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Jacques Donnez MD, PhD Professor EM ,
Marie-Madeleine Dolmans MD, PhD

PII: S1472-6483(20)30316-3
DOI: https://doi.org/10.1016/j.rbmo.2020.05.017
Reference: RBMO 2439

To appear in: *Reproductive BioMedicine Online*

Received date: 27 March 2020
Revised date: 15 May 2020
Accepted date: 29 May 2020

Please cite this article as: Jacques Donnez MD, PhD Professor EM , Marie-Madeleine Dolmans MD, PhD , Intramural myoma-related infertility: the place of hormone therapy in infertility management: from UPA to GnRH antagonist. A review, *Reproductive BioMedicine Online* (2020), doi: https://doi.org/10.1016/j.rbmo.2020.05.017

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Intramural myoma-related infertility: the place of hormone therapy in infertility management: from UPA to GnRH antagonist.

A review

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

Jacques DONNEZ*[1], Marie-Madeleine DOLMANS[2]

*** To whom correspondence should be addressed**

(1) Jacques Donnez, MD, PhD

Professor EM, Catholic University of Louvain

Director, Société de Recherche pour l'Infertilité (SRI)

143 Avenue Grandchamp, B-1150 Brussels, Belgium

E-mail: jacques.donnez@gmail.com

(2) Marie-Madeleine Dolmans, MD, PhD

Gynecology Department, Cliniques Universitaires St-Luc, Avenue Hippocrate 10, 1200 Brussels, Belgium: Pôle de Gynécologie, Institut de Recherche Expérimentale et Clinique, Université Catholique de Louvain, Avenue Mounier 52, bte B1.52.02, 1200 Brussels, Belgium

Email: marie-madeleine.dolmans@uclouvain.be

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ABSTRACT

Research Question: Uterine fibroids may cause infertility, depending not only on their size but also their location according to the FIGO classification. This review evaluate particularly the intramural-myomas related infertility.

Design: A research of the recent and relevant literature was conducted using the terms: "Uterine fibroids", "infertility".

Results: The mechanisms linking uterine fibroids and infertility are numerous: 1) Uterine cavity distortion (fibroids types 0, 1, 2, 2-5); 2)Impaired endometrial and myometrial blood supply; 3) Increased uterine contractility; 4) Hormonal, paracrine and molecular changes; 5) Impaired endometrial receptivity in gene expression (decrease in homeobox 10 [HOXA-10] expression); 6) Thicker capsule.

The negative impact of intramural 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 therapy are reviewed. Fertility after medical therapy (SPRMs, UPA) is analyzed.

Conclusions: Even if the mystery surrounding intramural myomas remains, there is an urgent need to develop new algorithms for intramural myoma-related infertility, and to evaluate the place of medical therapy as a primary approach.

Keywords (5): infertility, fibroids, intramural fibroids, medical therapy, ulipristal acetate, GnRH antagonist.

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Uterine fibroids are the most common form of benign uterine tumors, composed of large amounts of extracellular matrix (ECM) 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). Occurring in 50-60% of women, uterine fibroids cause morbidity due to 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. It should be emphasized that 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 Caucasian 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.

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Relevance of uterine fibroids and infertility

Uterine fibroids may cause infertility, depending not only on their size but also 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 we determine the mechanisms by which fibroids cause infertility.

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 deformation (types 5, 6) (Figure 1A and B). Indeed, the mechanisms linking uterine fibroids and infertility are numerous (Figure 2):

1) Uterine cavity distortion (fibroids types 0, 1, 2, 2-5) (Figure 1B).
2) Impaired endometrial and myometrial blood supply.
3) Increased uterine contractility.
4) Hormonal, paracrine and molecular changes.
5) Impaired endometrial receptivity and gene expression (decrease in homeobox 10 [HOXA-10] expression).
6) Thicker capsule.

1) Uterine cavity distortion

This first mechanism is self-evident and has been widely documented (Pritts et al., 2009; Donnez and Dolmans 2016). Since our manuscript focuses on intramural myomas, we will concentrate on intramural myoma-related infertility. In case of non-distorting uterine cavity fibroids, the mechanisms detailed in points 2, 3, 4, 5 and 6 are implicated.

