



# Fibroid and Assisted Reproductive Technology

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## Abstract

Infertility, in some cases, is attributable to fibroid of the uterus which is benign tumours that arise from the overgrowth of smooth muscle and connective tissues in the uterus. The association between fibroids and infertility is still unclear and it is assuming increasing relevance considering the increase in the incidence of infertility and the tendency to start a family at an age when natural female fertility is in decline with consequent increasing incidence of fibroids. The contemporary social trend to delay childbearing to the 4<sup>th</sup> or 5<sup>th</sup> decade of life, when fibroids and infertility are more prevalent, increases the chances of encountering this association in elderly infertile women. In the ART setting, which bypasses all the natural steps before egg-sperm interaction, the main outcomes measured are implantation, miscarriage rate and take-home baby rate. Despite the available information, it is still not easy to solve the current dilemma of the possible ill effect that small intramural fibroids may have on pregnancy potential. In the ART setting, which bypasses all the natural steps before egg-sperm interaction, the main outcomes measured are implantation, miscarriage rate and take-home baby rate.

**Keywords:** Fibroid; Myomectomy; *In-vitro* fertilization; Egg-sperm interaction; Infertility; Pregnancy

## Introduction

Uterine fibroids are benign tumours that arise from the overgrowth of smooth muscle and connective tissues in the uterus. The incidence and natural history of uterine fibroids remain not fully understood [1]. The prevalence varies with age and increased in the late reproductive period, and with ethnic origin, with African American women being more affected [2]. Fibroids of the uterus are common, they increase with advanced age and there is no doubt it is among the most common benign pelvic tumors, attaining an incidence of 25% to 40% in women during their reproductive years [3]. Infertility is a life crisis and has been reported to affect 10% to 15% of couples [4].

The relationship between fibroids and infertility still remains unsolved and it is assuming increasing relevance considering the increase in the incidence of infertility and the tendency to start a family at an age when natural female fertility is in decline with consequent increasing incidence of fibroids. In a study by Ajayi et al. [5] on fibroids among infertile women having laparoscopic myomectomy the non-gravid uterus was significantly bulkier (weeks) in primary ( $18.0 \pm 3.7$ ) than in secondary ( $14.1 \pm 2.4$ ) infertility. In another study among infertile women who had hysteroscopy, 15.5% of them had sub-mucous fibroids [6].

The effect of uterine leiomyoma on fertility is subject to continuous debate. The exact mechanism by which fibroids may affect infertility is not certain but is thought to include (i) blockage of the fallopian tubes; (ii) alterations of tubal motility and prevention of sperm-egg assembly; (iii) prevention of proper sperm migration through the cervical canal; (iv) dyspareunia; (v) thin, vascularized endometrium [7]; and (vi) abnormal uterine peristalsis [3].

The thin, vascularized endometrium and abnormal uterine peristalsis can explain the effects of fibroids on implantation and Assisted Reproductive Technologies (ART)/IVF results. IVF therefore provides a unique opportunity to examine the effect of leiomyoma on embryonic implantation rate.

Depending on the number, size and location, some fibroids may cause a variety of signs and non specific symptoms including pelvic mass, pressure, pain, heavy vaginal bleeding, infertility, miscarriage and premature delivery [7-8].

Occasional cases of large fibroids, encountered during delivery or caesarean section, including intracavity fibroids, add to the confusion of delineating clear roles and conclusions of which fibroids

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can cause pregnancy failure hence. It is hard to appraise accurately if a detected fibroid may affect fertility fully or marginally, directly or indirectly.

The knowledge of the effect of fibroids on infertility in the pre-IVF (*In vitro* fertilisation) era or in the non-ART setting is based on heterogeneous sets of data, some are outdated, from the 1970s and 1980s-collectively indicating that surgical myomectomy in infertile women is associated with a success rate of approximately 50% [9,10]. These studies, however, include fibroids of various sizes, numbers and different locations and they are all uncontrolled or non-randomized, which explains the high variability of the results between <10% to >70% success rate [11,12].

Nevertheless, as a consequence of all these studies, it was generally accepted, even if not systematically proven, that regardless of the means by which myomectomy is performed (hysteroscopy, laparoscopy or laparotomy), excision of submucous myoma can improve the chances of conception, whereas myomectomy of large intramural fibroids can improve the overall outcome of pregnancy [13].

Given this entire scenario, it is essential to clarify whether these benign tumours affect fertility and, if so, which kind of lesions deserves treatment?

## Art & Fibroids

The current social trend to delay childbearing to the 4<sup>th</sup> or 5<sup>th</sup> decade of life, when fibroids and infertility are more prevalent, increases the chances of encountering this association in elderly infertile women. However, at this age, most women suffer from infertility due to low-quality oocytes, which is the determining factor even if coexisting fibroids are detected. Hence, clinically, it is not easy to separate between infertility that is due to an existing fibroid or to other factors.

