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## Impact of fibroids on reproductive function

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There is debate regarding whether fibroids cause infertility or if they are simply an association. However, it is possible that fibroids are responsible for 2–3% of cases of infertility. The mechanisms by which these benign tumours could cause impaired reproductive function, both in terms of difficulty conceiving and early pregnancy loss, remain unclear. Myomectomy facilitates removal of a fibroid with preservation of reproductive potential. The procedure is associated with significant risks but, overall, some studies have suggested that this surgical option increases pregnancy rates significantly in women with fibroid-associated infertility. Miscarriage rates in women with fibroids and those who have undergone myomectomy vary considerably. It appears that miscarriage rates fall after myomectomy, although the overall rates of pregnancy loss remain higher than those seen in the general population. Fibroids affect 0.1–3.9% of pregnancies, and a number of complications encountered antenatally and post partum are thought to be directly related to the presence of these benign tumours. A number of contraceptive options exist for women with fibroids, with the choice depending on patient preference and both fibroid and patient characteristics.

**Key words:** leiomyomata; fibroids; myomas; infertility; reproduction; ART; myomectomy; miscarriage; pregnancy loss; obstetric outcome; contraception.

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## DO FIBROIDS CAUSE INFERTILITY?

Fibroids are known to occur more frequently in women with a history of infertility. Whilst these benign tumours are associated with subfertility in 5–10% of cases, when all other causes of reproductive dysfunction are excluded, fibroids may be responsible for only 2–3% of cases.<sup>1</sup> Despite the existence of many studies assessing the correlation between uterine myomas and infertility, the mechanisms by which fibroids have a detrimental effect on reproductive function remain largely unknown. However, a number of theories have been postulated (Table 1).

It has been suggested that the hyperoestrogenic environment associated with fibroids may result in subfertility.<sup>2</sup> Endometrial pathological changes such as endometrial atrophy, distortion of endometrial glands, endometrial venular ectasia and ulceration have been implicated as causative mechanisms for implantation failure.<sup>3,4</sup> Dysfunctional uterine contractility is thought to be responsible for interference with normal sperm, ovum and embryo transport, and can impair nidation. In addition, the anatomical location of a uterine myoma may be an important contributor to infertility. Fibroids that distort the uterine cavity or obstruct the tubal ostia have been particularly implicated. Fibroids distorting the uterine cavity may interfere with implantation and maintenance of an early pregnancy, whilst fibroids obstructing the tubal ostia have the potential to interfere with sperm and embryo transport. However, studies evaluating the impact of submucosal, intramural and subserosal fibroids on infertility have yielded conflicting data.<sup>5</sup> Generally, submucosal and, to a lesser extent, intramural fibroids are thought to have a negative influence on fertility, in terms of pregnancy and implantation rates, whilst the presence of subserosal myomas has little or no effect on fertility.<sup>1,6</sup>

Uterine fibroids may also cause infertility by disrupting the blood supply of the endometrium which, in turn, may have a negative effect on the normal process of nidation.<sup>7,8</sup> Finally, it has been postulated that local inflammation resulting from ulceration of submucosal fibroids is responsible for altering the normal biochemical environment of endometrial fluids. This is thought to create a hostile environment for sperm, leading to reduced reproductive potential.<sup>9</sup>

## FIBROIDS AND OUTCOMES OF ASSISTED REPRODUCTIVE TECHNOLOGY

The effect of uterine fibroids on fertility in association with the use of assisted reproductive technology (ART) has been the subject of many published articles. Studies of women undergoing ART such as in-vitro fertilization (IVF) and intra-cytoplasmic sperm injection (ICSI) have the advantage of being able to exclude other fertility variables

**Table 1.** Postulated mechanisms by which fibroids cause subfertility.

Interference with normal patterns of endocrine function
Distortion of the endometrium
Dysfunctional uterine contractility
Anatomical distortion of the uterine cavity
Distortion or obstruction of tubal ostia
Abnormal uterine vascularization
Chronic endometrial inflammation

such as abnormal pelvic anatomy, tubal disease and sperm function, all of which are known to have an influence on reproductive outcome.