2) Impaired endometrial and myometrial blood supply

The presence of fibroids close to the uterine cavity (type 3) interferes with endometrial blood flow. A number of studies using contrast magnetic resonance imaging (MRI) reported

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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 (3D) power doppler (PD) 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 authors also demonstrated that myoma volume increase was greater in highly vascularized myomas. Czuczwar et al. (2015) reported that 3-month therapy with ulipristal acetate (UPA) decreased fibroid volume and the vascular index, but Chia et al. (2016) demonstrated that gonadotropin-releasing hormone (GnRH) agonists reduced fibroid size while 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).

3) 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 (Orisaka et al., 2007; Miura et al., 2006). One study using MRI (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 favor 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.

4) 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 (WOI), 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 3 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 (IL)-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 (LIF) and cell adhesion molecules. IL-11 plays a role in the regulation of trophoblast invasion and, if myomas are present, its production declines during the WOI. 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 have a significant impact on 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.

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5) Impaired endometrial receptivity and gene expression: the role of transforming growth factor beta-3 (TGF-β3) and HOXA-10

In their first study, Rackow and Taylor (2010) found that endometrial mRNA expression of HOXA-10 (an important 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 impacted in the intramural group compared to the control group. In 2010, these authors 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 signaling pathway proceeds from intramural myomas to the endometrium, but has a less pronounced effect on endometrial receptivity (than seen with submucosal myomas) due to the greater distance and therefore lower concentration in the endometrium.

Later the same group showed that 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). Since HOXA-10 expression is regulated by BMP-2, they found that TGF-β acts as a diffusible signaling 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-β 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).

6) 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 increase in pseudocapsule thickness also increases the number of neuroendocrine fibers, but their presence may influence muscle contractility and uterine peristalsis (Tinelli et al., 2018, 2019).

Impact of non-cavity-distorting uterine fibroids

This 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, there is distortion of the uterine cavity, so resection is indicated and may be facilitated by preoperative medical therapy (GnRH agonist or selective progesterone receptor modulators [SPRM]) (Donnez and Dolmans, 2016). However, fibroids in other locations (types 3, 4, 5, 6, 2-5) 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 in vitro fertilization (IVF) cycles showed a significant decrease in clinical pregnancy rates (p=0.002) in women with non-cavity-distorting fibroids compared to 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 authors' conclusion was indeed rather curious. While 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. Based on one-center study, Yan et al. (2014) reported that non-cavity-distorting fibroids (types 3, 4, 5) do not affect IVF/ 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.

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

Following this study, Taylor (2018) wrote an editorial stating that large intramural myomas in close proximity to the endometrial cavity warrant removal prior to IVF, as they affect endometrial hemostasis and endometrial receptivity through molecular signaling.

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

In a meta-analysis totaling 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. Very 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 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 studies differed in terms of the assisted reproduction methods used, diagnostic tools, and the lack of exact assessment of the size and location of myomas.

In conclusion, all published studies and meta-analyses concur that non-cavity-distorting intramural fibroids do have a deleterious impact on IVF outcomes. Two factors appear to be key, namely (i) the size of myomas (if larger, there is greater secretion of TGF- β3), and (ii)

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 series/meta-analysis.

Several authors recommend surgical removal of these intramural fibroids (Taylor, 2018). However, the crucial question (Donnez and Dolmans, 2016) should be: if the negative impact is related to myoma size and proximity of the uterine cavity, why not try a medical approach to 1) reduce the size of the myoma, and 2) to push it back deeper into the myometrium (Figure 3).

Relevant medical therapy (Figure 4)

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 very limited benefits for women with fibroid-related infertility (De la Cruz and Buchanan, 2017; Donnez et al., 2018).

2) Levonorgestrel-releasing intrauterine system (LNG-IUS Mirena^{R})

The LNG-IUS 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, their benefits in terms of fibroid volume reduction remain limited (De la Cruz and Buchanam, 2017; Donnez et al., 2018).

3) Tranexamic acid

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

4) GnRH agonists

Preoperative administration of GnRH agonists (leuprolide, goserelin, triptorelin) boosts hemoglobin levels and significantly reduces fibroid volume, but long-term treatment is contraindicated because of bone mineral density (BMD) loss (Lethaby et al., 2002, Donnez et al., 1989, 2018). Moreover, menopausal symptoms (hot flushes, vaginitis, sweating, changes in breast size, loss of libido, etc) 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 prior to 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).

