Chapter

Fibroids and Infertility

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Abstract

Uterine fibroids (also known as leiomyomas or myomas) are the most common pelvic tumors, affecting more than 70% of women over 70 years of age and although most are asymptomatic, some women may experience symptoms, depending on their location and size, which can alter your quality of life, such as abnormal uterine bleeding, anemia, pelvic pain and pressure, dyspareunia, increased urinary frequency and constipation. Its relationship with infertility has been controversial and, although insignificant for subserous fibroids, it appears that submucosal and intramural fibroids that distort the endometrial cavity can affect embryo implantation and are associated with an increased risk of early pregnancy loss. Its treatment will depend on the patient's symptoms, size, location, whether it is one or multiple, and whether or not she suffers from infertility. It is clear that submucosal fibroids have a negative impact on fertility and with respect to intramural fibroids it is known that fibroids larger than 4 cm alter the probability of pregnancy, however there are studies that show that even smaller or multiple fibroids could affect pregnancy rates. There are multiple options for the treatment of fibroids; however, patients who are candidates for expectant, medical or surgical management should be individualized, and especially if they are going to be taken to surgery, an excellent mapping of fibroids prior to surgical intervention is recommended. Minimally invasive surgery continues to be the approach of choice, it should be left for the open approach in cases in which Laparoscopy is contraindicated or the patient with multiple myomatosis.

Keywords: Fibroids, leiomyoma, myomas, infertility, myomectomy, pregnancy

1. Introduction

Uterine fibroids are the most common benign tumors in women of reproductive age. They are monoclonal tumors of the myometrium or uterine smooth muscle and are composed of large amounts of extracellular matrix, containing fibronectin, collagen and proteoglycans [1]. Myomas are estrogen dependent tumors, which growth is clearly associated with exposure to circulating estrogen. They predictably decrease in size during menopause and under other hypoestrogenic conditions [2].

Fibroid's prevalence is variable and age dependent. They can be detected in up to 70% of white and 80% of black women by 50 years of age [2, 3]. Compared with Caucasian women with symptomatic myomas, women of African descent frequently present to their provider at a younger age and with a significantly worse myoma burden (larger size and number) and have a threefold higher risk of hysterectomy [4].

Fibroids can have a negative impact on the reproductive system and can be single, but are more often multiple, causing significant morbidity and deterioration of quality of life [5].

2. Risk factors

2.1 Race

Race constitutes an important risk factor for fibroid development, studies conducted using ultrasound have confirmed that the myoma prevalence is lower in Europe than in the United States, probably due to racial differences (**Figure 1**). In addition to a having greater lifetime incidence of fibroids, black women have fibroids diagnosed at earlier ages, are more likely to be symptomatic and are likely to have different responses to medical treatment than white women [5, 6].

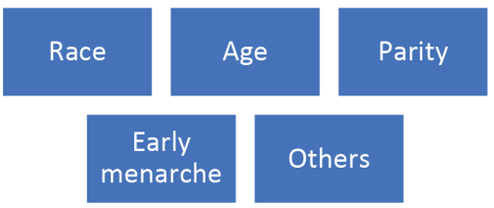

Figure 1.
Risk factors.

2.2 Age

Age is a significant risk factor for fibroid development. The incidence of pathologically diagnosed fibroids increases with age, reaching its maximum peak at age 50, is negligible before puberty, and also decreases with menopause [7].

2.3 Parity

Published evidence suggests that pregnancy is a protective factor against fibroid development, due to events that occur at the end of the pregnancy, at delivery or in the postpartum process [8]. Although a direct protective effect of pregnancy has been demonstrated, little is known of the mechanism. It has been suggested that fibroid tissue might be highly susceptible to ischemia during parturition and remodeling [9].

