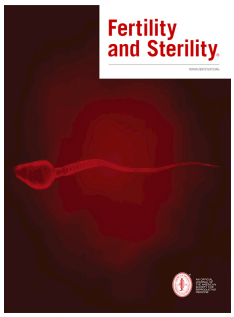
# Journal Pre-proof




Uterine fibroid-related infertility: mechanisms and management

Jacques DONNEZ, Hugh S. TAYLOR, Louis MARCELLIN, Marie-Madeleine DOLMANS

PII: S0015-0282(24)00170-5

DOI: https://doi.org/10.1016/j.fertnstert.2024.02.049

Reference: FNS 34691

To appear in: *Fertility and Sterility*

Received Date: 29 February 2024

Accepted Date: 29 February 2024

Please cite this article as: DONNEZ J, TAYLOR HS, MARCELLIN L, DOLMANS M-M, Uterine fibroid-related infertility: mechanisms and management, *Fertility and Sterility* (2024), doi: https://doi.org/10.1016/j.fertnstert.2024.02.049.

# Uterine fibroid-related infertility: mechanisms and management

**Jacques DONNEZ[1-2], Hugh S. TAYLOR[3], Louis MARCELLIN[4], Marie-Madeleine DOLMANS [5 6]**

[1] Prof Emeritus, Université Catholique de Louvain, Belgium

[2] Society for Research into Infertility (SRI), 143 Avenue Grandchamp, 1150 Brussels, Belgium

[3]Department of Obstetrics, Gynecology and Reproductive Sciences, Yale School of Medicine, New Haven, CT, USA

[4]Université Paris Cité, Département de Gynécologie Obstétrique II et Médecine de la Reproduction, Assistance Publique-Hôpitaux de Paris (AP-HP), Centre Hospitalier Universitaire (CHU) Cochin, Hôpital Universitaire Paris Centre (HUPC), Paris, France

[5]Pôle de Recherche en Gynécologie, Institut de Recherche Expérimentale et Clinique, Université Catholique de Louvain (UCL), Brussels, Belgium

[6]Gynecology Department, Cliniques Universitaires Saint-Luc, Brussels, Belgium

Corresponding author: Jacques DONNEZ (jacques.donnez@gmail.com)

**Abstract:**

Fibroids are a common pathology and increasingly observed in women seeking medical treatment for infertility. The longer reproductive horizon thanks to improvements in medical care and current trend for women to postpone childbearing are making fibroid-related infertility increasingly common.

The aim of this review is to critically analyze: 1) The link between uterine fibroids and infertility 2) Mechanisms by which uterine fibroids may impair fertility 3) Management of myoma-related infertility.

The association of fibroids with infertility is a source of controversy. As the focus of this review is infertility, it is crucial to analyze the mechanisms by which fertility may be impaired by the presence of fibroids.

Current management strategies involve mainly surgical interventions like myomectomy by hysteroscopy, laparotomy or laparoscopy, and non-surgical approaches such as uterine artery embolization (UAE) and focused ultrasound (FUS) performed under radiological or echographic guidance. The risks and benefits of each option should be discussed with patients and many factors need to be taken into account, including the skill of the surgeons, as well as the availability of different resources in different centers.

Concerning the efficacy of oral GnRH antagonists (elagolix , relugolix and linzagolix), they were shown to have a rapid impact on heavy menstrual bleeding in more than 70% of women. When used without add-back therapy, these drugs cause a significant reduction in fibroid volume, namely around 50% from baseline to week 24. 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.

**Keywords:** uterine fibroids infertility, surgery medical therapy

Fibroids are increasingly being encountered in women seeking a medical consultation for infertility issues. This is due primarily to the current trend for women to postpone childbearing, resulting in a longer reproductive lifetime (1-5). As fibroids occur more frequently in later reproductive years, these demographic trends will result in a higher incidence of fibroids in women attempting to conceive. An appropriate strategy involving a deeper mechanistic understanding of myoma-related infertility should be strongly advocated, as has been done in case of myoma-related heavy menstrual bleeding (3-6). In a study by Flynn et al (7), health care costs for management of uterine fibroids were estimated to be over $2 billion per year, with much of that cost associated with surgical intervention. There is no doubt that fibroids have a significant economic impact (8,9), so it is essential to develop and evaluate alternatives to surgical procedures, especially when fertility preservation is the goal (10,11).

The aim of this review is to critically analyze:

1) The link between uterine fibroids and infertility

2) Mechanisms by which uterine fibroids may impair fertility

3) Management of myoma-related infertility

**Is there a link between fibroids and infertility?**

The association of fibroids with infertility is a source of controversy, with wide swings in expert opinion over time. In 2007, Somigliana et al (12) considered this link proven by studies demonstrating that in IVF cycles, live birth rates are reduced in patients with fibroids, but are not affected in women who have undergone myomectomy. Surgical treatment appears to increase pregnancy rates, as 50% of women undergoing myomectomy for infertility subsequently conceive. However, the authors acknowledge that drawing clear guidelines is difficult due to the lack of large randomized trials aiming to determine which patients may benefit from surgery (12). In their meta-analysis and systematic review in 2021, some 15 years

later, Somigliana et al (13) concluded that the effect of uterine fibroids on natural fertility is unclear, has been insufficiently investigated, and that well designed studies are urgently needed in order to properly counsel infertile women with fibroids. The same conclusion was reached by Don et al (14, 15).

The debate is still unresolved and it is not easy to reach a consensus (16). Does this mean that nothing has been done in 15 years? No, it certainly does not! As stated by Dolmans et al in a recent 'Fertile Battle' article (17), not all myomas are the same and the first thing to do is consult the FIGO classification while over a decade old, two robust meta-analyses (18,19) show that submucosal myomas are indeed detrimental to fertility. Pregnancy rates, ongoing pregnancy rates and live birth rates in women with uterine fibroids are significantly lower than in women without fibroids. Since publication of the latter review by Pritts et al (19), the need to treat submucosal fibroids has been widely accepted, although it never confirmed by randomized studies .

With development of hysteroscopic techniques, the primary approach for type 0 and 1 myomas is resection (20,21). In case of type 2 myomas, distortion of the uterine cavity occurs, so resection is indicated and may be facilitated by preoperative medical treatment (gonadotropin-releasing hormone [GnRH] agonist/antagonist) (2,6).