5) SPRMs

The advantage of SPRMs over GnRH agonists is their absence of hypoestrogenic adverse effects and the fact that they do no cause BMD loss (Bouchard et al., 2011; Donnez et al., 2012a, 2012b). They induce progesterone receptor modulator-associated endometrial changes (PAECs), which are benign and reversible if intermittent therapy is proposed (three-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 1) a reduction in fibroid volume of more than 50% after 2 courses of 3 months, 2) restoration of hemoglobin levels, and 3) significant and very 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, while Courtoy et al. (2015, 2016, 2018a, 2018b) elucidated some of the in vivo mechanisms explaining its effect at the molecular level. UPA modifies matrix metalloproteinase activity and expression of genes related to apoptosis or the ECM, 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 therapy with ulipristal acetate (Figure 5)

A preliminary remark should be focused. There are only a few papers documenting pregnancy and live birth rates after medical therapy for intramural myoma-related infertility, and only 3 studies have reported pregnancies after medical therapy with SPRMs (UPA). 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, a number of 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 multicenter studies in Canada and Portugal respectively (De Gasperis-Brigante et al., 2018; Costa et al., 2020).

Among the 6 case reports, 4 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, and the third 53 patients and 55 pregnancies. From the 3 case series and 6 case reports, 126

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pregnancies were reported in total. There were no differences in miscarriage rates between the groups, with the rate ranging from 23% to 30%.

In the Canadian series, 2 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. SPRMs have provided an alternative for women wishing to preserve their fertility, and one drug in particular (UPA) is recommended in algorithms for patients with fibroids who would like to remain fertile (Donnez and Dolmans, 2016). The present paper reports 126 pregnancies in 3 case series and 6 case reports.

There are, however, some limitations in these case series. All were retrospective and only included women who had achieved pregnancy after UPA therapy. The exact interpretation and scientific value of the data are therefore uncertain, and no strict guidelines can be extrapolated. Indeed, in the majority of 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 PAECs are reversible and disappear 2 months after discontinuation of UPA treatment (if there were 2 menstrual bleeds) (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 following UPA cessation (Donnez et al, 2016).

Unfortunately, the Pharmacovigilance Risk Assessment Committee (PRAC) 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. UPA use will be temporarily suspended throughout the European union in the meantime. This follows in the wake of a 2018 EMA review of 5 cases of liver injury that led to transplantation.

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. However, in spite of adherence to these measures a new case of serious liver injury occurred, and the EMA is now starting another review.

It is unfortunate for us gynecologists, but it is even more unfortunate for our patients. Many of them have been successfully treated with this drug that is able to stop heavy menstrual bleeding due 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 minimize rates of drug-induced liver injury (DILI) could not prevent a new case of liver transplantation. Six out of over 1,000,000 cases is a lower rate than DILI induced by paracetamol, but they were neither dose-related nor predictable.

6) GnRH antagonists

Oral GnRH antagonists (elagolix, relugolix, linzagolix) are now in phase 3 clinical trials. Some of them are completed (Schlaff et l., 2020; Osuga et al., 2019). So far, they have been shown to have a very 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, estradiol concentrations fell very swiftly upon treatment and climbed very quickly after its discontinuation. Since BMD loss was encountered in several studies depending on the delivered dose, further phase 3 investigations are underway 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 very 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 >80% of women receiving this drug alone versus >70% of women given elagolix plus add-back therapy (1 mg estradiol and 0.5 mg norethindrone acetate once daily) (Figure 6). 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 respectively 68.5% and 76.5% in UF-1 and UF-2 (Figure 6). In the group of women who received elagolix with and without add-back therapy, 48.1% in UF-1 and 52.9% in UF-2 had amenorrhea (no bleeding or spotting) in the final month. The fibroid volume reduction evaluated by MRI as a mean percent change from baseline (Schlaff et al., 2020) was more or less 10%. BMD was significantly lower in the absence of add-back therapy but, interestingly, there were no significant differences 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) to leuprorelin acetate (Osuga et al, 2019), the primary efficacy endpoint

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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 amenorrhea 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 respectively -51% and -48%. 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 subjects who met the primary endpoint (menstrual blood loss <80 ml and >50% reduction from baseline) were 73.4% and 71.3% respectively in Liberty 1 and Liberty 2 (Figure 6). Amenorrhea rates were respectively 52.3% and 50.4% and spine BMD loss -0.36% and -0.13%.