2.4 Genetic factors

Genetic factors can play an important role in myomas development, the growth of multiple myomas in the same uterus implies that heritage can cause some women to be more predisposed than others [5]. Leiomyomas are monoclonal in origin and 40% of the tumors have karyotypic abnormalities including deletions in chromosome 7, trisomy of chromosome 12 and rearrangements the HMGA1 (6p21) and HGMA2 (12q14) involving genes. Whole exome approaches have identified heterozygous somatic mutations in the mediator complex subunit 12 (MED12) [10]. Alterations of several genes, protooncogenes, signaling pathways and epigenetic mechanisms have been associated with its etiology, some of them are HOXA10, HOXA11, BMP2, among others [7].

Other factors: early menarche, late age for menopause, caffeine and alcohol, family history of uterine fibroids, obesity [1].

3. Clinical features

The majority of uterine myomas are asymptomatic. When symptomatic, uterine fibroids commonly present with abnormal uterine bleeding (heavy or irregular menstrual bleeding) which is the main reason for gynecologic consultations of women aged 40 to 50 years [11]. The mechanism of leiomyoma associated excessive menstrual bleeding is unknown. Increased endometrial surface area, vascular dysregulation, and interference with endometrial hemostasis have been offered as possible explanations [12]. Other less common symptoms include pelvic pressure, bowel dysfunction, urinary frequency and urgency, urinary retention, low back pain, constipation and dyspareunia [10]. This latest situations are generally determined by large fibroids; Urinary symptoms associated with anterior fibroids, constipation with posterior ones [13]. Pain as a symptom is relatively infrequent. It's usually associated with torsion of a pedunculated myoma, cervical dilatation by a submucous myoma protruding through the uterine segment or degeneration associated with pregnancy. This conditions cause acute pain and require immediate attention [2]. With respect to reproductive prognosis, the degree to which fibroids contribute to infertility is controversial, but they seem to be implicated as the sole factor during diagnostic workup in less than 10% of infertile couples [14].

3.1 Classification

There are many fibroid classifications in the literature. Many issues have been considered among these, including the leiomyoma's relationship with the endometrium and the serosa, their location within the uterus (upper segment, lower segment, cervix, anterior, posterior, lateral), the size and the number of lesions [15]. The primary classification system reflects only the presence of one or more leiomyomas; In the secondary system, focus on differentiation of fibroids that involve the endometrial cavity (submucosal or SM) from others is the main point because it's known that submucosal myomas are those that most likely contribute to the genesis of abnormal uterine bleeding [16].

The international Federation of Gynecology and Obstetrics (FIGO) classification system for abnormal uterine bleeding [17] is intended to help better categorize the causes of bleeding and treatment planning [18]. They describe eight types of fibroids as well as a hybrid presentation (a myoma that fulfills criteria for 2 different types among the classification). This classification offers a more representative "map" of fibroid distribution [19] and also includes the categorization of intramural and subserosal leiomyomas [20].

A myoma FIGO type 0 is pedunculated and 100% intracavitary, type 1 is submucosal with less than 50% intramural extension; type 2 is submucosal with 50% or more intramural extension, type 3 is intramural but in contact with the endometrium without disrupting it, type 4 is 100% intramural not in contact with the endometrium, type 5 is subserosal with 50% or more intramural extension, type 6 is subserosal with less than 50% intramural extension, type 7 is subserosal and pedunculated, type 8 are other types of myomas including cervical and parasitic fibroids. Hybrid fibroids are given two numbers, the first number refers to the relationship with the endometrium and the other with the serosa, e.g. 2–5 has submucosal and subserosal component (**Figure 2**) [19].

