Published in final edited form as:
Womens Health (Lond Engl). 2009 July ; 5(4): 413–421. doi:10.2217/whe.09.29.

Management of uterine fibroids in the patient pursuing assisted reproductive technologies

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Abstract

Uterine leiomyomas are present in 30-70% of women of reproductive age. In addition to causing menstrual disorders and pain, uterine fibroids negatively affect fertility and pregnancy outcome for patients pursuing assisted reproduction. The two questions that have to be addressed are: which fibroids should be treated, and how they should be treated? Submucosal fibroids are associated with a 70% reduction in delivery rate. Intramural fibroids had a lesser effect and reduced the delivery rate approximately 30%. In contrast, studies on subserosal fibroids did not negatively impact fertility. Furthermore, both submucosal and intramural fibroids were associated with an increased risk of spontaneous miscarriage. Myomectomy is considered the treatment of choice to alleviate these detrimental effects. Further research is needed before alternative treatments can be recommended.

Keywords

Fibroids; infertility; ART; implantation rate; pregnancy rate; myomectomy

Introduction

Uterine leiomyomas (fibroids, myomas) are exceedingly common. The prevalence of fibroids was 77% by pathologic examination of hysterectomy specimens [1]. Fortunately many fibroids are asymptomatic. Depending on the methods used to detect fibroid tumors, the reported prevalence ranged from 30 to 70% [1-5]. The prevalence is increased in women of African American ethnicity. The incidence of fibroids also increases as women age. A large study evaluating 1,364 randomly selected women aged 35-49 years in an urban setting in the United States reported an estimated cumulative incidence of fibroids by age 50 of more than 80% for black women and nearly 70% for white women [3].

Uterine fibroids often cause menstrual disorders, mainly menorrhagia, as well as pelvic pressure and/or pain. Additionally, acute abdominal pain can arise from the degeneration of fibroids [6,7]. Likewise, it is clear that fibroids can adversely affect the reproductive outcome. The adverse effects include both a reduction in fertility and an association with early pregnancy complications [8-21]. As well, studies have shown that fibroids can contribute to adverse obstetric outcomes, such as preterm labor and delivery, placenta

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Financial Disclosure:
ME has nothing to disclose. JN has nothing to disclose. JS has nothing to disclose.

previa, intrauterine growth retardation, increased rate of cesarean section and postpartum hemorrhage [22-27]. Considering the significant health burden fibroids pose to women, development of appropriate evidence-based management strategies for uterine fibroids, addressing both efficacy and safety, is of crucial importance. Here we focus on the specific question of the impact of fibroids on fertility in general, and Assisted Reproductive Technology (ART) outcome in particular.

Regardless of their location, size, or number, uterine fibroids are found in about 5-10% of women with infertility [28-30]. For approximately 1.0-2.4% of women with infertility, fibroids are the only abnormal findings [28-30]. Many hypotheses have been proposed to explain the possible detrimental effect of fibroids on fertility, including impaired and/or obstructed gametes transport [28], dysfunctional uterine contractility [28,33], altered endometrial receptivity [34], abnormal vascularization [28,34], chronic inflammation and abnormal hormonal milieu [28,34]. For women undergoing ART, it is reasonable to conclude that altered endometrial receptivity is involved since other proposed mechanisms are bypassed by ART. The adverse endometrial effects of fibroids have been known for more than 30 years. The glandular atrophy in the endometrium overlying the fibroid is one of the most commonly observed histological alterations associated with fibroids [34,35]. In addition, existing evidence indicates that these effects are directly dependent on the proximity of the fibroid to the endometrium [36]. Furthermore histologic changes have been noted on the endometrial surface opposite the fibroid, which might be attributed to the mechanical pressure exerted by the fibroids [36]. More recently, experiments of Rackow and Taylor have demonstrated that the presence of submucosal and intramural fibroids results in a global reduction in endometrial HOX gene expression, which is not limited to the focal area overlying the fibroid(s) [37]. The authors suggested the observed impaired endometrial receptivity might be mediated by a diffusible signaling molecule(s) that is secreted from the fibroid, but exerts its effects across the entire endometrium.