The third oral GnRH antagonist in phase 3 clinical trials now is linzagolix. Linzagolix shows very limited bone loss (<2%) at a dose of 100 mg, possibly making add-back therapy unnecessary (Donnez et al., 2020). In an other randomized clinical trial (Primrose 2: https://www.obseva.com/wpcontent/uploads/2020/01/ObsEva_Investor_Deck_JPM_2020_final.pdf) (Figure 6), 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 amenorrhea rate was 80.6% and BMD loss was evaluated at -1.31% in the spine.

Compared to 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 respectively 29.4% in the placebo group versus respectively 56.7%, 77.2%, 77.7% and 93.9% in the 100 mg, 100 mg + ABT, 200 mg and 200 mg + ABT groups. Time needed to reduce menstrual blood loss was very fast in the 200 mg + ABT group, with 70% of women meeting the primary criteria after one week. Percentages of women in amenorrhea at 24 weeks were respectively 11.8%, 34.0%, 63.4%, 70.9% and 80.6% in the placebo, 100mg, 100 mg + ABT, 200 mg and 200 mg + ABT groups. 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 to 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.

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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 case of intramural myoma-related infertility. But, fibroids are a common pathology and increasingly observed in women requiring a medical opinion for infertility for 2 reasons:

1) A longer reproductive timeline in women thanks to improvements in medical care.

2) The current trend for women to postpone childbearing.

There is therefore an urgent need to develop new algorithms for intramural myoma-related infertility and to evaluate the place of medical therapy as a primary approach (Figure 7). 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.

ACKNOWLEDGMENTS

The authors thank Mira Hryniuk, B.A., for reviewing the English language of the article and Deborah Godefroidt for her administrative assistance.

FUNDING

This study was supported by grants from the Fonds National de la Recherche Scientifique de Belgique (5/4/150/5 grant to Marie-Madeleine Dolmans), the Fonds Speciaux de Recherche, the Foundation Against Cancer and the Ferrero Family.

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AUTHOR CONTRIBUTION STATEMENT

JD and MMD contribute equally to the redaction of the manuscript

CONFLICT OF INTEREST STATEMENT

JD is member of the SAB of Preglem/ Gedeon Richter and Obseva. He received grants and fees for lectures.

MM declares no conflict of interest.

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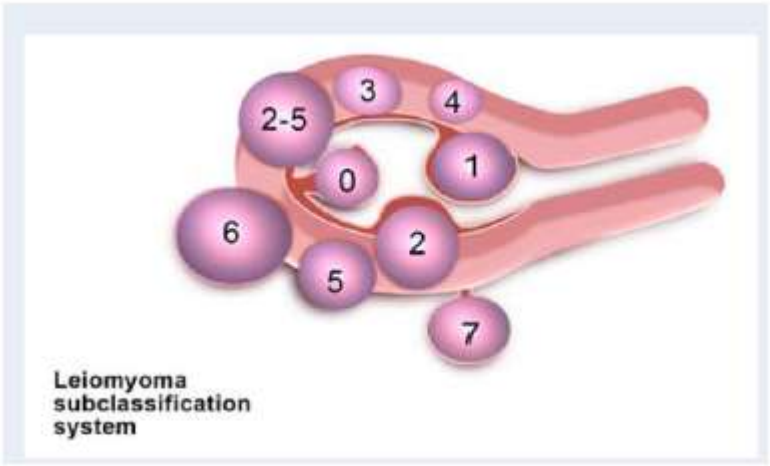
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Figures