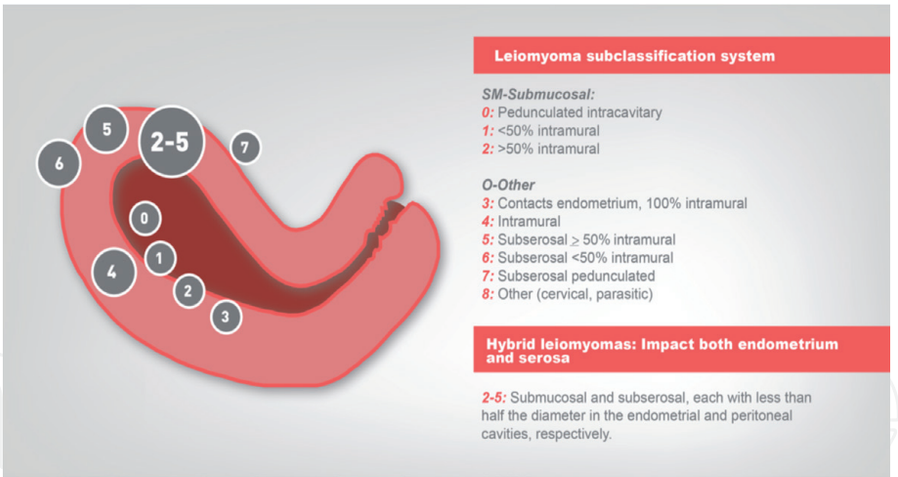

Figure 2.
Leimyoma subclassification system (FIGO). Image taken and edited from ref. [20].

4. Association of uterine fibroids and infertility

Uterine leiomyomas are associated as sole factor for infertility in <10% of infertility cases [14]. Many theories have been proposed to explain how myomas may cause infertility. They can cause clear anatomical disruption of the uterine architecture, also abnormal uterine contractility, hinder sperm transport [21], elongation of the uterine cavity and distortion of the vascularization [22]. In particular, submucosal leiomyomas may impact the endometrial cavity, altering embryo implantation and development [23]. Others have suggested that aberrant endometrial growth factors expression may also play a role [21] One of the sequences of signaling events in implantation has been defined with Hoxa-10, those genes are essential in the mouse for endometrial development and implantation, Matsuzai et al. reported Hoxa-10 mRNA and protein expression levels in endometrial stroma cells were significantly lower in infertile patients with endometriosis and in those with myomas and unexplained infertility compared with that in healthy fertile controls [24]. Hoxa-10 and Hoxa-11 are known factors to be necessary to the endometrial receptivity and are decreased in women with submucosal myomas [25].

Bone morphogenetic protein type II (BMP2) mediates HOXA10 expression and if there exists an increase endometrial resistance to BMP2, it may add up to a decreased expression of HOXA 10 in the endometrium of this patients [26].

In fertile women, glycodelin and glutathione peroxidasa3 genes expression rises during the luteal phase, more often during de implantation window and the expression of these genes decreased in women with myomas [27].

Many types of cytokines such as leukemia inhibitory factor (LIF), interleukin 1 and 11 are necessary for embryo implantation in mice. In humans LIF is expressed in the endometrial epithelium, and its maximum expression is observed in the middle late secretory phase of the menstrual cycle [28]. Pier et al. demonstrated decreased LIF in patients with non-cavity distorting leiomyomas greater than 3 cm compared to patients with a normal uterus [29].

The literature regarding uterine leiomyomas and their impact on reproductive outcome can be confusing. High heterogeneity of patient characteristics and clinical presentation of fibroids, as well as randomization difficulties related to remarkable emotional and economic considerations of fertility related treatments, have made evidence-based conclusions difficult to achieve. Current consensus is

that submucosal leiomyomas and intramural/submucosal (intramural fibroids encroaching the endometrial cavity) affect implantation and diminish pregnancy rates. Besides, it's clear that subserosal fibroids have no effect on fertility prognosis. Controversy lies on the effect of exclusively intramural fibroids that do not distort the endometrial cavity, on reproductive outcome. Evidence suggests that in this issue, size is the determining factor, with intramural fibroids larger than 4 to 5 cm being associated with impaired embryo implantation and diminished pregnancy rates. There is fair evidence that myomectomy for cavity-distorting myomas (submucosal or intramural with submucosal component) improves pregnancy rates and reduces the risk of early pregnancy loss [22, 30–32].