Questions about the impact of intramural myomas (types 3, 4, 5, 6, 2–5) on infertility remain a matter of concern and continue to present a clinical conundrum (2,6). Despite a plethora of studies in women with uterine fibroids over the past two decades, the effect of non-cavity-distorting uterine fibroids is still contentious. In 2010, Sunkara et al (22) systematically reviewed 19 observational studies and 6,087 IVF cycles, showing a significant decrease in clinical pregnancy rates in women with non-cavity-distorting fibroids compared to women without fibroids. However, several limitations were identified, including heterogeneity

between studies, diverse diagnostic methods to assess the normality of the uterine cavity, and variations in size and number of fibroids across studies. In a single-center study, Yan et al. (23) found that intramural myomas over 2.85 cm in size significantly impaired live birth rates in patients undergoing IVF/ICSI. In 2016, Marqueta et al (24) investigated a large series that found non-cavity-distorting intramural myomas to have a detrimental effect on clinical pregnancy and birth rates in patients undergoing IVF. In an observational study, Christopoulos et al (25) demonstrated that the deleterious impact on live birth rates was significant in women with two or more fibroids, and those with fibroids 3 cm across or more. Later, after evaluating 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), Yan et al (26) concluded that type 3 myomas have a negative effect on clinical pregnancy and live birth rates, particularly if single-fibroid diameter or total reported fibroid diameter is greater than 2 cm. This study did have some limitations, such as the inevitable selection bias in data analysis in a retrospective study. In an editorial on Yan et al's study (26), Taylor (27) stated that large intramural myomas near the endometrial cavity warrant removal before IVF, as they affect endometrial receptivity and impair blastocyst implantation.

A retrospective cohort study reporting a total of 929 fresh single-blastocyst transfer cycles revealed that even relatively small (>1.5 cm) intramural myomas may affect clinical pregnancy and live birth rates (28). In an updated systematic review totaling 28 studies and 9,189 patients, Wang et al (29) reported that non-cavity-distorting intramural myomas significantly reduce implantation, clinical pregnancy and live birth rates. Recently, Rikhraj et al (30) reviewed 15 quantitative studies (five were prospective) out of 139 records. The 5 prospective studies involving 5,029 subjects evidenced that patients with non-cavity-

distorting intramural fibroids undergoing IVF had 44% lower odds of a live birth than women without fibroids. Subgroup analysis of prospective studies demonstrated significantly reduced odds of a live birth in women with only intramural myomas, adding further weight to the conclusion.

A very recent systematic review by Favilli et al (31) concluded that FIGO type 3 myomas decreased live birth rates, clinical pregnancy rates and implantation rates very significantly compared to women without myomas, with greater fibroid number and size correlating with worsening of IVF outcomes. In another meta-analysis, Erden et al (32) found the presence of FIGO type 3 fibroids measuring 2-6 cm to be associated with significantly lower live birth rates, but not myomas of ≤2cm in size. All these meta-analyses are based on low-certainty evidence from observational studies, but all concluded (as for 20 years now) that high-level randomized controlled trials (RCTs) are needed before myomectomy can be routinely offered.

In conclusion, a type 3 (close to the endometrial lining) myoma of 2 cm or more may 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 for intervention, depending on the study or meta-analysis in question. A number of investigators have recommended surgical removal of such intramural fibroids (17,27). The crucial question (2,6) we should be asking is this: if the negative effect is related to the size of the myoma and its proximity to the uterine cavity, why not try a medical approach to reduce its size and push it back deeper into the myometrium, what we have termed the 'migration effect'?(6).

**Which mechanisms could impair fertility?**

As the focus of this review is infertility, it is crucial to analyze the mechanisms by which fertility may be impaired by the presence of fibroids (Fig1).

*Uterine cavity distortion*

This first mechanism is self-evident and has been widely documented (2,18,19). Changes in endometrial receptivity caused by myoma protrusions are responsible for impaired blastocyst implantation. Since 2009, uterine distortion has been associated with decreased IVF outcomes (2,6,19, 22-29). It is therefore important to clearly differentiate submucosal myomas and intramural myomas distorting the uterine cavity from those that are purely intramural.

*Impaired endometrial and myometrial blood supply*

The presence of intramural fibroids close to the uterine cavity interferes with endometrial blood flow. Several studies using contrast magnetic resonance imaging have reported reduced blood flow in fibroids and their surrounding myometrium (33). In a study using transvaginal ultrasound (34), uterine fibroids displayed diminished pulsatility in their uterine arteries, which suggests greater blood flow to myomas, facilitating their growth. In a prospective study, Niewenhuis et al (35) demonstrated that the increase in volume was greater in highly vascularized myomas. Their study underscores the hypothesis that highly vascularized fibroids, tend to grow faster than poorly vascularized fibroids indicating that blood supply modifications could interfere with blastocyst implantation, as suggested by Kim et al (36).

*Increased uterine contractility*

Contractile activity plays an important role in the human reproduction process. Indeed, it decreases in response to progesterone, probably to favor embryo implantation (37). According to Miura et al (38) and Orisaka et al (39), fibroids alter uterine peristalsis and hence blastocyst implantation. One study using magnetic resonance imaging (39) found that intramural myomas caused abnormal uterine peristalsis, resulting in lower embryo implantation rates.

*Hormonal, paracrine and molecular changes*

Complex series of interactions allow successful implantation of the embryo during the window of implantation, including apposition, adhesion and invasion (40). Fibroids can alter expression of important genes for implantation, such as glycodelin and bone morphogenetic protein (BMP) receptor type 2 (41). In a study by Ben-Nagi et al (42), decreased levels of glycodelin and interleukin-10 were found in uterine flushing fluid from women with fibroids. Diminished release of cytokines critical to implantation, such as leukemia inhibitory factor and cell adhesion molecules, are attributed to the presence of myomas (40). Production of interleukin-11 declines during the window of implantation if myomas are present. Decreased expression of the cell adhesion molecule E-cadherin has also been described in the endometrium of women with intramural myomas (40). As stressed by Vannuccini et al (43) and Ikhena and Bulun (40), uterine fibroids significantly impact the functioning and gene expression of endometrium.

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

In their first study, Rackow and Taylor (44) 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 myomas. 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 signaling pathway proceeds from intramural myomas to the endometrium, but has a less pronounced effect on endometrial receptivity (than seen with submucosal myomas) thanks to the greater distance and hence lower concentration in the endometrium.

The same group later showed that transforming growth factor beta-3 (TGF-β3) is elevated in leiomyoma-conditioned media, leading to repression of BMP receptor types 1B and 2 in

endometrium and eventually a lack of response to BMP (45). As 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 endometrial receptivity. According to Taylor (27), myoma size and distance from the uterine cavity are key aspects. Larger fibroids produce more TGF-β3 and those closest to the uterine cavity allow more TGF-β3, to reach endometrial cells. The amount of TGF-β3 reaching the uterine cavity varies by the square of the distance from the cavity ($1/x^2$, where x is the distance between the endometrium and the fibroid) (27).