Classification and Diagnosis

At present there is no universally accepted classification system for fibroids which has limited the research studying their effects on fertility outcome. Fibroids are typically classified based on their location as submucosal (SM), intramural (IM) and subserosal (SS) [8,38,39]. Considering that there is no mucosal epithelium in the uterus, the term “submucosal” is a misnomer; the more appropriate name is “subendometrial” but the term “submucosal” has been widely used in the literature. A broad definition is that submucosal fibroids are those that distort the endometrial cavity; however, submucosal fibroids can be further subdivided into three subtypes: Type 0, pedunculated fibroids without any intramural extension; Type I, sessile with less than 50% intramural extension; and Type II, sessile with more than 50% intramural extension [38]. Intramural fibroids by definition do not distort the endometrial cavity and less than 50% of their largest diameter protrudes into the serosal surface of the uterus. Subserosal fibroids, similar to intramural fibroids, do not distort the endometrial cavity but more than 50% of the fibroid extends beyond the serosal surface of the uterus. Subserosal fibroids can be either sessile or pedunculated [8,38,39].

One major limitation of the current classification is that it does not take into account size of the fibroids. Considering that the thickness of normal myometrium is typically only 15-20 mm [12], based on this classification, any fibroid larger than 4 cm that does not distort the uterine cavity would be classified as subserosal, even though it might be present in the entire thickness of the myometrium. A new classification system which takes into account location and size of uterine fibroids is under development at the National Institutes of Health (NIH) and may help in assessment of the effect of fibroids on fertility.

The two most commonly used modalities to evaluate the effects of fibroids on the uterine cavity are hysterosalpingogram (HSG) and transvaginal ultrasonography (TV US). The sensitivity and specificity of HSG for detection of intrauterine lesions may be as low as 50% and 20% respectively [40-44]. Transvaginal ultrasound was initially considered to have a sensitivity of as high as 90-100% and a specificity of 87-98% [45-48]. However, subsequent studies failed to reproduce the initial reports and showed sensitivities of as low as 69% [49-55] and specificity of 11% for accurate identification of submucosal fibroids [56]. More recently, saline infusion sonography or sonohysterography, particularly the three dimensional (3D) mode, has gained popularity as an accurate imaging modality for the evaluation of uterine cavity [56-58]. Hysteroscopy is considered the gold standard for the evaluation of uterine cavity. Compared to hysteroscopy, 2D and 3D sonohysterography have sensitivities of 98% and 100 % respectively [58]. More importantly 2D and 3D sonohysterography are reported to have specificities of 100%. In contrast, the specificity of transvaginal ultrasound can be as low as 11% when compared to hysteroscopy or 3D sonohysterogram [56-58]. In addition to hysteroscopy, MRI is another reliable diagnostic modality which may accurately identify and localize the fibroids, especially in complicated cases. Because it is expensive, MRI is usually performed as an ancillary imaging method [54,59]. Obviously, the method(s) used by investigators to ascertain the presence of fibroids may affect which subjects are diagnosed to have fibroids and could affect the studies' conclusions.

Fibroids and Infertility

Published reports of the effect of fibroids on reproductive outcome and fertility may be confusing or even contradictory. The contradictory findings can be explained in part by the lack of appropriate control groups, inconsistent evaluation of the uterine cavity, the imaging method used to diagnose fibroids or insufficient number of subjects (small sample size). An additional point is that pregnancy is multifactorial and variables other than fibroids contribute to fertility. Time to pregnancy is affected by these other variables, and the existence of these confounding variables may contribute to different outcomes across studies. ART provides unique advantages in analyzing the effects of fibroids on fertility because the tightly controlled nature of the procedures helps to mitigate the confounding effects of time to pregnancy, and other variables such as sperm concentration and tubal transport. There are numerous studies investigating the ART outcome in women with fibroids [60-74]. From these studies, and recent systematic reviews and meta-analyses, definitive conclusions can be drawn regarding the effects of fibroids on ART success.

Submucosal Fibroids

For fibroids that distort the cavity there is consensus of a negative impact on both the clinical pregnancy rate and delivery rate with odds ratio (OR) at 0.3 (95% CI for clinical pregnancy rate 0.1-0.7; 95% CI for delivery rate 0.1-0.8) [9-14]. In addition, studies have also reported an increased risk of spontaneous miscarriage with submucosal fibroids. One study reported an OR of 3.8 (95% CI: 1.12-13.27) [13] and the other an OR of 1.6 (95% CI: 1.3-2.0) [14]. Furthermore, with the presence of submucosal fibroids, there is good evidence that myomectomy can improve the fertility in general, and IVF outcome in particular (see below).