In a systematic review published on 2009 in Fertility and Sterility by Pritts et al. with 23 studies included in the data analysis, when evaluating the outcomes of women with any location of fibroid, the relative risks of clinical pregnancy, implantation, and ongoing pregnancy/live birth were all significantly lower in women with myomas than in control subjects; When the effect of the fibroid was evaluated by location, the women with SM fibroids, compared with infertile women without fibroids, demonstrated a significantly lower clinical pregnancy rate (CPR), implantation rate, and ongoing pregnancy rate (OPR)/Live birth rate (LBR) and a significantly higher spontaneous abortion rate. No difference was seen in rate of preterm delivery. According to Pritts systematic review removal of submucosal fibroids appears likely to improve fertility. Although intramural fibroids appeared to be associated with decreased fertility and increased pregnancy loss risk, it's surgical treatment failed to show an increase in pregnancy and live birth rates [33].

Casini et al. reported a tendency to have a higher pregnancy rate among the women who underwent a surgical treatment for fibroid removal compared with those who were not treated, although the results were not statistically significant in the IM and submucosal-intramural fibroids [34].

Bulleti et al. reported laparoscopic myomectomy improved pregnancy rates over non-surgical management of fibroids [35].

The diversity of myomas and patient characteristics also hinders the ability to determine whether size and location impact reproductive outcomes. Some studies have demonstrated conflicting reproductive outcomes related to fibroid size, for example some data support the notion that myomas larger than 3 cm negatively impact reproduction, nevertheless other studies suggest that leiomyomas less than 5 cm do not [23].

4.1 Fibroids and likelihood of achieving spontaneous pregnancy

There are few data assessing the impact of myomas on the likelihood of spontaneous pregnancy. Johnson et al. published in 2012 one retrospective study where a cohort of 3000 women in early pregnancy were enrolled, patients retrospectively report time to conception, and leiomyomas characteristics were determined by the first trimester ultrasound. Of the 3000 patients, 89% did not have leiomyomas and 11% had one or more, the most common fibroids were intramural and subserous. They found no significant association between myomas and time to pregnancy, in this study of women who were able to conceive without medical intervention; The presence of leiomyomata did not alter the length of time to conception [36]. Although this is the only evidence available of likelihood of achieving a spontaneous pregnancy on untreated patients with fibroids, it has an important bias since patients with previous fertility treatments were excluded.

4.2 Fibroids and likelihood of achieving pregnancy in IVF treatments

4.2.1 Intramural fibroids

Sunkara et al. Published in 2010 a systematic review and meta-analysis with 19 articles included and 6087 cycles, they found that the presence of non-cavity distorting intramural fibroids on average reduces the LBR 21% and the CPR by 15% per IVF cycle compared with no fibroids. The relatively lower chance of achieving a live birth compared with clinical pregnancy probably reflects the adverse influence of intramural fibroids on the course of pregnancy. With respect to implantation rate (IR) it showed a statistically non-significant 13% reduction in IR in women with non-cavity distorting intramural fibroids. They also did not find statistically difference in miscarriage rate [37].

Xiaodan Wang et al. published in 2018 an updated meta-analysis about the impact of non-cavity distorting intramural fibroids on the efficacy of In Vitro fertilization, they included a total of 28 studies involving 9189 IVF cycles, and showed a significant reduction in LBR, CPR and implantation rate, and also have a significant increase in miscarriage rate compared with control group [38].

Eric et al. published a retrospective case controlled analysis in 2001 and they found that LBR was not affected by the presence of intramural leiomyomas in IVF patients with normal endometrial cavity visualized in the hysteroscopic [21].

Somigliana et al. concluded in their critical analysis of the evidence that evidence support the vision that myomas may alter fertility, from the detrimental effect on implantation in IVF, delivery rate is also reduced in patients with fibroids, and second even if a randomized studies are lacking, surgical treatment appears to increase the pregnancy rate [13].

Hart et al. did the large prospective controlled study of the effect of the fibroids on the outcome of assisted reproduction. Their results showed that small IM fibroids reduces the chance of an embryo implanting by half., the presence or absence of an intramural fibroid was a significant factor influencing a woman's chance of having an ongoing pregnancy after ART [39].