It is obvious that not all fibroids produce infertility and the risk is that any detected fibroid might get undeserved attention and surgical treatment which is costly, time-consuming and not risk-free for patients who have a narrowing timeline to successful pregnancy. Therefore, it is important to distinguish between fibroids that do not affect the results, those that can marginally affect the results and those that deserve surgical management before proceeding to IVF.

In the ART setting, which bypasses all the natural steps before egg-sperm interaction, the main outcomes measured are implantation, miscarriage rate and take-home baby rate.

A retrospective, controlled trial on effect of uterine leiomyoma on IVF treatment conducted in 1995 drew attention to the fact that implantation rates and pregnancy outcomes were not different in a group of 46 women with fibroids in comparison to women with mechanical infertility without fibroids [14]. However, when during hysteroscopy, the leiomyoma was found to distort the uterine cavity, implantation rate was affected. The authors also suggested that in such patients with an abnormal uterine cavity, surgical treatment should be considered prior to IVF due to the reduced implantation rate [14].

The findings on the submucous fibroids were later confirmed by other non-randomized studies [13,15,16]. However, some of these studies also reported that intramural fibroids, which supposedly lack an intrauterine component, may have a deleterious effect on IVF results. As a result, excision of such fibroids should be considered.

This conclusion remained controversial and was not confirmed by others [12], requiring further clarification. Despite few randomized control trials, a provisional summary of the literature permitted one to conclude that fibroids that impinge on the uterine cavity may lower implantation rates, and thus myomectomy prior to IVF might solve the problem. Conversely, the effect of intramural fibroids not encroaching on the uterine cavity warrants further investigation [17].

Despite the available information, it is still not easy to solve the current dilemma of the possible ill effect that small intramural fibroids may have on pregnancy potential. Pritts EA [18] reported on a meta-analysis of six studies [13,19] and found a pregnancy rate of 9 and 33.5%, respectively, in women with fibroids that impinged on the uterine cavity compared with women with fibroids that did not have an intracavitary component versus 40% in the control groups. The authors concluded that the large variations among the publications, the lack of proper diagnosis methodology and agreed definitions of fibroid location cast doubts on the true weight of these publications.

Check et al. [20] in 2002 found that implantation and pregnancy rates were statistically similar in patients with or without intramural fibroids smaller than 5 cm; however, a trend toward higher abortion and lower delivery incidence was observed. He indicated the need for larger randomized controlled trials to solve the dilemma of myomectomy before IVF.

Oliviera et al. [21] concluded that in patients with intramural fibroids smaller than 4 cm that do not encroach into the uterine cavity, there is no negative effect on implantation or miscarriage rate over one cycle follow-up, a fact that also represents the limitation of the study.

In a study comprised of 606 cycles published in 2006, Khalaf et al. [22] evaluated the cumulative effect of small intramural fibroids (<5 cm) not distorting the uterine cavity on implantation, ongoing pregnancy and live birth rate in three successive treatment cycles. Pregnancy, ongoing pregnancy and live birth rates were 23.6%, 18.8% and 14.8% in the study group, respectively, compared with 32.9%, 28.5% and 24%, respectively, in the control group. Regression analysis showed an approximate 40% reduction in success rates ( $p < 0.05$ ), which leads to the conclusion that small fibroids have a less distinctive effect that might be missed when studying a single cycle but becomes statistically apparent when looked at in a cumulative manner over several cycles.

Most available studies show conflicting results on IVF outcome only with intramural fibroids that are smaller than 5 cm and lack an intracavity component. Meanwhile large intramural fibroids or fibroids that distort the uterine cavity were clearly shown to impact the results of IVF, and hence, these women may, theoretically, benefit from surgical removal prior to IVF treatment.

Sunkara et al. [23], in another systematic review and meta-analysis on the effect of intramural fibroids without uterine cavity involvement on the outcome of IVF treatment, reviewed 19 observational studies comprised of 6087 cycles were analyzed and reported a significant decrease in the live birth (RR=0.79, 95% CI: 0.70-0.88,  $P < 0.0001$ ) and clinical PRs (RR=0.85, 95% CI: 0.77-0.94,  $P = 0.002$ ) in women with non-cavity-distorting intramural fibroids compared with those without fibroids, following IVF treatment.

Somigliana et al. [24] published a prospective study in 2011 that in asymptomatic patients with intramural fibroids smaller than 5 cm not invading the cavity, the results were not affected which is similar

to Check et al. [20] findings in 2002. They concluded that “future efforts should be aimed to identify the subgroup of women” in whom the fibroid can increase risk. However, like others, they do not advise as to how the authors should identify these patients other than by size and location [24].