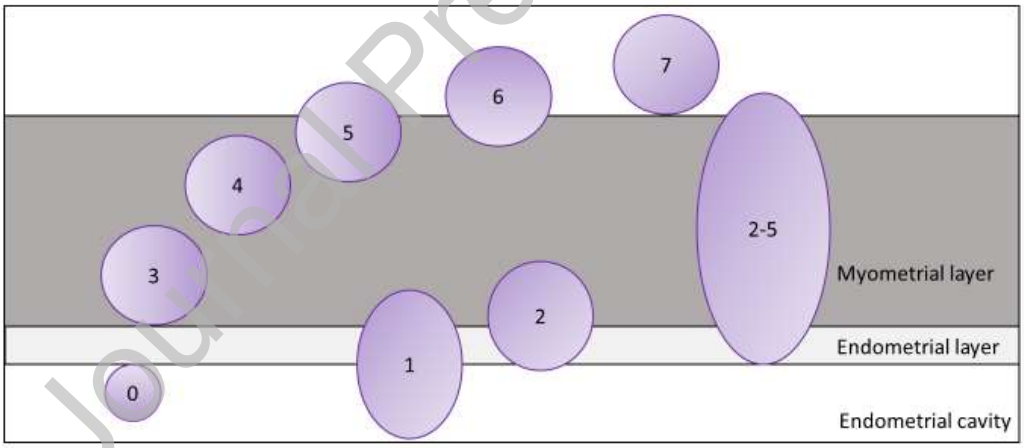
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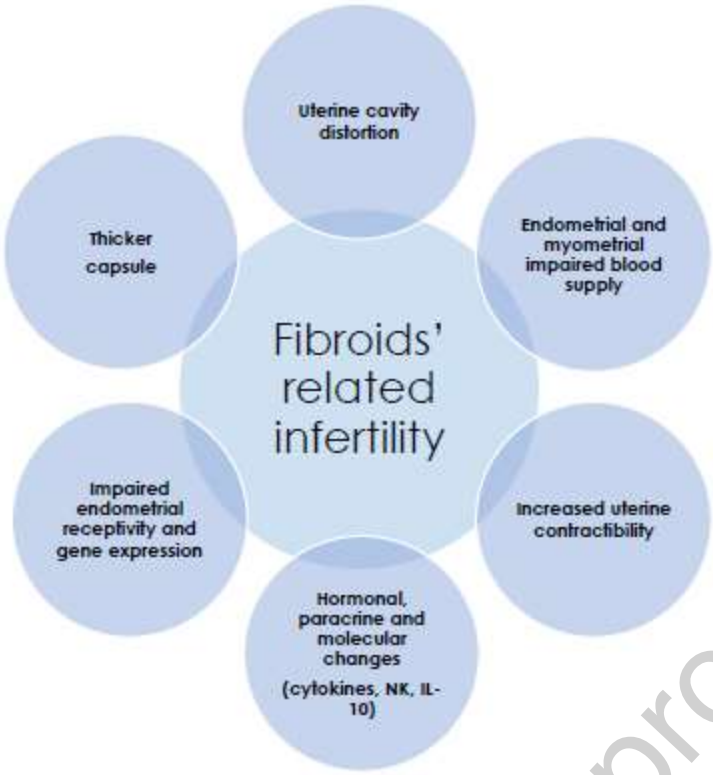
Figure 1B