Raikhraj et al. found in the systematic review that patients with noncavity-distorting intramural fibroids undergoing IVF had 44% lower odds of live birth and 32% lower odds of clinical pregnancy than patients without fibroids. A trend was also found toward lower implantation rates and higher miscarriage rates.

4.2.2 Type 3 fibroid

FIGO type 3 fibroids are intramural extra cavitary lesions that abut the endometrium without distorting the uterine cavity [20]. Lei Yan et al. in a retrospective study with 228 women with type 3 fibroid undergoing IVF-ICSI cycles, reported that those myomas affect implantation, clinical pregnancy and live birth rates but do not significantly increase the clinical miscarriage rate, the deleterious impact of this type of fibroid was remarkable in women with single fibroid diameter or total reported fibroid diameter >2 mm [40].

Xi Bai et al. published in 2020 a retrospective case–control study about the impact of FIGO type 3 fibroids on the outcome of IVF cycles. They reported that type 3 fibroids ≥30 mm might exert deleterious impact on implantation, clinical pregnancy and live birth rates of IVF cycles [41].

Available evidence suggests that FIGO type 3 fibroids are a transition between submucosal and intramural fibroids, that are intramural location wise but behave as submucosal in terms of reproductive outcome, even when they are of limited size.

Localization	Number of studies included	Breslow-Day test (P-value)	Common OR(95% CI)
Clinical			
Pregnancy rate			
Submucosal	2	0.92	0.3 (0.1–0.7)
Intramural	7	0.38	0.8 (0.6–0.9)
Subserosal	3	0.92	1.2 (0.8–1.7)
Intramural and/or subserosal	11	0.30	1.0 (0.8–1.2)
All types	16	0.24	0.8 (0.7–1.0)
Delivery rate			
Submucosal	2	0.79	0.3 (0.1–0.8)
Intramural	7	0.09	0.7 (0.5–0.8)
Subserosal	3	0.94	1.0 (0.7–1.5)
Intramural and/or subserosal	11	0.68	0.9 (0.7–1.1)
All types	16	0.43	0.8 (0.6–0.9)

Table taken and edited from ref. [13].

Table 1.
Meta-analyses on the influence of fibroids on IVF outcome according to the localization of the lesion.

4.2.3 Intracavitary fibroids

Submucosal leiomyomas and intramural fibroids distorting the uterine cavity negatively impact assisted reproduction outcomes. Many retrospective and small prospective studies indicated that these tumors disrupt implantation by 33–70% and decrease clinical pregnancy by up to 67% [31].

Somigliana et al. reported in their meta-analysis that myomas negatively affect pregnancy rate, specially submucosal lesions appear to strongly interfere with the chance of pregnancy OR(95% IC) of conception and delivery is 0.3 (0.1–0.7) and 0.3 (0.1–0.8) respectively (**Table 1**) [13].

Klatsky et al. in their systematic review stated that patients with submucosal fibroids had the strongest association with lower ongoing pregnancy rates primarily through decreased implantation [42].

Pritts et al. investigated the effect of fibroids on fertility and published a systematic literature review and meta-analysis reporting that women with submucosal component led to decreased clinical pregnancy and implantation rates compared with infertile control subjects [33].

Many studies are focused on association between fibroids and IVF outcomes. The most extensively investigated factor is myoma location. There is a consensus that submucous uterine fibroids or intramural fibroids with submucosal component that distorts the uterine cavity are associated with lower clinical pregnancy and delivery rates and higher spontaneous miscarriage rate after IVF/ICSI treatment [26].

5. Treatment

The ideal treatment should satisfy three goals: relief of symptoms, sustained reduction of fibroid size, and maintenance or improvement of fertility [43]. Having into account the heterogeneity of the fibroid presenting patient population, the confounding evidence about fibroid effect on reproductive outcome and its relationship

with assisted reproductive techniques for infertility treatment, the therapeutic decisions should be based on personalized and patient specific considerations.

