 1,000,000 cases is a lower rate than drug-induced liver injury caused by paracetamol, but they were neither dose-related nor predictable.

GnRH antagonists

Oral GnRH antagonists (elagolix, relugolix, linzagolix) are now in phase 3 clinical trials. Some of them are completed (*Osuga et al., 2019*; *Schlaff et al., 2020*). So far, they have been shown to have a rapid effect on heavy menstrual bleeding (*Schlaff et al., 2020*), and cause a significant reduction in fibroid volume (around 40% from baseline to week 24 in Japanese women) (*Osuga et al., 2019*). Indeed, oestradiol concentrations fell swiftly upon treatment and climbed quickly after its discontinuation. Since BMD loss was encountered in several studies depending on the delivered dose, further phase 3 investigations are under way to assess administration of GnRH antagonist with low-dose hormone add-back therapy to mitigate the effects of hypoestrogenism without undermining the benefits. In a recent study (*Schlaff et al., 2020*), the primary efficacy endpoint was menstrual blood loss, of less than 80 ml during the final month of treatment, and at least a 50% reduction in menstrual bleeding from baseline to the final month. In these two phase 3 trials (Elaris 1 and 2), 300 mg elagolix twice a day was effective at reducing heavy menstrual bleeding in over 80% of women receiving this drug alone versus over 70% of women given elagolix plus add-back therapy (1 mg oestradiol and 0.5 mg norethindrone acetate once daily) (FIGURE 5). Among women who received elagolix alone, 84.1% in group UF-1 (Elaris 1) and 77% in group UF-2 (Elaris 2) met the criteria for the primary endpoint. Percentages of women who received elagolix with add-back therapy were 68.5% and 76.5%, respectively, in UF-1 and UF-2 (FIGURE 5). In the group of women who received elagolix with add-back therapy, 48.1% in UF-1 and 52.9% in UF-2 had amenorrhoea (no bleeding or spotting) in the final month. The fibroid volume reduction evaluated by magnetic resonance imaging as a mean per cent change from baseline (*Schlaff et al., 2020*) was about 10%. In the absence of add-back therapy, BMD was significantly lower but, interestingly, no significant differences were observed between women who received elagolix with add-back therapy and those who received a placebo with respect to the change in bone mineral density in the lumbar spine, total hip or femoral neck from baseline to 6 months. In a randomized clinical trial comparing relugolix (40 mg, once daily) with leuprorelin acetate (*Osuga et al, 2019*), the primary efficacy endpoint was the percentage of women with a total pictorial blood loss assessment chart score of less than 10 for weeks 6–12. The proportion of women who met the primary endpoint was 82.2% in the relugolix groups and 83.1% in the leuproreline acetate group.

The rate of amenorrhoea at weeks 6–12 was similar in both groups, at around 77%. Myoma and uterine volumes decreased more rapidly in the relugolix group. At week 12, reductions in myoma volume were 51% and 48%, respectively. A decrease in BMD was observed in both groups. Median percentage changes in BMD from baseline to week 24 were –4.4% in both the relugolix and leuprorelin groups.

In two other clinical trials (Liberty 1: https://investors.myovant.com/static-files/a97565b8-8702-4188-96ba-bea0bbcec77d; Liberty 2: https://investors.myovant.com/static-files/776bb297-c59d-419d-8a2e-8ba04cdb3659), women received 40 mg relugolix with add-back therapy. Proportions of participants who met the primary endpoint (menstrual blood