*Thicker capsule*

A capsule that surrounds the fibroid can be considered a separate entity (46,47). This pseudocapsule consists of compressed myometrium and contains nerves. An increase in pseudocapsule thickness may increase the number of neuroendocrine fibers, influencing muscle contractility and uterine peristalsis (46,47).

**How to manage myoma-related infertility**

The real question is this: is there a place for surgical management? As stressed by Stewart (5) and Somigliana et al (13), there are areas of uncertainty concerning the management of myomas and only a few randomized trials have compared different therapies. Indeed, the risks and benefits of each option should be discussed with patients and many factors need to be taken into account, including the skill of the surgeons, as well as the availability of different resources in different centers. Current management strategies involve mainly surgical interventions like myomectomy by hysteroscopy, laparotomy or laparoscopy, and non-surgical approaches such as uterine artery embolization (UAE) and focused ultrasound (FUS) performed under radiological or echographic guidance (2).

In a recent 'Fertile Battle' article (17), Stewart claimed that surgeons have a familiarity bias towards surgical therapies because their understanding of intramural fibroids and fertility is limited and they cannot be fully objective. She proposes being more open to a range of alternatives, including UAE and magnetic resonance-guided FUS rather than automatically opting for surgery. Although non-surgical fibroid intervention does sound appealing, there is strong evidence that only surgical treatment of submucosal fibroids improves pregnancy and live birth rates in case of uterine fibroid-related infertility. (19)

**Hysteroscopic myomectomy**

Over recent decades, advances in instruments and techniques have promoted hysteroscopic myomectomy to the rank of a standard surgical procedure for submucosal myomas. Repeated and progressive passage of a cutting loop allows the surgeon to cut the myoma into small fragments until the myometrial fasciculate fibers are visualized (20,21)**.** If the myoma is large (>3 cm in diameter and especially in case of type 2 myomas), there is an increased risk of operative complications (perforation, bleeding and fluid intravasation). However, preoperative treatment with GnRH agonist or antagonist (48,49) may facilitate surgery by reducing myoma size prior to surgery. Even for type 3 myomas, some skilled surgeons like Isaacson (17) are in favor of hysteroscopic management, arguing that it provides better protection of the myometrium.

In terms of reproductive outcomes, studies report post-hysteroscopic pregnancy rates ranging from 16.7% to 76.9%, averaging at 45% (50), but most studies are retrospective (51-52). Nevertheless, the authors of several reviews (51-53) acknowledge that the benefits of hysteroscopic removal of submucosal myomas to improve the chances of pregnancy cannot be excluded.

**Laparoscopic myomectomy**

Laparoscopic myomectomy is perceived by many gynecologists to be more difficult, but the advantages of a laparoscopic approach are obvious and real. However, there have been reports of uterine rupture after laparoscopic myomectomy, emphasizing the key importance of adequate closure of the myometrial defect (2). There is no evidence of any difference in recurrence risk between laparoscopy and open myomectomy (54).

Reviewing a number of prospective and retrospective studies evaluating fertility after laparoscopic myomectomy, Donnez and Dolmans (2, 50) reported a pooled pregnancy rate of 49%, which is similar to the post-myomectomy pregnancy rate of 57% reported by Somigliana et al (12). Nevertheless, the lack of randomized trials represents a serious drawback, as stressed in recent papers (13-15).

Robotic laparoscopic myomectomy has been assessed in a few retrospective series, but no prospective studies have yet been published and there is considerable scepticism around the real advantages of this technique over the conventional laparoscopic approach. A review by Arian et al (55) did show advantages compared with laparotomy, but very recent COMPARE-UF concluded that the probability of live births does not differ appreciably after myomectomy (56).

***The specific question of the route for removal of type 3 myomas,***

Given that current data strongly support removing type 3 myomas to enhance embryo implantation, the only question is how: by laparotomy, laparoscopy or hysteroscopy? It has been widely documented that laparoscopic surgery is associated with faster recovery and lower risk of blood loss and infection than laparotomy and does not put patients at higher risk of uterine dehiscence during pregnancy (2-5). It has also been demonstrated that removal of the entire myoma as opposed to part of it yields the best long-term outcomes (2).

For Isaacson and Zhang (17), the myomectomy technique of choice for type 3 myomas measuring 2-4 cm is hysteroscopy and not laparoscopy for the following reasons. Fibroids are monoclonal and derived from a single cell, displacing but not invading normal myometrium. When a type 2 or 3 myoma is removed hysteroscopically using a bipolar loop electrode, surgery is confined to the pseudocapsule and no normal myometrium is damaged (17).

In the early 2000's, Dubuisson (57) was among the first to offer a laparoscopic approach to treat intramural myomas of less than 9 cm in size. However, the decision for a laparoscopic approach must be balanced between the uterine pathology and the experience of the surgeon. According to Gordts (17), laparotomy is sometimes preferable if multiple incisions are required for removal of myomas to allow adequate approximation of the deep layers, concluding that "*there is much more to gain for patients and surgeons by a well performed myomectomy through laparotomy than by a difficult laparoscopy and inappropriate suturing".*

**Uterine artery embolization**

Although UAE is a widely implemented uterine-sparing intervention with sound evidence from RCTs demonstrating relief from heavy menstrual bleeding following treatment (58), there are very limited data on reproductive outcomes after this procedure in women with uterine fibroid-related infertility. Indeed, a majority of reproductive surgeons will not promote this approach because of the risks of impairing endometrial function and diminishing the ovarian reserve (2). Systematic reviews have shown better reproductive outcomes after myomectomy than UAE (58-60). While underpowered, the recent FEMME RCT showed similar pregnancy and live birth rates in a group of women whose mean age was in their early 40s (61,62).

Although UAE is highly effective for treating symptoms (reduction in bleeding and fibroid size), the risk of reoperation is a reality. Indeed, surgical intervention is required in 15–20% after

306 successful embolization and up to 50% in case of incomplete infarction (58). The impact of
307 UAE on the ovarian reserve is another concern (58), but a systematic review of 15 RCTs and
308 prospective cohort studies demonstrated that loss of ovarian function occurred primarily in
309 women aged over 45 years (63). More subtle damage to the ovarian reserve in patients
310 already challenged by infertility is nevertheless a major concern.
311
312 **Magnetic resonance- and ultrasound-guided FUS**
313 The principal limitations to use of magnetic resonance-guided FUS are that only a fraction of
314 patients with fibroids meet the inclusion criteria and future fertility may be compromised.
315 Numerous recent studies promote use of ultrasound-guided FUS, but no data are available on
316 obstetric outcomes.
317
318 **Medical treatment (table 1)**
319 *Oral contraceptives and progestogens*
320 Although oral contraceptives may reduce abnormal uterine bleeding, they do not decrease
321 fibroid volume, so have limited benefits for women with fibroid-related infertility (64-66).
322 Moreover, since progesterone is implicated in the pathogenesis of uterine fibroids (65-68),
323 using progestogens to manage fibroids is like constantly adding fuel to the fire, leading to
324 fibroid growth and rendering this treatment ineffective.
325
326 *GnRH agonists*
327 Preoperative administration of GnRH agonists (leuprolide, goserelin, triptorelin) boosts
328 hemoglobin levels and significantly reduces fibroid volume, but long-term treatment is
329 contraindicated because of bone mineral density (BMD) loss (48,65,69,70). For more than 3

330 decades now (48), GnRH agonists have been widely used to reduce the size of type 1 and 2
331 myomas prior to hysteroscopic resection. Indeed, significant volume reduction and decreased
332 endometrial thickness and vascularization facilitate surgical fibroid removal
333 by hysteroscopy and lower the risk of fluid overload. However, no studies reporting obstetric
334 outcomes after GnRH agonist vs a placebo in infertile women with uterine fibroids are
335 available.