The differences between the various studies are probably due to the difficulty in evaluating the true location of the fibroids and their relationship to the uterine cavity rather than only to the size of the fibroids.

## Myomectomy and Art

One of the controversial unsettled issues is the role of myomectomy in infertility. The assumption that myomectomy can overcome the decreased fertility associated with certain fibroids is not supported by many published experience. Some of the available evidence suggests that fibroid size prior to ART can cause lower implantation rates. In patients with intramural fibroids >50 mm, myomectomy before IVF has been shown to positively impact pregnancy outcomes [25]. A study by Bulletti et al. [25] in 2004 compared 84 women who chose to undergo myomectomy before IVF with 84 women who started IVF but did not undergo surgery. The women who did undergo surgery had a 25% rate of delivery and a clinical pregnancy rate of 33%, compared to 12% and 15% in the nonsurgical group [25]. This study suggested that myomectomy before ART is likely to improve pregnancy outcomes in infertile patients with submucosal fibroids, and with intramural fibroids >5 cm [25]. For subserosal fibroids, myomectomy before ART does not affect pregnancy outcomes.

Earlier retrospective studies have investigated the determinates of pregnancy rate and outcome following laparoscopic myomectomy and concluded that fertility and pregnancy after laparoscopic myomectomy depends primarily on patient age, duration of infertility before myomectomy and existence of associated infertility factors [26]. While this is in line with what is known, it does not prove that myomectomy was required in all patients with fibroid.

A review, published in 2012, examined the issue of whether myomectomy can result in improvement of fertility and what is the preferred mode of operation [27]. The authors considered 243 studies for evaluation, of which 23 were recognized randomized studies but only three studies complied with the level of evidence that was set [28,29]. The only study that qualified to answer the first question on the effects of fibroids on fertility included 170 patients and looked only at cases with one fibroid greater than 4 cm in diameter [28]. Collectively, this Cochrane review based on one study found no improvement in fertility and no evidence of reduction in the miscarriage rate following myomectomy in infertile women regardless of whether the fibroids were submucous, intramural, or a combination of submucous and intramural or subserous and intramural.

Yoshino et al. [30] found that myomectomy decreases the abnormal uterine peristalsis, which is reported to increase with the presence of intramural fibroids. However, this has not been linked to having any significant effects on fertility.

It is also important to note that myomectomy, particularly open myomectomy, can also have unwanted effects on the state of the uterus thereby affecting fertility. Ajayi et al. [31] previously reported that uterine procedures like open myomectomy, Dilatation and Curettage and Caesarean section and the number of times these procedures are carried out were important risk factors for uterine

adhesions in infertile black African women.

Uterine adhesion was common amongst infertile women who had hysteroscopy in a study of 1115 infertile women with an incidence of 30.3% and the leading procedure reported by the women before presentation was open myomectomy [32]. The effects of uterine adhesions on implantation rates are not favorable.

## Conclusion

Some clinical questions are not easy to solve, even with randomized controlled trials, especially when so many variables exist. Fibroids vary in the size, location, number, distance from the endometrium and the age of the patient. They can affect fertility, but not necessarily in every pregnancy.

The current social trend to delay childbearing to the fourth or fifth decade of life, when fibroids and infertility are more prevalent, increases the chances of encountering this association in specific patients. At 40 years of age, infertility is mainly due to decreased ovarian reserve and lower quality eggs. While fibroids are very common, they infrequently exert a negative effect on pregnancy potential. With the high rate of association of these two problems and the lack of a gold standard to diagnose which fibroids affect the chances to conceive, it is not surprising that many physicians tend to lean towards myomectomy as the partial solution to the problem. However, the role of myomectomy remains ambiguous.

Most studies agreed that it is acceptable to perform myomectomy prior to IVF in women with submucous fibroids and fibroids that are encroaching into the uterine cavity. Considering that the uterine wall is no more than 2 cm in thickness, it is possible that all the intramural fibroids that are larger than 5 cm have some submucous component and therefore deserve surgical consideration.

On the other hand, it is not advisable to perform myomectomy on intramural fibroids that are smaller than 5 cm and definitely not on those smaller than 3 cm. The final decision on those cases remains at the discretion of the treating physician and the patient, based on personal experience with IVF and surgical skills in myomectomy, and the kind of pregnancy failure that they are experiencing.

The less pronounced effect of intramural fibroids on the outcome is probably one of the reasons for the miscellaneous results; different studies with newer tools to evaluate the fibroids *vis-à-vis* the uterine cavity will be of great help.

Most available studies show conflicting results on IVF outcome only with intramural fibroids that are smaller than 5 cm and lack an intracavity component. Meanwhile large intramural fibroids or fibroids that distort the uterine cavity were clearly shown to impact the results of IVF, and hence, these women may, theoretically, benefit from surgical removal prior to IVF treatment.

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