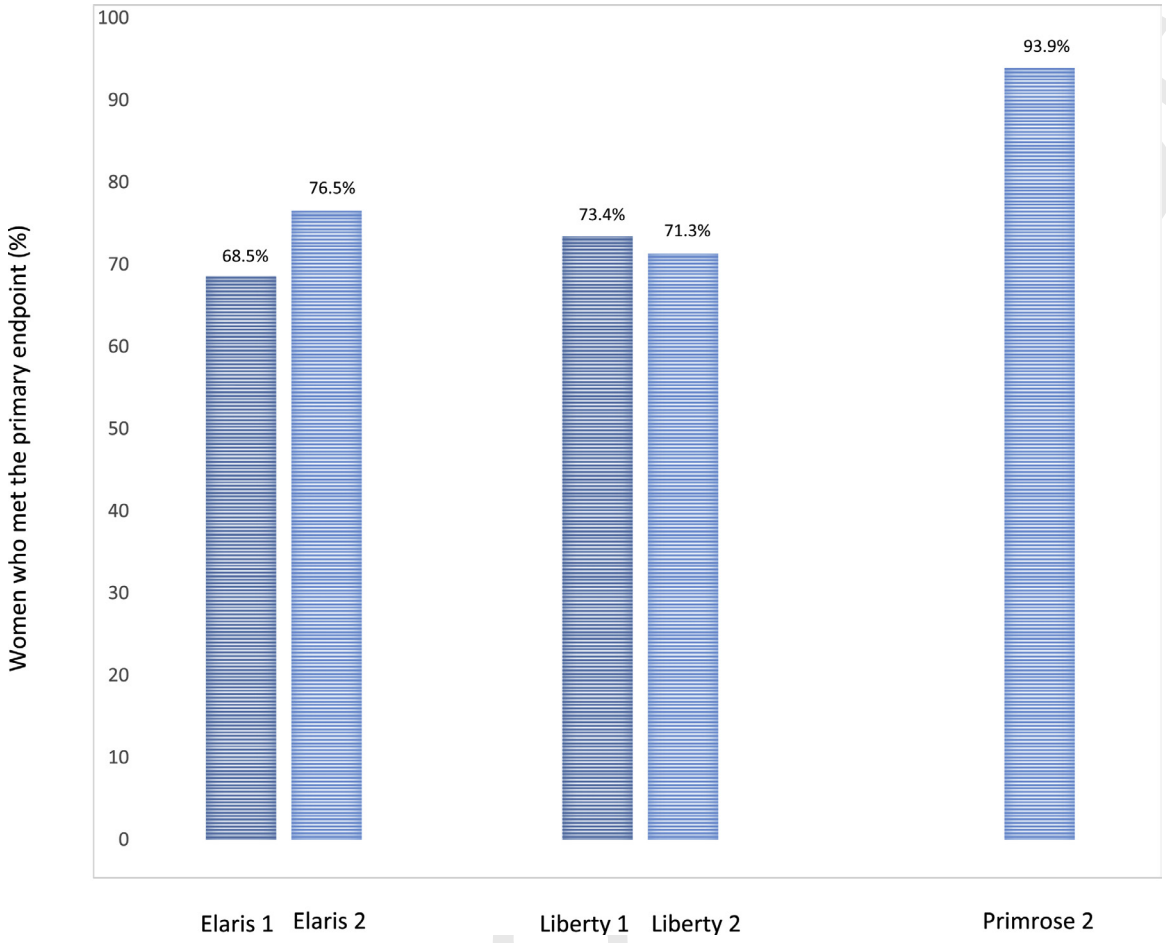


FIGURE 5 Percentage of women who met the primary endpoint (proportion of women with menstrual blood loss less than 80 ml and 50% or over from baseline in three clinical trials with oral gonadotrophin releasing hormone antagonist (300 mg elagolix twice daily + ABT [Elaris 1 and 2]; 40 mg relugolix twice daily + ABT [Liberty 1 and 2], 200 mg linzagolix once daily + ABT [Primrose 2]).

loss <80 ml and >50% reduction from baseline) were 73.4% and 71.3%, respectively, in Liberty 1 and Liberty 2 (FIGURE 5). Amenorrhoea rates were 52.3% and 50.4%, respectively, and spine BMD loss –0.36% and –0.13%.

The third oral GnRH antagonist in phase 3 clinical trials now is linzagolix. Linzagolix shows limited bone loss (<2%) at a dose of 100 mg, possibly making add-back therapy unnecessary (*Donnez et al., 2020*). In another randomized clinical trial (Primrose 2: https://www.obseva.com/wpcontent/uploads/2020/01/ObsEva_Investor_Deck_JPM_2020_final.pdf) (FIGURE 5), the proportion of women who met the primary endpoint (the same as in elagolix and relugolix trials) was 93.9% at a dose of 200 mg plus add-back therapy. The amenorrhoea rate was 80.6% and BMD loss was evaluated at –1.31% in the spine.