336 **Selective progesterone receptor modulators (SPRMs)**

337 The advantage of SPRMs over GnRH agonists is their absence of adverse hypoestrogenic
338 effects and the fact that they do not cause BMD loss (71-73). The benefits of ulipristal acetate
339 (UPA) in particular have been clearly demonstrated in various studies (72-73), showing a
340 reduction in fibroid volume of more than 50% after two courses of 3 months, restoration of
341 hemoglobin levels, and significant and swift control of bleeding.

342 Only a few papers have been published documenting pregnancy and live birth rates after
343 medical treatment for intramural myoma-related infertility and just 3 studies have recorded
344 pregnancies after medical treatment with SPRMs (UPA). Since the first publication by our
345 group in 2014 of a case series of 15 patients (74), a second series of 40 women and third series
346 of 53 women who conceived after UPA treatment were reported in multicenter studies in
347 Canada and Portugal respectively (75,76). Maintaining fertility is an important goal in the
348 management of symptomatic uterine fibroids. For women wishing to preserve their fertility,
349 SPRMs have provided an alternative, and UPA especially was recommended in algorithms for
350 patients with fibroids who would like to remain fertile (77).

351 Unfortunately, the Pharmacovigilance Risk Assessment Committee of the European
352 Medicines Agency (EMA) concluded that there is a risk of rare but serious liver injury with UPA,
353 and its use was strictly limited. It was subsequently denied approval in the United States. This

is regrettable for gynecologists, but even more so for patients. We found an effective drug, but it came with rare yet serious side effects, and safety must remain the primary objective.

**GnRH antagonists**

Like SPRMs, GnRH antagonists have a rapid onset of action and can treat fibroids promptly. In three phase 3 RCTs, 3 oral GnRH antagonists (elagolix [78], relugolix [79] and linzagolix [49]) were shown to have a rapid impact on heavy menstrual bleeding in more than 70% of women. The reduction in menstrual bleeding was maintained when add-back therapy (1 mg estradiol and 0.5 mg norethindrone acetate) was given along with the antagonists, while BMD loss was minimal. When used without add-back therapy, these drugs cause a significant reduction in fibroid volume, namely around 50% from baseline to week 24 (49). When used with add-back therapy, fibroid volume reduction evaluated by magnetic resonance imaging was found to be only 10-15 % (49,79). Dose is also important; elagolix is not effective at reducing fibroid size at the dose recommended for endometriosis (80), but works at higher doses. 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. Optimal preoperative therapy will require adequate dosing without add-back therapy, a regimen that is not currently available in most of the world.

**Why do we need new algorithms?**

Fibroids are highly prevalent and constitute a heavy health burden. Indeed, about 30% of women with leiomyomas will request treatment due to morbidities like heavy menstrual bleeding, abdominal pain, pressure symptoms and/or infertility. There is no doubt that fibroids have a significant economic impact and markedly affect quality of life. Current therapies are mainly surgical and expensive. Available evidence suggests that levels of satisfaction with current treatment options are poor. It is essential to personalize the medico-

surgical strategy and propose a tailored approach based on the main symptoms (HMB, infertility), which is what patients really want. GnRH antagonist without add-back therapy for a short period of 3 months may help restore distorted uterine cavities that cause infertility and thereby reduce the need for uterine surgery. In previous papers (3,6), we proposed new algorithms that consider both myoma type (according to the FIGO classification) and the issue of infertility (Fig 2). They do, of course, require confirmation by clinical trials.

**Conclusion**

The mystery surrounding intramural myomas remains unresolved and only new prospective RCTs investigating medical versus surgical therapy will address the question of the best approach to take in case of intramural myoma-related infertility. Fibroids are a common pathology and increasingly observed in women seeking medical treatment for infertility. The longer reproductive horizon thanks to improvements in medical care and current trend for women to postpone childbearing are making fibroid-related infertility increasingly common. New algorithms are urgently needed for intra-mural myoma-related infertility, as is scrutiny of the role of medical therapy as a primary approach. Depending on the response to medical therapy, remaining myoma size and patient age, women can be guided towards natural conception (or IVF if required) or surgical therapy.

**Acknowledgments**

The authors thank Mira Hryniuk, BA, for reviewing the English language of this article and Deborah Godefroidt for her administrative help.

**Funding**

This study was supported by grants from the Fonds National de la Recherche Scientifique de Belgique (FNRS-PDR Convention grant number T.0077.14 awarded to M.M.D), the Fonds Spéciaux de Recherche.

**Legends to figures**

Fig 1: Mechanisms by which fertility may be impaired by the presence of fibroids

Fig 2: Proposed algorithm in cases of uterine fibroid-related infertility (adapted from Dolmans et al , J of clin Med,(3)