Although the impact of fibroids remains an area of debate, many studies have demonstrated that submucosal and intramural fibroids in the presence of distortion of the endometrial cavity are associated with reduced implantation and pregnancy rates compared with women with similarly located fibroids in the absence of endometrial cavity distortion. This has been shown with both small (<5 cm diameter)<sup>10,11</sup> and large (>4 cm) intramural fibroids.<sup>9</sup> Some studies have also reported impaired IVF and ICSI outcomes in the presence of subserosal fibroids.<sup>9,11</sup> In contrast, other authors have shown that ART outcomes are not affected by the presence of subserosal myomas.<sup>5</sup> In the latter study, significantly lower pregnancy and implantation rates were reported in the presence of both intramural and submucosal fibroids, even when associated with an undistorted endometrial cavity. However, Farhi et al concluded from their studies that fibroids which distort the endometrial cavity impair outcomes after ART significantly in terms of implantation and pregnancy rates, whereas fibroids in the presence of a normal endometrial cavity do not.<sup>10</sup> Similarly, Surrey et al demonstrated that IVF outcomes are not affected by the presence of intramural fibroids associated with a normal endometrial cavity.<sup>12</sup> A meta-analysis of IVF studies by Pritts concluded that submucosal and intracavity fibroids hinder outcomes of ART significantly, whilst neither subserosal nor intramural fibroids have an adverse effect on fertility.<sup>13</sup>

The relationship between uterine fibroids and ART has been investigated repeatedly, and whilst study outcomes are often conflicting, overall the evidence supports the concept that submucosal and intramural fibroids which distort the endometrial cavity have a negative effect on outcomes of ART. However, the effects on fertility of both subserosal and intramural fibroids in the presence of a normal endometrial cavity remain unclear. More prospective observational studies, with control groups and randomization processes to eliminate confounding variables and reduce bias, are required to identify the exact role of fibroids in outcomes of ART.

## FERTILITY FOLLOWING MYOMECTOMY

Whilst hysterectomy remains the gold standard treatment for fibroids, in terms of eliminating fibroid-associated symptoms immediately and guaranteeing no recurrence of symptoms, it is an unacceptable treatment option for women who wish to conserve their fertility. Myomectomy, which involves removal of fibroid(s) with conservation of normal myometrial tissue and thus fertility, remains the alternative surgical treatment option for women who wish to conceive in the future, although the actual effects of the procedure on fertility remain uncertain. The procedure may be performed abdominally, laparoscopically or vaginally. All these techniques are associated with risks such as significant intra-operative blood loss, the risk of converting to emergency hysterectomy with consequent loss of fertility, disfigurement of the uterine cavity and increased risk of uterine rupture in future pregnancy or labour. Myomectomy is also associated with the risk of postoperative adhesion formation, which may result in further compromise of reproductive capacity, chronic pelvic pain, an increased risk of ectopic pregnancy if conception is achieved and, less commonly, bowel obstruction. In addition, myomas have the potential to recur such that 20–25% of women who undergo myomectomy require a secondary procedure.<sup>14</sup> Whilst laparoscopic myomectomy involves a shorter postoperative recovery period and less postoperative pain, it is more of a technical challenge, often more time consuming and, in some cases, not a feasible surgical option.<sup>15</sup> Vaginal resection of

uterine myomas using a hysteroscopic technique is also associated with less intra-operative blood loss, less patient discomfort, shorter recovery time and overall reduced complication rate. It is therefore the preferred technique for resection of submucosal fibroids <4–5 cm in diameter and with more than 50% of their mass in the uterine cavity.