Compared with a placebo, 100 mg and 200 mg linzagolix with or without add-back therapy significantly decreased heavy menstrual bleeding. Indeed, the proportion of patients who met the primary endpoint was 29.4% in the placebo group versus 56.7%, 77.2%, 77.7% and 93.9% in the 100 mg, 100 mg + ABT, 200 mg and 200 mg + ABT groups, respectively. Time needed to reduce menstrual blood loss was fast in the 200 mg + ABT group, with 70% of women meeting the primary criteria after 1 week. Percentages of women in amenorrhoea at 24 weeks were 11.8%, 34.0%, 63.4%, 70.9% and 80.6% in the placebo, 100 mg, 100 mg + ABT, 200 mg and 200 mg + ABT groups, respectively. Fibroid volume change from baseline was significant in the 200 mg linzagolix (–49.5%, $P < 0.001$) and 200 mg linzagolix + ABT (–29.4%) groups.

In conclusion, results from phase 3 clinical trials with three oral GnRH antagonists, currently in phase 3 studies (elagolix, relugolix, linzagolix), have demonstrated excellent control of fibroid-related heavy menstrual bleeding and proved that the reduction in menstrual bleeding is maintained when add-back therapy is taken with the antagonists, and BMD loss is curbed. The reduction in fibroid volume is, however, more limited in the group with ABT compared with the group without ABT. Further studies are required to find the best protocol and optimal dosage if a reduction in myoma volume is the main goal, as in case of myoma-related infertility.

In conclusion, the mystery surrounding intramural myomas remains and only prospective randomized studies investigating medical versus surgical therapy will address the question of the best approach to take in the case of intramural myoma-related infertility. Fibroids, however, are a common pathology and increasingly observed in women requiring a medical opinion for infertility for two reasons: longer reproductive timeline in women thanks to improvements in medical care, and the

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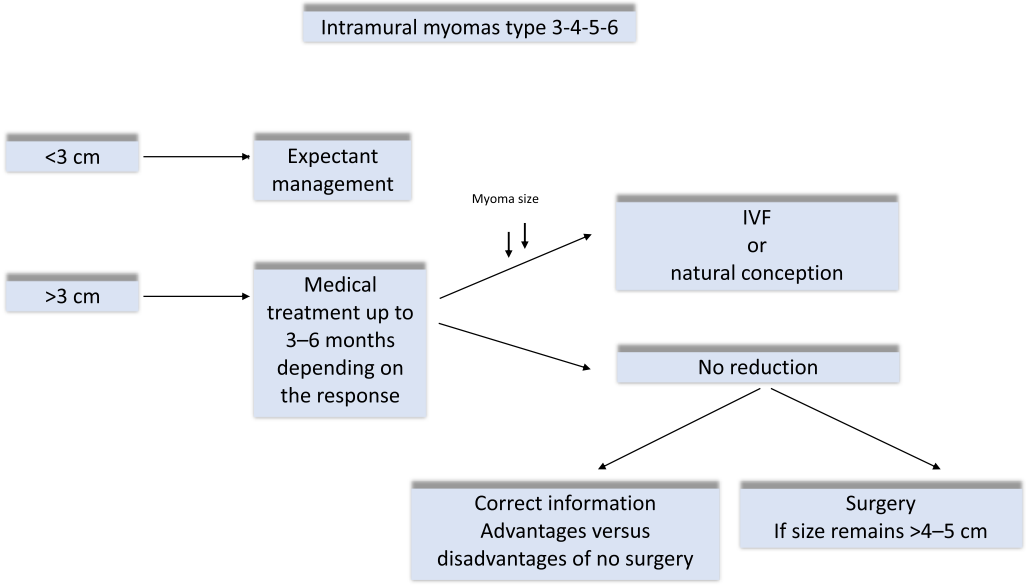


FIGURE 6 Proposed algorithm for intramural myoma-related infertility. If the myoma measures more than 3 cm, a medical treatment could be proposed as the primary approach to decrease myoma size and induce migration of the myoma as far as possible from the endometrium.

current trend for women to postpone childbearing.

The development of new algorithms for intramural myoma-related infertility are urgently needed, as is the evaluation of the place of medical as primary approach (FIGURE 6). Then, depending on the response to medical therapy, remaining myoma size, and patient age, natural conception (or IVF if required) or surgical therapy can be proposed.

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