**FIGURES**

**Figure 1**

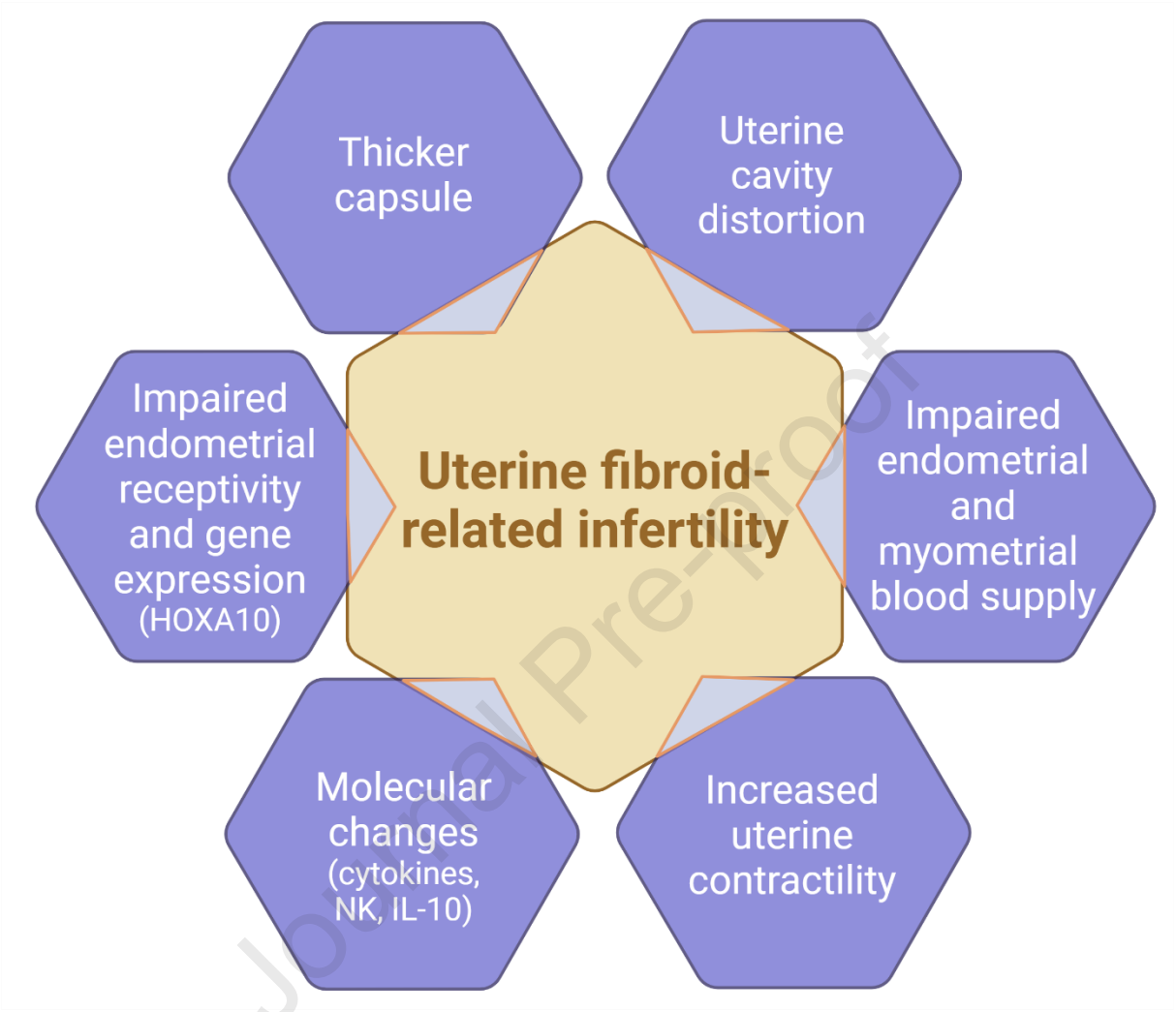
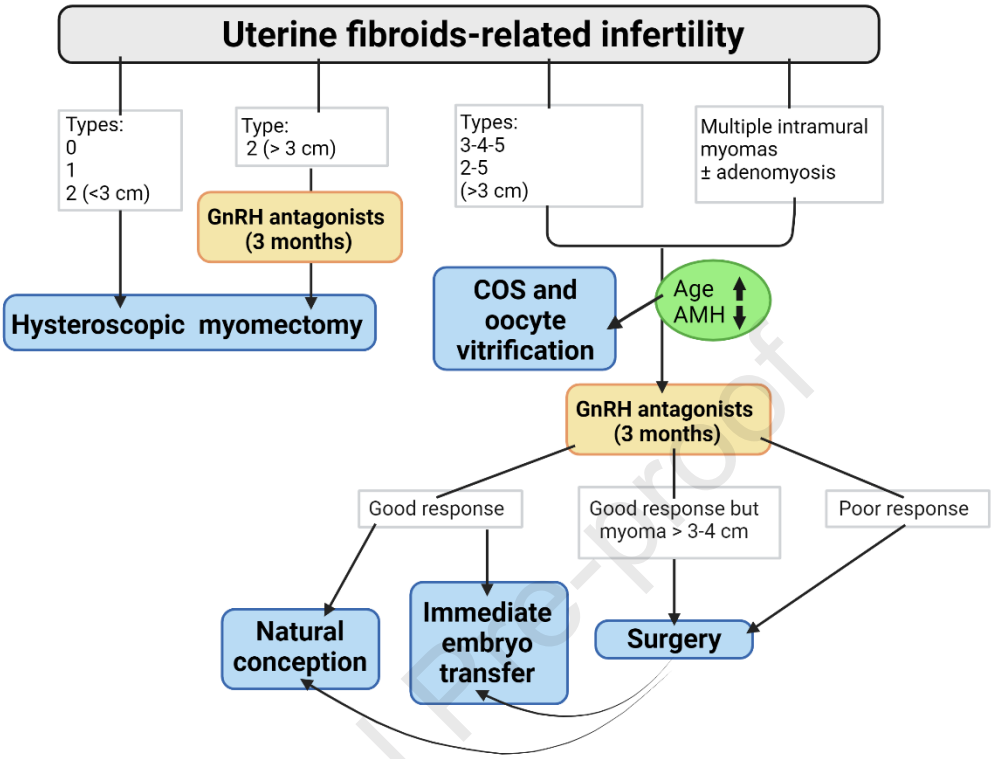


**Figure 2**



480 **Table 1**

481

482 **Table 1.** Advantages and disadvantages of various medical therapies for intramural myomas.

| Treatment type (medical therapy) | Advantages | Disadvantages |
|---|---|---|
| Estro-progestogens | May reduce AUB in case of moderate disease. | No fibroid volume reduction. |
| Tranexamic acid/mefenamic acid | Reduces HMB in women without uterine fibroids; improves health-related quality of life. | Impact on fibroids unknown. |
| LNG-IUS | Treatment of choice for HMB in the absence of fibroids; provides contraception. | Cannot be used if the uterine cavity is distorted by fibroids; high expulsion rate with submucosal fibroids. |
| SPRMs | Curtail HMB and shrink fibroids; not associated with menopausal side effects or bone demineralization (restricted indications by the EMA. | Associated with endometrial alterations known as progesterone receptor modulator-associated endometrial changes(PAEC); risk of liver injury (DILI) |
| Mifepristone | Able to reduce bleeding and pressure symptoms for up to 6 months. | Uncertain impact on fibroid volume. |
| GnRH agonists | May be given for 3–6 months before surgery to decrease uterine and fibroid size; serve to correct iron deficiency anemia. | Treatment beyond 6 months can reduce BMD; vasomotor and other menopausal symptoms are common. |
| GnRH antagonists | Fast effect on HMB; reduce fibroid volume and correct anemia; dose-dependent efficacy and side effects; low doses cause limited loss of BMD. | High doses erode BMD, so require add-back therapy for long-term treatment; other menopausal symptoms commonly observed at high doses. |

483

484 AUB: abnormal uterine bleeding

485 HMB: heavy menstrual bleeding

486

487

488

489

490

491

492

493

494

495

## REFERENCES


1. Critchley HO, Babayev E, Bulun SE, Clark S, Garcia-Grau I, Gregersen PK, et al. Menstruation: Science and society. Am. J. Obstet. Gynecol. 2020;223(5):624–664.