Intramural Fibroids

The effect of intramural fibroids (those not distorting the uterine cavity) on reproductive outcome was unclear until recently. Farhi *et al* in 1995 [60] did not find a detrimental effect for fibroids that did not affect the uterine cavity. However in 1998, two separate groups, Eldar-Geva *et al* [61] and Stovall *et al* [62] reported reduced pregnancy rate and

implantation rate in women with intramural fibroids, even in the absence of cavity distortion. Subsequent studies were inconsistent, with some supporting a negative effect of intramural fibroids [64,66,73] while the others did not show an effect on the ART outcome [65,67,68,70,71,74]. The disparate findings of these studies have been resolved in recent years.

Benecke *et al* [11] conducted a structured literature review in 2005 that evaluated 150 articles. Six studies met their inclusion criteria. The authors noted a significant negative impact on implantation rate in the intramural fibroid group versus the control, 16.4% vs. 27.7, OR 0.62 (95% CI: 0.48-0.8). They also noted a significantly lower delivery rate in the fibroid group, 31.2 vs. 40.9, OR 0.69 (95% CI: 0.50-0.95). The investigators concluded that intramural fibroids without cavity distortion had a negative impact on pregnancy outcome in IVF/ICSI cycles and myomectomy should be considered for these fibroids, particularly in patients with previously failed cycles.

In 2007, Somigliana *et al* [12] reported a meta-analysis of the literature on the effects of fibroids on fertility and ART outcome. Data for intramural fibroids were pooled from 7 different studies and meta-analysis demonstrated a statistically significant detrimental effect on both the clinical pregnancy rate with OR of 0.8 (95% CI: 0.6-0.9) and the delivery rate with OR 0.7(95% CI: 0.5-0.8).

In 2008 Pritts *et al* [14] published an updated systematic review of the existing controlled studies on the effects of fibroids on fertility. The authors evaluated 347 studies of which 23 met the inclusion criteria. They were able to confirm the previously suggested negative impact of intramural fibroids on ART outcome with a RR of 0.8 (95% CI: 0.69-0.94) for clinical pregnancy rate and 0.7 (95% CI: 0.58-0.84) for live birth rate. Pritts *et al* [14] also found that intramural fibroids were associated with an increased risk of spontaneous miscarriage with a RR of 1.7 (95% CI: 1.2-2.4). Collectively, the results of these structured reviews and meta-analyses suggest that the discrepant findings of the initial studies on intramural fibroids were most likely due to small sample sizes and the more modest reduction in implantation and pregnancy rates with intramural fibroids (0.7) compared to submucosal fibroids (0.3).

Subserosal Fibroids

The evidence regarding the possible effects of subserosal fibroids on reproductive outcome is consistent. Neither the original studies [62,63,69,71] nor the meta-analyses [9-14] detected any detrimental effects on ART outcome associated with subserosal fibroids. Furthermore no beneficial effect on fertility was noted when myomectomy was performed for subserosal fibroids [72].

Management of Uterine Fibroids in Women Considering ART

The two questions confronting women with fibroids who desire ART and their healthcare providers are: which fibroids should be treated, and how they should be treated? From the preceding paragraphs, it is clear that intracavity, submucosal and in some cases intramural fibroids should be treated before ART to offer the patient the best chance for success. Myomectomy has long been regarded as the standard treatment for the various symptoms associated with fibroids, such as pelvic pressure, pain or menorrhagia. Myomectomy in most cases is the best option for women who are interested in preserving their fertility [75].

Specifically regarding submucosal fibroids, Pritts et al [14] demonstrated that compared to infertile women with fibroids in situ, myomectomy improved the clinical pregnancy rate with the RR of 2.03 (95% CI: 1.08-3.82). In addition, if the control group was selected as

infertile women without fibroids, myomectomy appeared to return the fertility outcome to the baseline of infertile women without fibroids [14].

One randomized trial evaluating the effects of myomectomy on fertility was reported in 2006. Casini et al [72] randomized 181 women with a combination of SM, IM and SS fibroids to either surgery or expectant management and reported the pregnancy rates in each subgroup following timed intercourse. The authors found that myomectomy resulted in a statistically significant higher pregnancy rate among women with submucosal fibroids (43% vs. 27%), as well as those with a combination of submucosal and intramural fibroids (36% vs. 15%).