5.1 Hormonal therapy

5.1.1 Ulipristal acetate

Ulipristal acetate (UPA) is the first selective progesterone receptor modulator (SPRM) to be approved for the treatment of uterine fibroids. It was initially allowed for preoperative treatment of moderate to severe uterine fibroid symptoms in women of reproductive age. Afterwards, the indication was extended in United States to include the intermittent treatment of moderate to severe symptoms [44]. UPA has shown to be effective in controlling uterine bleeding related to myomas, to reduce the size and to have a good safety profile [45]. The PEARL studies have shown that ulipristal acetate offers a good alternative treatment option for long term management of uterine fibroids associated with heavy uterine bleeding, it has been shown to be effective in reducing pain and fibroid volume [46].

Mathieu et al. reported a retrospective analysis of a series of 52 patients, 21 of them wished to conceived upon treatment with UPA completion with variable periods of time (from 3 to 12 months). Of these 21 patients, 19 (90.5%) underwent myomectomy at the end of therapy, according to the protocol; 2 patients did not require surgery because an almost complete disappearance of their fibroids. Fifteen women (71%) became pregnant, resulting in 18 pregnancies, 12 resulted in the delivery of 13 healthy babies, and 6 ended in early miscarriage. Of those 18 pregnancies, 12 were spontaneous and 6 by IVF [47].

Despite the good results that UPA has in the treatment of fibroids, it has been linked to some cases of liver damage, on 2018 European Medicine Agency (EMA) recommended that several measures should be put in place to minimize the risk of rare but serious liver injury with UPA and that UPA should only be used for treatment in patients who are not candidates for surgical fibroid resection.

Detailed review of the latest phase III trials showed isolated transient increases in several liver function tests before, during and/or after treatment in a very small number of patients, some individuals exposed to a therapeutic dose of UPA may go on develop idiosyncratic drug-induced liver injury (DILI), and there are no biomarkers to identify the individuals susceptible, nevertheless UPA is not recommended in patients with moderate or severe hepatic impairment [48].

In conclusion for patients with moderate to severe symptoms due to uterine fibroids who are to undergo surgery, treatment with UPA allows to have rapid relief from heavy bleeding with improvement in quality of life. The reduction of fibroid size and uterine volume may allow for an easier or less invasive surgery, and in some cases to avoid it [49].

5.1.2 GnRH agonists

Preoperative administration of aGnRH boosts hemoglobin levels and significantly reduces fibroid volume, but long term treatment is contraindicated because bone mineral density [50]. A rationale for the use of preoperative medical therapy before surgery for fibroids is to make surgery easier [51].

5.2 Surgical treatment

Women with infertility or pregnancy loss and myomas present a challenge because, in absence of symptoms, treatment recommendations are less clear given the quality of evidence regarding the impact of myomectomy on infertility outcomes [23].

Minimally invasive techniques allow careful dissection of tissues, causing minimal damage, while still removing the entirety of fibroid tumor [52].

5.2.1 Hysteroscopic myomectomy

This has been the standard minimally invasive surgical procedure for submucous myomas. Small fibroids less than 2 cm are routinely removed in outpatient setting, depending on personal experience and available equipment, the gynecologist has a choice of several alternative procedures [1]. Casini et al. reported in a prospective controlled study that women who underwent surgery of submucous fibroids had statistically significant higher pregnancy rates than women who were not treated surgically [34].

In a Cochrane review updated on 2018 they reported that in women with otherwise unexplained subfertility and submucous fibroids, it remains uncertain whether hysteroscopic myomectomy improves the clinical pregnancy rate compared to expectant management [53].

The ASRM reported in their guide published in 2017 there is fair evidence that hysteroscopic myomectomy for submucosal fibroids improves clinical pregnancy rate, and that there is insufficient evidence to conclude that hysteroscopic myomectomy reduces the likelihood of early pregnancy loss in women with infertility and submucous fibroid [23].