2. Donnez J, Dolmans MM. Uterine fibroid management: From the present to the future. Hum. Reprod. Update 2016;22(6):665–686.

3. Dolmans MM, Cacciottola L, Donnez J. Conservative Management of Uterine Fibroid-Related Heavy Menstrual Bleeding and Infertility: Time for a Deeper Mechanistic Understanding and an Individualized Approach. J Clin Med. 2021;10(19):4389.

4. Lumsden MA, Hamoodi I, Gupta J, Hickey M. Fibroids: Diagnosis and management. BMJ 2015;51:h4887.

5. Stewart EA. Clinical practice. Uterine fibroids. N. Engl. J. Med. 2015;372(17):1646–1655.

6. Donnez J, Dolmans MM. Hormone therapy for intramural myoma-related infertility from ulipristal acetate to GnRH antagonist: A review. Reprod. Biomed. Online 2020;41(3):431–442.

7. Flynn M, Jamison M, Datta S, Myers E. Health care resource use for uterine fibroid tumors in the United States. Am J Obstet Gynecol. 2006;195(4):955-64.

8. Cardozo ER, Clark AD, Banks NK, Henne MB, Stegmann BJ, Segars JH. The estimated annual cost of uterine leiomyomata in the United States. Am J Obstet Gynecol. 2012;206(3):211.e1-9

9. Soliman AM, Yang H, Du EX, Kelkar SS, Winkel C. The direct and indirect costs of uterine fibroid tumors: a systematic review of the literature between 2000 and 2013. Am J Obstet Gynecol. 2015;213(2):141-60.

10. Donnez J, Courtoy GE, Donnez O, Dolmans MM. Ulipristal acetate for the management of large uterine fibroids associated with heavy bleeding: A review. Reprod. Biomed. Online 2018;37(2):216–223.

11. Donnez J, Donnez O, Dolmans MM. With the advent of selective progesterone receptor modulators, what is the place of myoma surgery in current practice? Fertil Steril. 2014;102(3):640-8.

12. Somigliana E, Vercellini P, Daguati R, Pasin R, De Giorgi O, Crosignani PG. Fibroids and female reproduction: a critical analysis of the evidence. Hum Reprod Update. 2007;13(5):465-76.

13. Somigliana E, Reschini M, Bonanni V, Busnelli A, Li Piani L, Vercellini P. Fibroids and natural fertility: a systematic review and meta-analysis. Reprod Biomed Online. 2021;43(1):100-110.

14. Don EE, Mijatovic V, Huirne JAF. Infertility in patients with uterine fibroids: a debate about the hypothetical mechanisms. Hum Reprod. 2023;38(11):2045-2054.

15. Don EE, Mijatovic V, van Eekelen R, Huirne JAF. The effect of myomectomy on reproductive outcomes in patients with uterine fibroids: A retrospective cohort study. Reprod Biomed Online. 2022;45(5):970-978.

16. Donnez J. Intramural myomas related infertility: Should the myomas be removed??? Not easy to reach a consensus. Fertil. Steril.2021;116(4):943-944.

17. Dolmans MM, Isaacson K, Zhang M, Gordts S, Munro M, Steward E, et al. Intramural myomas more than 3–4 centimeters should be surgically removed before in vitro fertilization. Fertil. Steril. 2021;116(4):945-958.

18. Pritts EA. Fibroids and infertility: a systematic review of the evidence. Obstet Gynecol Surv. 2001;56(8):483-91.

19. Pritts EA, Parker WH, Olive DL. Fibroids and infertility: an updated systematic review of the evidence. Fertil Steril. 2009;91(4):1215-23.

20. Bettocchi S, Ceci O, Nappi L, Di Venere R, Masciopinto V, Pansini V, Pinto L, Santoro A, Cormio G. Operative office hysteroscopy without anesthesia: analysis of 4863 cases performed with mechanical instruments. J Am Assoc Gynecol Laparosc. 2004;11(1):59-61.

21. Di Spiezio Sardo A, Calagna G, Di Carlo C, Guida M, Perino A, Nappi C. Cold loops applied to bipolar resectoscope: A safe "one-step" myomectomy for treatment of submucosal myomas with intramural development. J Obstet Gynaecol Res. 2015;41(12):1935-41.

22. Sunkara SK, Khairy M, El-Toukhy T, Khalaf Y, Coomarasamy A. The effect of intramural fibroids without uterine cavity involvement on the outcome of IVF treatment: a systematic review and meta-analysis. Hum Reprod. 2010;25(2):418-29.

23. Yan L, Ding L, Li C, Wang Y, Tang R, Chen ZJ. Effect of fibroids not distorting the endometrial cavity on the outcome of in vitro fertilization treatment: a retrospective cohort study. Fertil Steril. 2014;101(3):716-21.

24. Marqueta B, Barri PN, Coroleu B, Barri Soldevila PN, Rodriguez I. Effect of Non-Cavity Distorting Intramural Fibroids on Assisted Reproduction Outcomes: A Cohort Study. Journal of Endometriosis and Pelvic Pain Disorders. 2016;8(3):111-115.

25. Christopoulos G, Vlismas A, Salim R, Islam R, Trew G, Lavery S. Fibroids that do not distort the uterine cavity and IVF success rates: an observational study using extensive matching criteria. BJOG. 2017;124(4):615-621.

26. Yan L, Yu Q, Zhang YN, Guo Z, Li Z, Niu J, Ma J. Effect of type 3 intramural fibroids on in vitro fertilization-intracytoplasmic sperm injection outcomes: a retrospective cohort study. Fertil Steril. 2018;109(5):817-822.e2.

27. Taylor HS. Fibroids: When should they be removed to improve in vitro fertilization success? Fertil. Steril. 2018;109(5):784–785.

28. Behbehani S, Polesello S, Hasson J, Silver J, Son WY, Dahan M. The Effect of Intramural Myomas Without an Intracavity Component on In Vitro Fertilization Outcomes in Single Fresh Blastocyst Transfer Cycles. J Minim Invasive Gynecol. 2018;25(7):1241-1248.

29. Wang X, Chen L, Wang H, Li Q, Liu X, Qi H. The Impact of Noncavity-Distorting Intramural Fibroids on the Efficacy of In Vitro Fertilization-Embryo Transfer: An Updated Meta-Analysis. Biomed Res Int. 2018;2018:8924703.