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Figure 2

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Figure 3

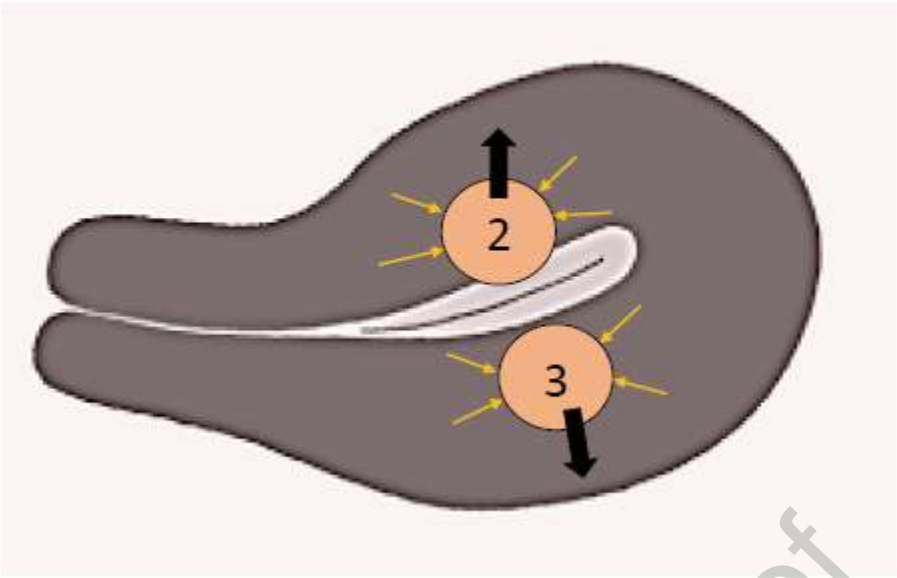


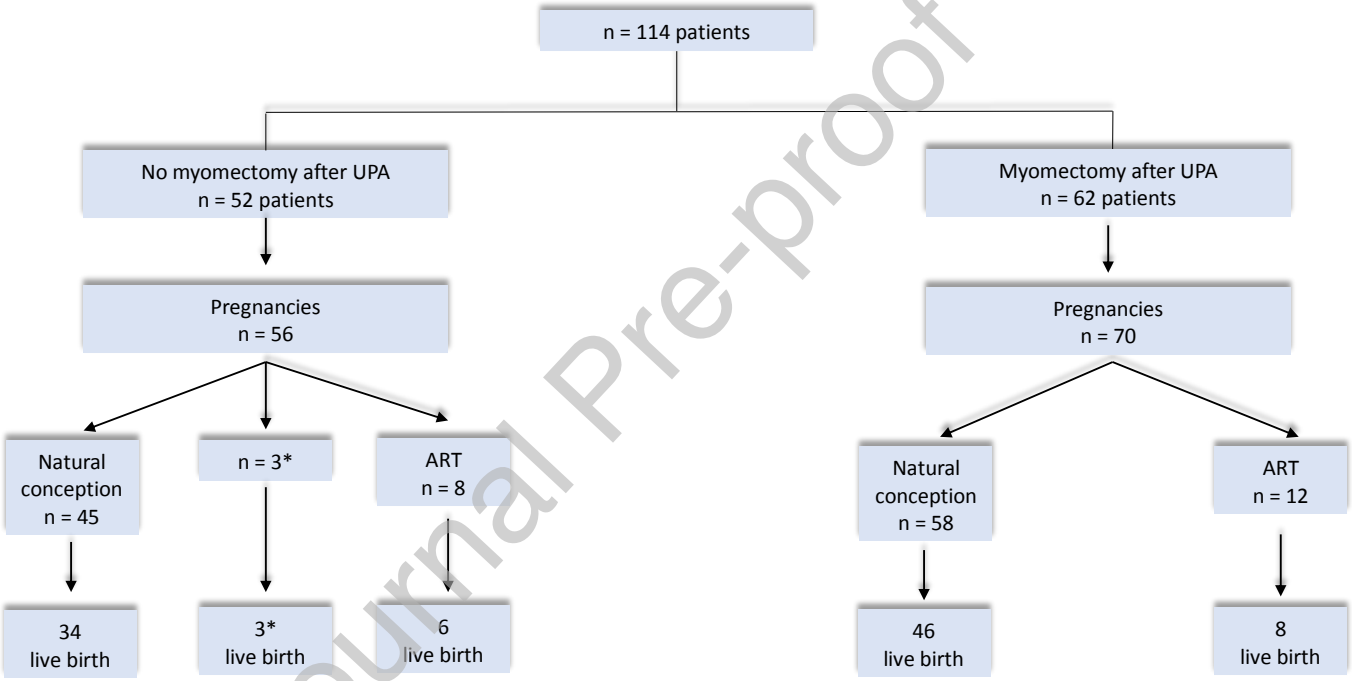
Figure 4

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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 (UPA) to "manage moderate to severe symptoms" of uterine fibroids and for intermittent long-term use; correction of anemia.	Associated with endometrial changes known as called PAECs; need for liver enzyme monitoring
Mifepristone	Can reduce bleeding and pressure symptoms for up to six months	Uncertain effect on fibroid volume
Gonadotropin-releasing hormone agonists	Can be used for 3-6 months presurgery to reduce uterine and fibroid size; helps correct iron deficiency anemia	Long-term therapy beyond six months can reduce bone density: vasomotor and other menopausal symptoms are common
Gonadotropin-releasing hormone antagonists	Now in phase 3 study evaluation; very fast effect on heavy menstrual bleeding; reduces fibroid volume and corrects anemia; efficacy and side effects are dose dependent, low dose causes very 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