Concerning intramural fibroids, Bulletti and colleagues [76] reported significant improvement in spontaneous pregnancy rate in a cohort of 106 women with fibroids of various types (submucosal, intramural and subserosal) who underwent myomectomy, compared to 106 women with fibroids who did not undergo myomectomy (42% vs. 11%). The same group reported a significant improvement in pregnancy and delivery rate in IVF/ICSI cycles following myomectomy for intramural and subserosal fibroids in women with normal uterine cavity but with at least one intramural fibroid larger than 5 cm (pregnancy rate 34% in the myomectomy group vs. 15% in the group with fibroids in situ and delivery rate 25% vs. 12%, respectively) [77]. Furthermore, in the randomized clinical trial reported by Casini and colleagues [72] there was a clinically significant trend towards better pregnancy rate in the group with intramural fibroids after myomectomy (56% vs. 41%), although the difference did not reach statistical significance. Based on these studies, it appears that myomectomy is beneficial and corrects the adverse reproductive outcome associated with submucosal and intramural fibroids. As with any major surgical procedure, myomectomy carries risks, such as bleeding, infection and damage to other organs. Furthermore, myomectomy is associated with adhesion formation [78,79], although this is not a concern for women who are planning to pursue ART. Another consideration is the possible impact of myomectomy on the mode of delivery in a future pregnancy. Uterine rupture during labor following myomectomy has been reported [80-82]. Despite the paucity of good quality evidence, if the myomectomy involves a transmural incision or entry into the uterine cavity, most obstetricians recommend elective caesarean delivery. In many cases with intracavity or submucosal fibroids, myomectomy can be accomplished via hysteroscopic approaches, except for larger fibroids (>4 cm). In summary, myomectomy should be considered in women affected with submucosal and/or intramural fibroids who are pursuing fertility treatments, particularly in cases of previously failed IVF/ICSI cycles. While studies indicate better pregnancy outcomes after myomectomy for submucosal and intramural myomas, additional randomized well-controlled studies are needed. Since pregnancy-related concerns depend on the location of the leiomyoma, the importance of an in depth discussion of a management plan between patients and physicians cannot be over-emphasized.

GnRH agonists and antagonists

GnRH agonists have long been used to induce a transient state of hypogonadotropic hypogonadism, clinically mimicking the menopausal status. These agents work by causing a “medical menopause” leading to reduction in estrogen. The subsequent hypoestrogenic state can result in a rapid and significant 35-65% reduction in the fibroid size within 3-6 months [83]. Notably, GnRH antagonists are particularly effective and can cause a 30% reduction in size of the fibroids within 2 weeks [84,85]. Unfortunately, side effects associated with prolonged use, such as bone loss, preclude use of these agents for longer than 6 months and fibroids rapidly return to their pretreatment size upon discontinuation of treatment. Moreover these agents inhibit ovulation and therefore are of limited use in fertility

treatment, except as part of IVF/ICSI protocols. Nevertheless, for some women with fibroids, the small but notable and rapid reduction in the size of fibroids with GnRH agonists and antagonists may prove beneficial immediately prior to ART, or preoperatively to reduce fibroid size.

Uterine artery embolization

Uterine artery embolization (UAE) has been developed as an alternative to myomectomy for women with symptomatic uterine fibroids who desire to avoid surgery. This therapeutic modality results in a significant reduction in the dominant fibroid size, leading to a 77-86% symptomatic relief for bleeding-related complaints within three months of the procedure [86]. However, fibroid size is only reduced by 40-75% [87]. Compared to myomectomy, UAE results in shorter hospital stay, quicker recovery but higher minor complication rates after discharge [88]. In terms of major complications, UAE is similar to myomectomy [88]. A substantial concern for the application of UAE for patients considering ART is the compromise of the ovarian blood supply with the resultant adverse effect on ovarian reserve and reduction in the number of oocytes [89,90]. Additionally, UAE has in some cases caused permanent endometrial atrophy [91]. Although successful pregnancies have been reported after UAE [92], most studies have reported a significantly increased risk of miscarriage as well as obstetric complications such as preterm delivery, malpresentations, IUGR, abnormal placentation and postpartum hemorrhage in pregnancies achieved after UAE [86-90,93,94]. One of the largest series reporting the pregnancy outcomes in 56 pregnancies after UAE suggested that in addition to increased risk of preterm delivery, caesarean section and postpartum hemorrhage, there was a significantly increased risk of miscarriage after UAE compared to the general population (30% vs. 10-15%) [93]. Another study concluded that pregnancies after UAE had higher rates of preterm delivery (odds ratio 6.2, 95% confidence interval 1.4-27.7) and malpresentation (odds ratio 4.3, 95% confidence interval 1.0-20.5) when compared to pregnancies following laparoscopic myomectomy [94]. With these considerations in mind, it seems advisable to reserve the option of UAE for women who do not desire future pregnancy and UAE is not recommended for women pursuing ART [94,95].