30. Rikhraj K, Tan J, Taskin O, Albert AY, Yong P, Bedaiwy MA. The Impact of Noncavity-Distorting Intramural Fibroids on Live Birth Rate in In Vitro Fertilization Cycles: A Systematic Review and Meta-Analysis. J Womens Health (Larchmt). 2020;29(2):210-219.

31. Favilli A, Etrusco A, Chiantera V, Laganà AS, Cicinelli E, Gerli S, Vitagliano A. Impact of FIGO type 3 uterine fibroids on in vitro fertilization outcomes: A systematic review and meta-analysis. Int J Gynaecol Obstet. 2023;163(2):528-539.

32. Erden M, Uyanik E, Polat M, Ozbek IY, Yarali H, Mumusoglu S. The effect of ≤6 cm sized noncavity-distorting intramural fibroids on in vitro fertilization outcomes: a systematic review and meta-analysis. Fertil Steril. 2023;119(6):996-1007.

33. Forssman L. Blood flow in myomatous uteri as measured by intra-arterial 133Xenon. Acta Obstet Gynecol Scand. 1976;55(1):21-4.

34. Sladkevicius P, Valentin L, Marsál K. Transvaginal Doppler examination of uteri with myomas. J Clin Ultrasound. 1996;24(3):135-40.

35. Nieuwenhuis LL, Keizer AL, Stoelinga B, Twisk J, Hehenkamp W, Brölmann H, Huirne J. Fibroid vascularisation assessed with three-dimensional power Doppler ultrasound is a predictor for uterine fibroid growth: a prospective cohort study. BJOG. 2018;125(5):577-584.

36. Kim A, Jung H, Choi WJ, Hong SN, Kim HY. Detection of endometrial and subendometrial vasculature on the day of embryo transfer and prediction of pregnancy during fresh in vitro fertilization cycles. Taiwan J Obstet Gynecol. 2014 ;53(3):360-5.

37. Fanchin R, Righini C, Schönauer LM, Olivennes F, Cunha Filho JS, Frydman R. Vaginal versus oral E(2) administration: effects on endometrial thickness, uterine perfusion, and contractility. Fertil Steril. 2001;76(5):994-8.

38. Miura S, Khan KN, Kitajima M, Hiraki K, Moriyama S, Masuzaki H, Samejima T, Fujishita A, Ishimaru T. Differential infiltration of macrophages and prostaglandin production by different uterine leiomyomas. Hum Reprod. 2006;21(10):2545-54.

39. Orisaka M, Kurokawa T, Shukunami K, Orisaka S, Fukuda MT, Shinagawa A, Fukuda S, Ihara N, Yamada H, Itoh H, Kotsuji F. A comparison of uterine peristalsis in women with normal uteri and uterine leiomyoma by cine magnetic resonance imaging. Eur J Obstet Gynecol Reprod Biol. 2007;135(1):111-5.

599 40. Ikhena DE, Bulun SE. Literature Review on the Role of Uterine Fibroids in Endometrial
600 Function. Reprod Sci. 2018;25(5):635-643.

601 41. Horcajadas JA, Goyri E, Higón MA, Martínez-Conejero JA, Gambadauro P, García G,
602 Meseguer M, Simón C, Pellicer A. Endometrial receptivity and implantation are not affected
603 by the presence of uterine intramural leiomyomas: a clinical and functional genomics analysis.
604 J Clin Endocrinol Metab. 2008;93(9):3490-8.

605 42. Ben-Nagi J, Miell J, Mavrelos D, Naftalin J, Lee C, Jurkovic D. Endometrial implantation
606 factors in women with submucous uterine fibroids. Reprod Biomed Online. 2010;21(5):610-5.

607 43. Vannuccini S, Clifton VL, Fraser IS, Taylor HS, Critchley H, Giudice LC, Petraglia F. Infertility
608 and reproductive disorders: impact of hormonal and inflammatory mechanisms on pregnancy
609 outcome. Hum Reprod Update. 2016;22(1):104-15.

610 44. Rackow BW, Taylor HS. Submucosal uterine leiomyomas have a global effect on molecular
611 determinants of endometrial receptivity. Fertil Steril. 2010;93(6):2027-34.

612 45. Doherty LF, Taylor HS. Leiomyoma-derived transforming growth factor-β impairs bone
613 morphogenetic protein-2-mediated endometrial receptivity. Fertil Steril. 2015;103(3):845-52.

614 46. Tinelli A, Kosmas I, Mynbaev OA, Favilli A, Gimbrizis G, Sparic R, Pellegrino M, Malvasi A.
615 Submucous Fibroids, Fertility, and Possible Correlation to Pseudocapsule Thickness in
616 Reproductive Surgery. Biomed Res Int. 2018;2018:2804830.

617 47. Tinelli A, Favilli A, Lasmar RB, Mazzon I, Gerli S, Xue X, Malvasi A. The importance of
618 pseudocapsule preservation during hysteroscopic myomectomy. Eur J Obstet Gynecol Reprod
619 Biol. 2019;243:179-184.

620 48. Donnez J, Schrurs B, Gillerot S, Sandow J, Clerckx F. Treatment of uterine fibroids with
621 implants of gonadotropin-releasing hormone agonist: assessment by hysterography. Fertil
622 Steril. 1989;51(6):947-50.

623 49. Donnez J, Taylor HS, Stewart EA, Bradley L, Marsh E, Archer D, Al-Hendy A, Petraglia F,
624 Watts N, Gotteland JP, Bestel E, Terrill P, Loumaye E, Humberstone A, Garner E. Linzagolix with
625 and without hormonal add-back therapy for the treatment of symptomatic uterine fibroids:
626 two randomised, placebo-controlled, phase 3 trials. Lancet. 2022;400(10356):896-907.

627 50. Donnez J, Donnez O, Dolmans MM. With the advent of selective progesterone receptor
628 modulators, what is the place of myoma surgery in current practice? Fertil Steril.
629 2014;102(3):640-8.

630 51. Bosteels J, van Wessel S, Weyers S, Broekmans FJ, D'Hooghe TM, Bongers MY, Mol BWJ.
631 Hysteroscopy for treating subfertility associated with suspected major uterine cavity
632 abnormalities. Cochrane Database Syst Rev. 2018;12(12):CD009461.

633 52. Metwally M, Cheong YC, Horne AW. Surgical treatment of fibroids for subfertility.
634 Cochrane Database Syst Rev. 2012;11:CD003857.

635 53. Bosteels J, Weyers S, Puttemans P, Panayotidis C, Van Herendael B, Gomel V, Mol BW,
636 Mathieu C, D'Hooghe T. The effectiveness of hysteroscopy in improving pregnancy rates in
637 subfertile women without other gynaecological symptoms: a systematic review. Hum Reprod
638 Update. 2010;16(1):1-11.