5.2.2 Surgical techniques

Hysteroscopic myomectomy is usually performed with a progressive slicing of the intracavitary portion of the submucosal fibroid, a subsequent cold loop pushing of the intramural part and finally a slicing resection of it [54]. The two steps resectoscopic surgery is the most widely performed surgical technique for submucosal fibroids with a difficult approach due to the deep or size of intramyometrial location, it consists of a partial myomectomy to resect the intracavitary portion of the myoma, followed by a second surgery to remove the remaining portion.

Hysteroscopic resection is the most popular technique to remove intrauterine abnormalities [55]. This technique can be performed only with a nonconducting electrolyte-free fluid to irrigate and distend the uterine cavity [56]. Another technique used for the intracavitary fibroids are the hysteroscopic tissue removal systems (HTRs), they opened a new scenario for hysteroscopic myomectomy, data suggest that morcellator is safe and does not increase the complication rate and postoperative adhesions with respect to resectoscopy [54].

Comparison between the resectoscope and the morcellator: The extent of successful myoma resection depends more on the type and size of the fibroid rather than the technique used, data remain unclear on which technique is truly superior [55].

Another technique is the blunt dissection with the tip of the hysteroscope under direct visualization. After complete enucleation cervical dilation must be performed and a new designed bilumen intracervical cannula is inserted at the dilated cervix. This device has two lumens through which the Bettochi's hysteroscope and a laparoscopic tenaculum forceps can be introduced into the uterine cavity simultaneously avoiding the retrograde fluid loss and allowing comfortable maneuvering with both instruments to perform previously enucleated fibroid removal under direct visualization. Absence of thermal damage to neighboring myometrium and the use of isotonic fluid distention media diminishes risks of surgical complications, offers a rapid recovery and efficiently restores the intrauterine microenvironment necessary to allow embryo implantation [57]. Besides, the need for second look hysteroscopy or additional surgical steps is less frequent.

Ideal hysteroscopic myomectomy should be done in one surgical session regardless of the intramural development of the myoma, Mazzon et al. reported 87% of completely resected fibroid in a single step procedure, and 12.3% needed multiple step procedures, the grading and the size of the myoma play a crucial role in completing the procedure in a single step, only the diameter greater than 3 cm in type 2 fibroids is correlated to a higher risk of multiple steps procedure [58].

Although complications from hysteroscopy are rare, they can be potentially life threatening. The most common complication are uterine perforation, fluid intravasation, metabolic complications and adhesion formation [53].

5.2.3 Open vs. laparoscopic myomectomy

Open myomectomy was frequently performed, however laparoscopic myomectomy has recently become more common because it's less invasive. Open surgery is used only in cases in which laparoscopy is contraindicated, including patients with multiple fibroids [59].

In infertile population, cumulative pregnancy rates by the laparoscopic and minilaparotomy approaches are similar, but laparoscopic approach is associated with a quicker recovery, less postoperative pain and less febrile morbidity [12].

Laparoscopic myomectomy is the gold standard treatment for the majority of myomas, with advantages over open myomectomy as reduced postoperative pain, faster return to activity, improved cosmetic results and less adhesion formation [12, 60]. The incidence of uterine rupture after laparoscopic myomectomy is not well defined. Although some report an incidence close to 1%, a clear publication bias probably makes this complication to be overestimated [61].

With respect to recurrence rate, Kotani et al. reported lower recurrence after open surgery, concluding that it was the result of manual fibroid removal with a more exhaustive extraction of smaller myomas as performed during laparoscopy. Fewer residual myomas left after open surgery contribute to a lower postsurgical recurrence rate [59].

Chelsea et al. determined the effects of fibroids and their removal on assisted reproductive treatment outcomes with a retrospective cohort study on infertility patients who underwent myomectomy prior IVF or IUI (intrauterine insemination). They found that among women undergoing IVF, the cumulative incidence of clinical pregnancy was significantly higher in the myomectomy group than in the in situ fibroid group [62].