Studies on clinical outcomes following myomectomy have yielded inconsistent data, and tend to be of poor design, many being retrospective and uncontrolled. In a retrospective study, Surrey et al did not find a significant difference in outcomes in terms of implantation, ongoing pregnancy or early pregnancy loss rates when comparing both pre-cycle abdominal myomectomy (resection of large submucosal lesions with a significant intramural component or intramural lesions that impinge upon or distort the endometrial cavity) and hysteroscopic resection of small submucosal fibroids with controls.<sup>16</sup> In contrast, a number of retrospective observational studies have highlighted that fertility outcomes do improve after myomectomy.<sup>17–20</sup> However, there are no published randomized controlled studies with sufficient power to support the theory that myomectomy improves fertility outcome. Similarly, there is no evidence at present to suggest that there is any difference in clinical pregnancy and livebirth rates between the various techniques available to remove fibroids.<sup>21</sup> Hysteroscopic myomectomy is currently the best option for many women with submucous fibroids, whilst abdominal and laparoscopic myomectomy remain the best alternatives.<sup>22</sup>

Despite the lack of evidence from randomized studies, it does appear that surgical intervention for uterine fibroids does increase pregnancy rates, with an estimated 50% of women conceiving following myomectomy for fibroid-associated infertility.<sup>23</sup> Recently, a multicentre randomized controlled study comparing myomectomy performed by laparoscopy or mini-laparotomy was conducted in Italy.<sup>24</sup> The authors assessed the safety and efficacy of the two procedures, with surgical outcome being the main outcome measure. They found that both techniques were safe, and the size and location of the fibroid(s) were the strongest predictors of surgical outcome. They concluded that the latter fibroid characteristics were important factors that should influence the choice of myomectomy technique.

Overall, the management of women considering myomectomy for fibroid-associated fertility should be individualized, with specific counselling about the risks of myomectomy and risks of pregnancy in the presence of fibroid(s).

## **DO FIBROIDS CAUSE MISCARRIAGE?**

Fibroids have the potential to cause a number of problems in pregnancy, including miscarriage and pregnancy wastage. A number of studies have shown that spontaneous miscarriage rates in the first and second trimesters of pregnancy are higher in women with fibroids. Some believe that the rates of miscarriage are likely to be higher if implantation occurs over a submucosal myoma. It has been shown that fibroids in close proximity to the placenta are more likely to be associated with bleeding in early pregnancy and spontaneous miscarriage.<sup>25,26</sup> Benson et al demonstrated almost double the rate of spontaneous pregnancy loss in women with fibroids compared with age-matched women with normal uteri.<sup>27</sup> In addition, the loss rate observed was found to be higher in women with multiple fibroids compared with women with a single myoma, whilst no association between loss rate and fibroid size or location was noted. Miscarriage rates in women with fibroids vary widely in the literature, with loss rates of 40% in the first trimester and 17% in the second trimester being reported in the presence of intramural and submucosal fibroids.<sup>28</sup>

The exact mechanisms by which fibroids cause pregnancy loss remain poorly understood. Richards et al found the host myocytes of fibroid uteri to be structurally abnormal compared with those of normal myometrium.<sup>4</sup> It has been postulated that this specific abnormality may affect calcium metabolism in the fibroid tissue which, in turn, may cause abnormal uterine contractility, resulting in pregnancy loss. Growth and degeneration of fibroids have also been implicated as causes for spontaneous miscarriage.<sup>29</sup>

Miscarriage rates reported after myomectomy tend to be similar, with estimates of 26–27% being reported in the literature.<sup>17,30,31</sup> Most of the pregnancy losses reported were found to occur in the first trimester. Reductions in miscarriage rates of 60 to 24% and 41 to 19%, before and after myomectomy, have been reported.<sup>1,28</sup> These rates of miscarriage after myomectomy, nonetheless, are higher than those seen in the general female population. The causes of the latter are thought to be due to other factors such as increased maternal age.

## FIBROIDS AND THEIR IMPACT ON ANTENATAL COMPLICATIONS OF PREGNANCY AND LABOUR

The prevalence of uterine fibroids in pregnant women ranges from 0.1 to 3.9%.<sup>32,33</sup> It is likely, however, that this will increase with time as women continue to delay having a family until later in life, and the use of antenatal uterine imaging increases. Despite the frequency with which fibroids are encountered in pregnancy, there is still considerable controversy regarding their effects on the antenatal period, labour and post partum. During pregnancy, these benign tumours have been linked to a number of complications, including early pregnancy bleeding, first- and second-trimester miscarriage, pelvic pain, intra-uterine growth restriction, premature rupture of membranes, placental abruption and preterm labour. Myomas have also been linked with problems in labour such as fetal malpresentation, dystocia of labour, operative vaginal delivery, caesarean section, postpartum haemorrhage, retained placenta and puerperal infection. The size and location of a fibroid has also been shown to influence obstetric outcome, with myomas >3 cm in diameter being associated with increased rates of pelvic pain, placental abruption, preterm labour, fetal malpresentation and caesarean section delivery.<sup>32–36</sup>