639 54. Kotani Y, Tobiume T, Fujishima R, Shigeta M, Takaya H, Nakai H, Suzuki A, Tsuji I, Mandai
640 M, Matsumura N. Recurrence of uterine myoma after myomectomy: Open myomectomy
641 versus laparoscopic myomectomy. J Obstet Gynaecol Res. 2018;44(2):298-302.

642 55. Arian SE, Munoz JL, Kim S, Falcone T. Robot-assisted laparoscopic myomectomy: current
643 status. Robot Surg. 2017;4:7-18.

644 56. Wise LA, Thomas L, Anderson S, Baird DD, Anchan RM, Terry KL, Marsh EE, Wegienka G,
645 Nicholson WK, Wallace K, Bigelow R, Spies J, Maxwell GL, Jacoby V, Myers ER, Stewart EA.
646 Route of myomectomy and fertility: a prospective cohort study. Fertil Steril.
647 2022;117(5):1083-1093.

648 57. Dubuisson JB. Management of leiomyomata. Hum Reprod Update. 2000;6(6):587.

649 58. Gupta JK, Sinha A, Lumsden MA, Hickey M. Uterine artery embolization for symptomatic
650 uterine fibroids. Cochrane Database Syst Rev. 2014;(12):CD005073.

651 59. S. Sud, A. Maheshwari, S. Bhattacharya. Obstetric outcomes after treatment of fibroids by
652 uterine artery embolization: a systematic review. Expert Rev Obstet Gynecol. 2009:4(4):429-
653 441.

654 60.Zanolli NC, Bishop KC, Kuller JA, Price TM, Harris BS. Fibroids and Fertility: A Comparison of
655 Myomectomy and Uterine Artery Embolization on Fertility and Reproductive Outcomes. Obstet
656 Gynecol Surv. 2022;77(8):485-494.

657 61. Manyonda I, Belli AM, Lumsden MA, Moss J, McKinnon W, Middleton LJ, Cheed V, Wu O,
658 Sirkeci F, Daniels JP, McPherson K; FEMME Collaborative Group. Uterine-Artery Embolization
659 or Myomectomy for Uterine Fibroids. N Engl J Med. 2020;383(5):440-451.

660 62. Stewart EA. Comparing Apples to Apples for Fibroids. N Engl J Med. 2020;383(5):489-490.

661 63. Kaump GR, Spies JB. The impact of uterine artery embolization on ovarian function. J Vasc
662 Interv Radiol. 2013;24(4):459-67.

663 64. De La Cruz MS, Buchanan EM. Uterine Fibroids: Diagnosis and Treatment. Am Fam
664 Physician. 2017;95(2):100-107.

665 65. Donnez J. Uterine Fibroids and Progestogen Treatment: Lack of Evidence of Its Efficacy: A
666 Review. J Clin Med. 2020;9(12):3948.

667 66. Reis FM, Bloise E, Ortiga-Carvalho TM. Hormones and pathogenesis of uterine fibroids.
668 Best Pract. Res. Clin. Obstet. Gynaecol. 2016;34:13–24.

669 67. Kim JJ, Sefton EC. The role of progesterone signaling in the pathogenesis of uterine
670 leiomyoma. Mol. Cell. Endocrinol. 2012;358(2):223–231.

671 68. Bulun SE. Uterine fibroids. N Engl J Med. 2013;369(14):1344-55.

672 69. Lethaby A, Vollenhoven B, Sowter M. Efficacy of pre-operative gonadotrophin hormone
673 releasing analogues for women with uterine fibroids undergoing hysterectomy or
674 myomectomy: a systematic review. BJOG. 2002;109(10):1097-108.

675 70. Tan YH, Lethaby A. Pre-operative endometrial thinning agents before endometrial
676 destruction for heavy menstrual bleeding. Cochrane Database Syst Rev. 2013;(11):CD010241.

677 71. Donnez J, Tatarchuk TF, Bouchard P, Puscasiu L, Zakharenko NF, Ivanova T, et al; PEARL I
678 Study Group. Ulipristal acetate versus placebo for fibroid treatment before surgery. N Engl J
679 Med. 2012;366(5):409-20.

680 72. Donnez J, Tomaszewski J, Vázquez F, Bouchard P, Lemieszczuk B, Baró F, et al; PEARL II
681 Study Group. Ulipristal acetate versus leuprolide acetate for uterine fibroids. N Engl J Med.
682 2012;366(5):421-32.

683 73. Donnez J, Donnez O, Matule D, Ahrendt HJ, Hudecek R, Zatik J, et al. Long-term medical
684 management of uterine fibroids with ulipristal acetate. Fertil Steril. 2016;105(1):165-173.e4.

685 74. Luyckx M, Squifflet JL, Jadoul P, Votino R, Dolmans MM, Donnez J. First series of 18
686 pregnancies after ulipristal acetate treatment for uterine fibroids. Fertil Steril.
687 2014;102(5):1404-9.

688 75. De Gasperis-Brigante C, Singh SS, Vilos G, Kives S, Murji A. Pregnancy Outcomes Following
689 Ulipristal Acetate for Uterine Fibroids: A Systematic Review. J Obstet Gynaecol Can.
690 2018;40(8):1066-1076.e2.

691 76. Costa AR, Carvalho AP, Martins DR, et al. Series of 55 pregnancies following ulipristal
692 acetate treatment of symptomatic uterine fibroids. Journal of Endometriosis and Pelvic Pain
693 Disorders. 2020;12(3-4):170-175.77.

694 78. Schlaff WD, Ackerman RT, Al-Hendy A, Archer DF, Barnhart KT, Bradley LD, et al. Elagolix
695 for Heavy Menstrual Bleeding in Women with Uterine Fibroids. N Engl J Med. 2020;382(4):328-
696 340.

697 79. Al-Hendy A., Lukes AS, Poindexter AN 3rd, Venturella R, Villarroel C, Critchley HOD, et al.
698 Treatment of uterine fibroid symptoms with relugolix combination therapy. N. Engl. J. Med.
699 2021;384(7):630–642.

700 80. Taylor HS, Giudice LC, Lessey BA, Abrao MS, Kotarski J, Archer DF, Diamond MP, Surrey E,

701 Johnson NP, Watts NB, Gallagher JC, Simon JA, Carr BR, Dmowski WP, Leyland N, Rowan JP,

Duan WR, Ng J, Schwefel B, Thomas JW, Jain RI, Chwalisz K. Treatment of Endometriosis-Associated Pain with Elagolix, an Oral GnRH Antagonist. N Engl J Med. 2017;377(1):28-40.