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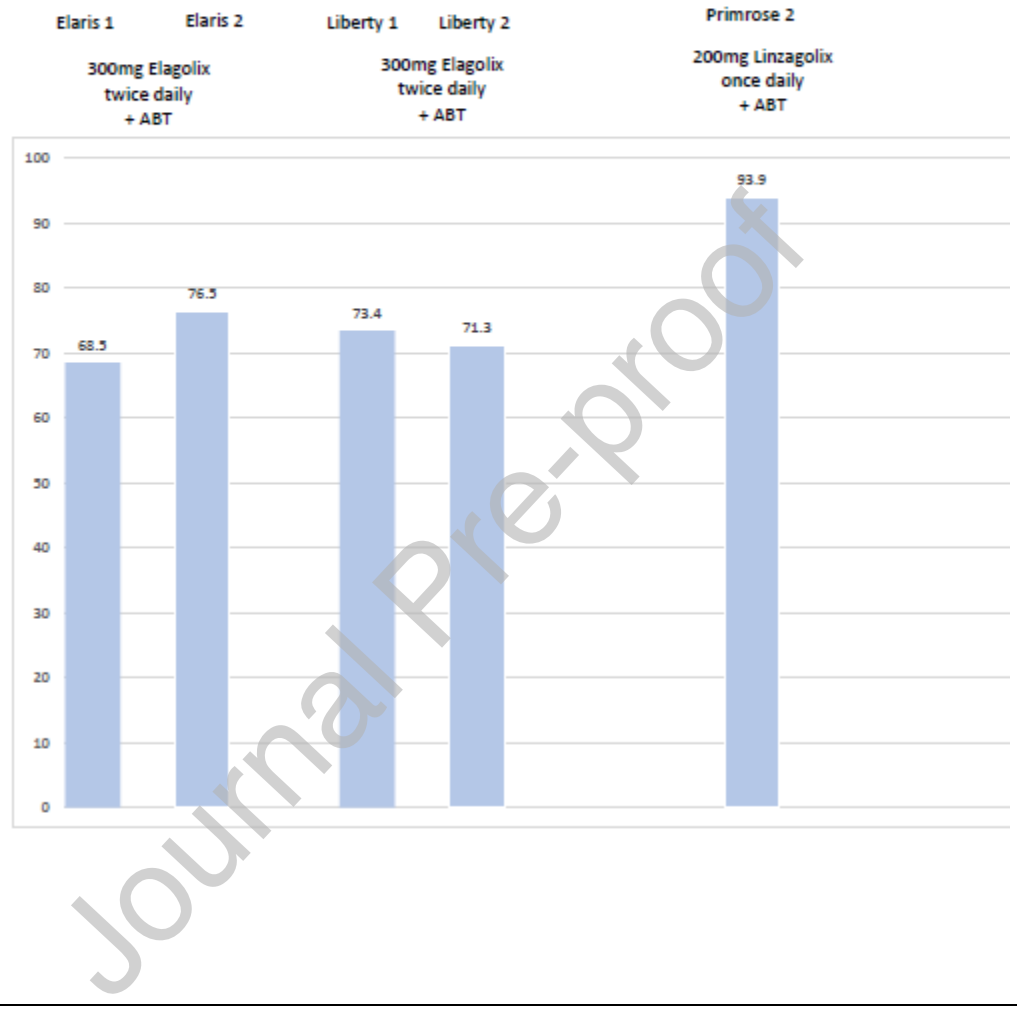
Figure 5