Qidwai et al found that fibroids were significantly associated with placenta praevia and preterm delivery, but were not significantly associated with premature rupture of membranes or placental abruption.<sup>33</sup> In contrast, both Coronado et al and Rice et al demonstrated increased rates of placental abruption, with Coronado et al observing a nearly four-fold increase in placental abruption among women with fibroids compared with controls.<sup>32,36</sup> Both groups found that leiomyomas in a retroplacental location were more likely to be associated with abruption. Data regarding the association between fibroids and premature rupture of membranes tend to be inconsistent. However, the positive association between the presence of fibroids and placental praevia, malpresentations such as breech presentation, operative delivery and caesarean section has been demonstrated repeatedly.<sup>32,33,36</sup> Qidwai et al observed that whilst women with fibroids greater  $\geq 10$  cm had slightly higher rates of caesarean section delivery compared with women with smaller myomas, 70% of women with a fibroid  $\geq 10$  cm who were deemed suitable for a trial of vaginal delivery achieved a vaginal birth.<sup>33</sup>

The exact mechanisms by which fibroids are associated with obstetric complications remain uncertain. However, it is highly likely that these benign tumours physically interfere with pregnancy and labour via mechanical obstruction. It has also been

hypothesized that they interfere with uterine contractility, but this association with obstetric complications is less clear.

Women should always be counselled about the risk of uterine rupture following myomectomy. During pregnancy and labour, this complication is generally thought to occur rarely.<sup>17,30,37,38</sup> It is, however, difficult to determine which characteristics of a fibroid (e.g. size, location and number) increase the likelihood of uterine rupture, and which method of myomectomy predisposes to an increased risk of this complication. Nonetheless, adhering to well-established surgical principles during myomectomy (regardless of the method) and using oxytocics in labour with consideration and caution, assist in reduction of this risk during pregnancy and labour.

## POSTPARTUM SEQUELAE OF FIBROIDS

During the puerperium, the blood supply to the uterus is greatly reduced from that occurring throughout pregnancy. This may result in ischaemic degeneration of uterine fibroids. The latter provides an ideal culture medium for anaerobic organisms which commonly invade the uterine cavity during the postpartum period. This, in turn, may result in endometritis. In its mild form, such infection may be treated with antibiotics, but rarely, hysterectomy may be required for more florid infections unresponsive to antibiotic treatment. Occasionally, fibroids or fibroid tissue may be expelled spontaneously per vaginam in the puerperium or, less commonly, require surgical intervention during this period.

## CONTRACEPTIVE OPTIONS IN THE PRESENCE OF FIBROIDS

A woman's exposure to oestrogens and progesterones is influenced by her use of hormonal contraception, which, in turn, has the potential to influence the natural course of fibroids, the growth of which is known to be partly hormone dependent. A number of contraceptive options are available for women with uterine myomas and these include the combined oral contraceptive pill (COCP), the progesterone-only pill (POP), injectable depo medroxy progesterone acetate (DMPA) and the levonorgestrel-releasing intra-uterine system (LNG-IUS).

A number of studies have been carried out to evaluate the effect of oral contraceptive use in women with fibroids. Results are conflicting, with some authors demonstrating reduced risk of fibroids in association with oral contraceptive use<sup>39,40</sup>, whilst others have shown little or no association<sup>41,42</sup> or increased risk.<sup>43</sup> Marshall et al found that the risk of uterine fibroids was increased significantly amongst women who first used oral contraceptives (for at least 2 months) in their early teenage years compared with women who had never used oral contraceptives.<sup>44</sup> Studies evaluating the influence of COCPs on fibroids in later life, however, have been conflicting. Ross et al found the risk of fibroids to be reduced by just over 30% in women who used the COCP for 10 years.<sup>40</sup> Others have demonstrated that prolonged use of the COCP results in a significant reduction in duration of menses, in association with a significant increase in haematocrit and no change in uterine or fibroid size.<sup>45</sup> More recently, Wise et al concluded, from a prospective study of over 20 000 African-American women, that the use of hormonal contraception, both combined and progesterone-only preparations, was not associated with a risk of fibroids relative to non-users of hormonal contraception.<sup>46</sup> In keeping with the findings of Marshall et al, however, they did find weakly elevated fibroid risks for women commencing oral contraception at a younger age. Thus, it appears from the evidence that use of the COCP and the POP for contraceptive