Bulleti et al. reported in 1999 higher delivery rates (42%) in infertile women underwent myomectomy than women who did not (11%), $p < 0.001$ [35]. Then in 2004, this same group reported the beneficial role of laparoscopic surgery for myomas performed before attempting IVF programs, when intramural myomas were larger than 5 cm. They found statistically significant increase in cumulative pregnancy and delivery rates among patients who underwent surgery than in the group that underwent IVF without surgical removal of their myomas [63].

Oliveira et al. reported in their retrospective study that patients with subserosal or intramural fibroids <4 cm had IVF-ICSI outcomes similar to their controls, but patients with intramural fibroids >4 cm had lower pregnancy rates than patients with intramural fibroids <4 cm; Whether or not women with fibroids >4 cm could benefit from fibroid treatment remains to be determined [64].

In our center InSer Medellín we perform laparoscopic myomectomy on those patients undergoing IVF who have intramural fibroids larger than 4 cm. Smaller intramural myomas might also be considered for surgical treatment in patients with previous failed IVF attempts [65].

Robot assisted laparoscopic myomectomy (RALM).

The use of RALM has several advantages which allows the articulation of instruments by 540° as well as easier intracorporeal suturing. It also may considered in complex surgical cases for which traditional laparoscopy is not indicated [66]. It should be clearly stated that RALM constitutes the minimally invasive alternative to open myomectomy in those cases that cannot be adequately and consistently addressed with conventional minimally invasive surgery [52].

5.3 Other methods

Uterine artery embolization (UAE) technique has been studied as an alternative to myomectomy and hysterectomy mainly in women who no longer desire children, one of the contraindication is infertility or desire for future pregnancy because of lower pregnancy rates and higher miscarriage rates following UAE [12].

Magnetic resonance guided focused ultrasound (MRgFUS) was approved in 2004 by the FDA for leiomyoma treatment. Initial fertility studies were encouraging but randomized controlled trials need to be done [67]. This technique involves the destruction of uterine fibroid tissue through coagulative necrosis by heating tissue to over 70°C, focusing high frequency ultrasound beams on the target tissue [12].

Cryomyolisis is a variation on the laparoscopic technique in which the myoma tissue is coagulated rather than removed. It has the advantage of being minimally invasive and easier to perform than laparoscopic myomectomy and for this reason may present an alternative to myomectomy and hysterectomy for selected women with symptomatic intramural or subserous fibroids who wish to preserve their uterus but do not desire future fertility [68].

6. Conclusion

Myomatosis in infertility remains to be a challenge for clinician. It's management will depend on the symptoms and for infertile women, on fibroid location, number and size. A good ultrasound mapping of the fibroids determining the location, size and especially the degree of the endometrial involvement are essential to determine the treatment modality required. It's clear that intracavitary and intramural fibroids that deform the cavity have negative impact on ART.

The presence of intramural fibroids not distorting the endometrial cavity and their impact on fertility outcome is less clear, however there is also evidence of diminished clinical pregnancy and live birth rates in women who undergo IVF especially with intramural fibroids larger than 4 cm.

Treatment must be individualized according to the symptoms and whether or not there is infertility. Minimally invasive surgery continues to be the therapy of choice.

7. Take home points

When we talk about fibroids and infertility, we must take into account the age of the patient and the fibroid number, size and localization.

Type 0,1,2 fibroids can affect implantation and embryo development and hysteroscopic myomectomy may be considered.

Myomectomy should be considered for infertile patients with intramural fibroids that are larger than 4 cm, multiple or that distort the endometrial cavity. Previous failed IVF cycles should be taken into account when making a decision about surgical treatment.

Cumulative pregnancy rates are similar with laparoscopic and abdominal myomectomy approaches; however laparoscopy is associated with quicker recovery, less pain and less adhesion formation.

Subserosal fibroids do not appear to affect fertility outcome and do not require surgery to improve pregnancy rates.

Clinicians should wait 3 months after surgery prior to IVF, but in older women with low ovarian reserve, embryo cryopreservation and cryopreserved embryo transfer after appropriate uterine scarring should be considered.

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