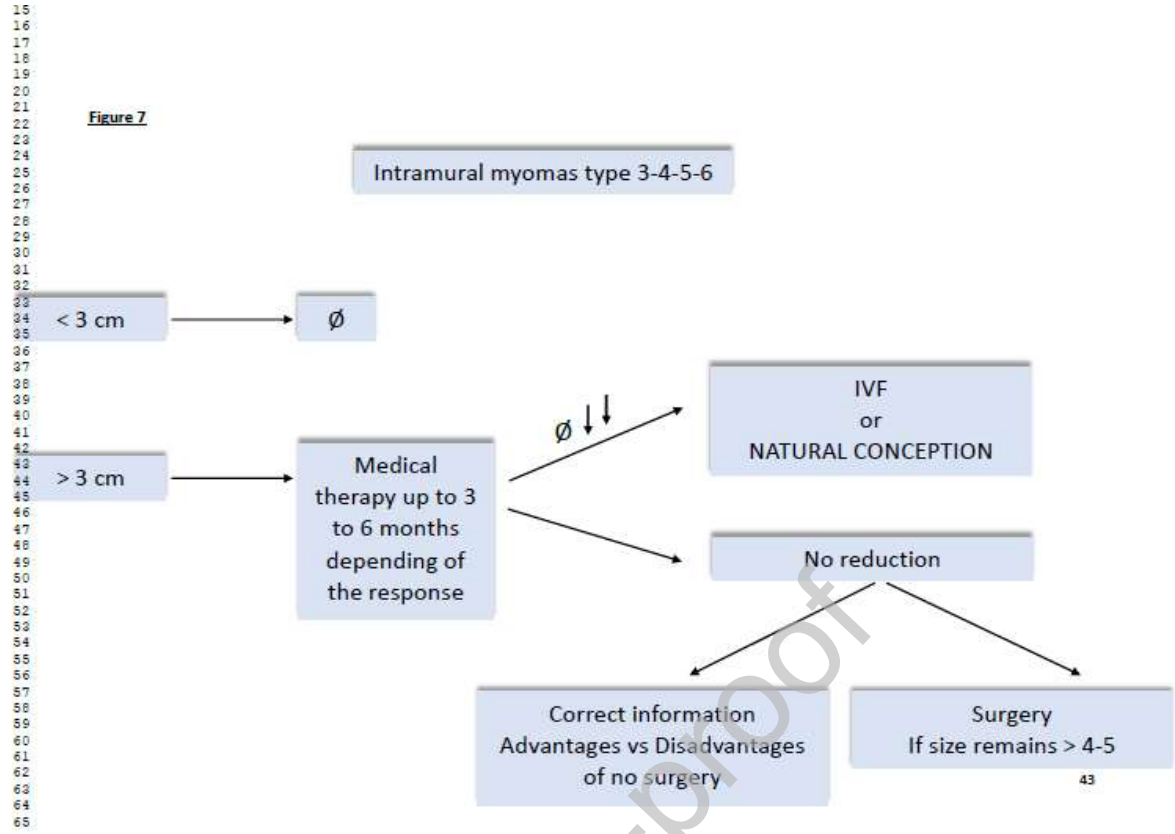
*: method of conception unknown
ART: Assisted Reproductive Technology

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Figure 6



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Legend to figures

Figure 1A

Leiomyoma subclassification according to FIGO classification of uterine fibroids according to Munro et al (2011). Fibroid types range 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; 8 = Other (e.g. cervical, parasitic). Where two numbers are given (e.g. 2-5), the first number refers to the relationship with the endometrium, while 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.

Figure 1B

Relationship between myomas and myometrium adapted by Donnez and Dolmans from the Munro classification.

Figure 2

Mechanisms linking uterine fibroids and infertility.

Figure 3

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

Figure 4

Advantages and disadvantages of different medical treatment options.

Figure 5

Pregnancies (reported from three case series and 6 case reports) after UPA treatment.

Figure 6

Percentage of women who met the primary endpoint (proportion of women with menstrual blood loss <80ml and ≥50% from baseline in 3 clinical trials with oral GnRH antagonist (elagolix + ABT; relugolix + ABT, linzagolix + ABT).

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Figure 7

Proposed algorithm for intramural myoma-related infertility. If the myoma measures more than 3 cm, a medical therapy could be proposed as the primary approach in order to 1) decrease myoma size, and 2) induce migration of the myoma as far as possible from the endometrium.



Prof Jacques DONNEZ has focused his research activities on three main topics in the field of reproductive medicine: tubal infertility, endometriosis and finally, ovarian cryopreservation and transplantation. He published over 700 original articles in peer-review journals.
Since 2012, he is Professor Emeritus at the Catholic University of Louvain and Director of Society of research and infertility in Brussels
He was the president of the
- European Society of Gynecological Endoscopy
- World Endometriosis Society
- International Society of Gynecological Endoscopy
- International Society for Fertility Preservation

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.
Prospective randomized studies investigating medical (including new molecules like GnRH antagonist) vs surgical therapy should address the question of the best approach in case of intramural-related infertility.

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