purposes in premenopausal women with uterine fibroids is a reasonable option. As with the normal female population, the non-fibroid risks associated with these preparations must be considered prior to commencing the oral contraceptive.

The use of the injectable progestagen DMPA, also known as depo provera, is another valuable contraceptive option in women with uterine fibroids. As well as its contraceptive benefit, it has also been shown to improve menstrual bleeding patterns significantly, increase haemoglobin levels and reduce fibroid volume after 6 months of use.<sup>47</sup> Wise et al demonstrated a decreased risk of fibroids in DMPA users relative to non-users of hormonal contraception.<sup>46</sup> Whilst there are both contraceptive and non-contraceptive benefits in terms of alleviation of fibroid-associated symptoms, with the use of DMPA, hypo-oestrogenism can increase the risk of osteoporosis with prolonged use, which must be borne in mind when prescribing this injectable progestagen to women as a long-term contraceptive option.

The LNG-IUS is a highly effective contraceptive with few contra-indications and side-effects. Also known as the Mirena IUS, it induces a marked reduction in endometrial proliferation and increase in endometrial apoptosis<sup>48</sup>, resulting in significant reduction in menstrual blood loss shortly after its insertion. The LNG-IUS is therefore very useful in the long-term management of women with fibroid-associated menorrhagia, for both contraceptive and menstrual purposes. It has been shown to be effective in controlling bleeding in conjunction with improvements in haematocrit and haemoglobin levels after 6 months of use in women with uterine myomas, in the absence of uterine volume reduction.<sup>49</sup> In contrast, Magalhaes et al demonstrated significant uterine volume reduction in both women with idiopathic menorrhagia and fibroid-associated menorrhagia who used the LNG-IUS for up to 36 months.<sup>50</sup> They did not, however, find a significant reduction in fibroid volume in their group of women. It is worth remembering that whilst the levonorgestrel secreting intrauterine system (LNG-IUS) is an excellent contraceptive choice for many women with uterine fibroids, it has the potential to be expelled spontaneously by some women with excessively heavy periods, and may also be of little menstrual benefit to women with large fibroid uteri associated with large uterine cavities. In addition, it may not be possible to insert the device in the presence of significant uterine cavity distortion caused by the presence of intramural and, more commonly, submucosal fibroids. Whilst the LNG-IUS may not be of benefit to all women with uterine myomas, the contraceptive efficacy of this device in women with fibroids, with or without menorrhagia, appears to remain intact.<sup>51</sup> It should therefore be considered as both a contraceptive and therapeutic option in a select group of women with fibroids.

Thus it appears that there are a number of contraceptive options available to women with uterine myomas, with the choice depending on individual preference, age, uterine and fibroid size (as well as number, size and location), and the presence or absence of fibroid-associated symptoms.

## **FIBROIDS, INFERTILITY AND UTERINE ARTERY EMBOLIZATION**

Uterine artery embolization (UAE) is a minimally invasive radiological technique which has been used for the treatment of symptomatic fibroids for just over a decade. Since its introduction in 1995<sup>52</sup>, the safety and efficacy of this procedure have been evaluated in a number of studies worldwide.<sup>53–56</sup> The procedure appears to be safe, and current literature suggests that it is effective in reducing menstrual blood loss, uterine volume and pelvic pain in the majority of women with symptomatic fibroids.