MRI-guided focused ultrasound

MRI-guided focused ultrasound is the newest among the emerging non-surgical management options for symptomatic uterine fibroids [96]. In this procedure, energy from multiple elements of a phased array transducer is directed through the anterior abdominal wall resulting in coagulative necrosis of the fibroid where the ultrasound waves converge. In a recent publication reporting the 24 months follow up data for 359 women who underwent this procedure, it was concluded that MRI-guided focused ultrasound resulted in sustained relief of fibroid symptoms, equivalent to other accepted fibroid treatments [96]. However, the maximal reduction in fibroid size at 12 months after the procedure was approximately 25% [96]. Of note, like the UAE reports, these investigators focused on the bleeding and pain and not on fertility-related issues or pregnancy. Considering that neither the ovarian nor the endometrial blood supply should be affected during this procedure, the method may prove promising for women who seek fertility treatment. There have been case reports of pregnancies after MRI-guided focused ultrasound surgery [97,98] but there are no controlled trials to date to address its use for fertility indications. For most women, however, fibroid size and location will require myomectomy prior to ART.

Conclusion

It is clear that intra-cavitary, submucosal and intramural fibroids have an adverse effect on fertility and ART outcome. The detrimental effect of submucosal fibroids (i.e. cavity distorting fibroids) is well established. Furthermore, recent evidence suggests that intramural fibroids, even in the absence of cavity distortion, may have a negative impact on fertility at ART. Conversely, there is good evidence that subserosal fibroids do not affect ART outcomes. Myomectomy is often indicated prior to ART to normalize the uterine cavity. Although alternative treatments with a good safety and efficacy profile have become available for the management of symptomatic fibroids for indications other than infertility, myomectomy remains the treatment of choice for women seeking fertility treatment. The rising number of women who have delayed childbearing for personal reasons, together with the observed increase in the prevalence of fibroids with increasing age have led to an increased prevalence of uterine fibroids in women seeking assisted reproduction.

Future Perspective

Future research should seek to further elucidate the mechanisms by which fibroids exert their detrimental effect on endometrium, with particular emphasis on clarifying the relative importance of fibroid size, number and proximity to the endometrium.

Acknowledgments

This work was supported in part by the Program in Reproductive and Adult Endocrinology, NICHD, NIH, Bethesda, MD, USA.

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Executive Summary

Introduction

- Uterine fibroids are present in 30% to 70% of reproductive-aged women.
- Fibroid are associated with menstrual disorders, pelvic pain, infertility and adverse obstetric outcomes.
- ART offers a unique opportunity to study the effects of fibroids on fertility.

Classification and Diagnosis

- Fibroids are classified as submucosal, intramural and subserosal. Submucosal fibroids are further subdivided into Type 0, type I and type II.
- Transvaginal ultrasonography and hysterosalpingography (HSG) are imaging modalities often used to evaluate uterine fibroids and/or the effects of fibroids on uterine cavity but hysteroscopy and saline infusion sonography are the most accurate diagnostic methods.

Fibroids and Infertility

- Submucosal and intramural fibroids clearly have an adverse effect on fertility in general and ART outcome in particular.

Submucosal Fibroids

- Submucosal fibroids (cavity distorting fibroids) adversely affect ART outcomes, resulting in reduced pregnancy and live birth rates with an OR of 0.3.
- Altered expression of critical genes, such as HOX genes, has been implicated as the possible etiologic mechanism to explain the reduction in embryo implantation.

Intramural Fibroids

- Intramural fibroids (in the absence of cavity distortion) adversely affect ART outcomes, resulting in reduced pregnancy and live birth rates with an OR of 0.7.

Subserosal Fibroids

- Subserosal fibroids do not affect ART outcome.

Clinical Management of Uterine Fibroids in Women Considering ART

- Myomectomy is the standard treatment for the symptoms associated with uterine fibroids, particularly for women who desire to preserve fertility.
- Myomectomy can reverse the detrimental effects of fibroids on ART outcome.
- GnRH agonists and antagonists might have some role for the treatment of uterine fibroids preoperatively.
- Uterine artery embolization (UAE) and MRI-guided focused ultrasound surgery are alternative treatment modalities for women whose main symptoms are bleeding and/or pain, but neither is considered a first-line therapy for women pursuing assisted reproduction.