In addition, embolization for the treatment of symptomatic fibroids has been shown to improve overall health-related quality of life in a manner similar to that of hysterectomy.<sup>57,58</sup>

Premature menopause induced by UAE has been estimated at up to 25% in women above the age of 45 years and 1% in younger women.<sup>59</sup> Whilst most women undergoing the procedure tend to have completed their family, this is an important aspect to consider for women who wish to retain their fertility. Certainly, a number of successful pregnancies have been reported since the introduction of UAE as a fertility-sparing procedure, although a number of complications following conception have also been published.<sup>60</sup> To date, only one randomized controlled trial comparing UAE with myomectomy has been published.<sup>61</sup> The authors of this study, however, have not published data regarding reproductive outcome; information that will be invaluable in terms of counselling women regarding the fertility-sparing therapeutic options for symptomatic fibroids.

Until there are more data from larger randomized, prospective and comparative studies evaluating the effects of UAE on fertility and pregnancy, the procedure should not be offered routinely to women who wish to preserve their reproductive potential.

## SUMMARY

Current evidence for the relationship between fibroids and infertility remains inconclusive. However, studies investigating the link between fibroids and outcomes after the use of ART support the concept that both submucosal and intramural fibroids which distort the endometrial cavity have a negative effect on the outcomes of ART in terms of implantation, pregnancy, miscarriage and delivery rates. The effect of intramural and subserosal fibroids, in the absence of endometrial cavity distortion, is less clear. Overall, it is thought that submucosal, intramural and subserosal fibroids interfere with reproductive capacity in decreasing order of importance. Miscarriage rates after myomectomy appear to be reduced, although these rates remain higher than those of the normal age-matched female population.

Myomectomy for fibroid-associated infertility increases pregnancy rates such that approximately 50% of women undergoing the procedure for this problem subsequently conceive. The chosen technique for myomectomy should be individualized, depending on operator skill, fibroid characteristics and patient preferences. Hysteroscopic myomectomy should be considered when a woman has submucous fibroids. Open laparotomy and the laparoscopic approach tend to be used in the treatment of intramural and subserosal fibroids. All women should be counselled thoroughly regarding the risks of myomectomy when considering their therapeutic options. In particular, they should be made aware of the potential for surgical complications such as major haemorrhage and intra-operative conversion to hysterectomy, postoperative adhesion formation, uterine rupture during pregnancy or labour, and the risk of fibroid recurrence. They should also be made aware of the risks of fibroids during pregnancy. With this balanced approach, women should be able to make an informed choice regarding the subsequent management of their fibroid-associated infertility.

A number of antenatal complications have been reported in women with fibroids. In particular, the location of the myoma in relation to placental site is an important determinant of pregnancy outcome.

There are a number of contraceptive options available to women with fibroids. Choice should be individualized, taking into consideration the woman's preferences, age and fibroid characteristics.



UAE is becoming an increasingly popular therapeutic option for symptomatic fibroids. Its role in the treatment of fibroid-associated fertility, however, needs further investigation. Indeed, larger prospective trials with randomization processes and the presence of control groups (to eliminate confounding variables) are required in order to improve understanding of the true impact of fibroids on fertility. Until clear evidence-based guidelines are available, each woman's situation should be considered individually, with the benefits and risks of each potential therapeutic option being evaluated and an individual management plan being instituted thereafter.

### Practice points

- submucosal and intramural fibroids which distort the endometrial cavity have a negative effect on ART outcomes
- miscarriage rates decrease whilst pregnancy rates increase after myomectomy with ~50% of women conceiving after the procedure
- hysteroscopic myomectomy should be considered when a woman has submucous fibroids
- the pros and cons of myomectomy as well as fibroid-related risks in pregnancy should be discussed with all women who wish to consider fertility-sparing surgery
- a variety of contraceptive options are available to women with fibroids. Choice should be individualized
- UAE may be a potential alternative to myomectomy for the treatment of fibroid-associated infertility. Further studies are required before this treatment modality can be offered routinely to women with this problem

### Research agenda

- large prospective studies evaluating the relationship between fibroids and infertility with comparisons made with normal matched female controls
- randomized controlled trials of the different myomectomy techniques
- randomized controlled trials of myomectomy versus other uterine-sparing modalities such as UAE

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