Fibroids and fertility

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ABSTRACT

Uterine fibroids are the most common pelvic tumours in reproductive age women. Although most women with fibroids are fertile, fibroids may interfere with fertility secondary to anatomical distortion and alterations to the uterine environment. Whilst fibroids are associated with infertility in 5-10% of cases, they are estimated to be the sole cause of infertility in 2-3% of cases.

Observational epidemiological studies aimed at elucidating the relationship between fibroids and infertility are inconclusive due to methodological limitations. However, two main pieces of clinical evidence support the opinion that fibroids interfere with fertility. Firstly, in IVF treatment, women with fibroids have an adverse pregnancy outcome. Available evidence suggests that submucosal and intramural fibroids interfere with fertility in decreasing order of importance and subserosal fibroids have no impact on fertility. Secondly, although randomised studies are lacking, myomectomy appears to increase the pregnancy rate in women with submucosal fibroids and possibly in women with intramural fibroids.

Keywords fibroids; myomas; leiomyomas; infertility; IVF; miscarriage; myomectomy; laparoscopy; hysteroscopy; uterine artery embolisation.

INTRODUCTION

Leiomyomas are benign smooth muscle tumours that arise as a result of proliferation of myocytes. They are associated with variable amounts of collagen and fibrous tissue and it is this pathological feature which has led them to being termed as “fibroids”.

Uterine fibroids are the most common pelvic tumours, occurring in 30% of women over the age of 30 years. Their incidence increases with age, and they are more common in certain ethnic populations. The frequency of fibroids reported in literature varies widely due to differences in diagnostic tests used, populations studied and study design. The largest study to date, prospectively followed up 95 061 female nurses in America aged 25-44 years with questionnaires every two years, to determine the incidence of fibroids among premenopausal women by age and race 1. The diagnosis of fibroids was self reported and confirmed for a sample of cases. The crude incidence rate in this study was 12.8 per 1000 woman years. The standardised rates were much higher in black women than in white women, 30.6 and 8.9 per 1000 woman years respectively. Even after adjusting for variables such as body mass index, infertility and contraception, the rates among black women were significantly higher than those amongst white women (RR 3.25; 95% CI 2.71-3.88). Another large American survey included 1364 women aged 35–49 years who were randomly selected from an urban health plan. All recruited women underwent a transvaginal ultrasonography. The cumulative incidence of fibroids at 50 years of age was 70 and >80% for whites and African Americans respectively. The prevalence of fibroids is lower in Europe, although still remarkable from the healthcare point of view. An Italian cohort study documented an incidence of ultrasonographically detectable fibroids of 21% in a series of 341 unselected women residing in an urban zone aged 30–60 years2. A Swedish study recruiting 335 unselected subjects from an urban district and who accepted to undergo a transvaginal ultrasonography showed a prevalence of 3% in women aged 25–32 years and 8% in those aged 33–40 years 3.

Classification of fibroids

Fibroids are traditionally classified according to their anatomical location and are divided into submucous, intramural (the commonest site) or subserous fibroids. Submucous fibroids are those that distort the uterine cavity and are further divided into three subtypes: pedunculated (type 0), sessile with <50% intramural extension of the fibroid (type I) and sessile with ≥50% intramural extension (type II). Intramural fibroids are those which do not distort the uterine cavity and with <50% of the tumour protruding into the serosal surface of the uterus. Fibroids protruding ≥50% out of the serosal surface are considered subserosal, they are further divided into sessile or pedunculated. Fibroids are multiple in two thirds of cases.

Pathogenesis

The underlying pathogenesis and pathophysiology of leiomyomas is highly complex and is far from being completely understood. Cytogenetic examination of leiomyomas reveals that about 40% of them have chromosomal abnormalities 4. These consist of translocations, trisomies, deletions and rearrangements. The rest appear chromosomally normal but exhibit mosaicism within the monoclonal tumour. These karyotype abnormalities have been shown to correlate with fibroid size and site. The mechanisms that link the clinical phenotypes to their underlying genotypes vary. For example, translocations can either up regulate or down regulate a gene and its expressed protein, depending on where the gene sequence is spliced. Trisomies on the other hand generally increase gene expression, through increased gene dosing.
There has also been research looking into the familial inheritance of fibroids. Twin studies have shown a strong susceptibility to fibroid development, with monozygotic twins twice as likely to develop fibroids compared to dizygotic twins5. Familial clustering has been described and there are also several inherited disorders associated with fibroids.

Ovarian steroids oestrogen and progesterone are important in the pathogenesis of fibroids. It has been shown that fibroids have increased levels of oestrogen and progesterone receptors when compared to normal myometrium, and that they also have an increased expression of enzyme P450 that allows the cells to synthesise their own endogenous oestradiol. Oestrogens affect tumour growth by stimulating the proliferation of uterine smooth muscle cells. Progesterone on the other hand, through its production of the bcl-2 protein, increases tumour bulk, by inhibiting programmed cell death 6.

Growth factors increase smooth muscle proliferation and act in a paracrine or autocrine way. They are also responsible for the increase in the extracellular matrix (collagens, proteoglycans and fibronectin) associated with fibroids. The growth factors, transforming growth factor ß (TGFß), heparin binding factor and insulin like growth factor (IGF) have been identified in fibroids 7-9.

Clinical presentation

Despite the epidemiological burden, the majority of women with fibroids remain asymptomatic. Symptoms associated with fibroids include heavy and prolonged periods, pelvic pressure (from large fibroids), pain (resulting from torsion of a pedunculated fibroid or fibroid degeneration), urinary symptoms and constipation resulting from pressure by anterior and posterior fibroids. Whether fibroids cause infertility is the subject of considerable speculation.

Although most women with fibroids are fertile, fibroids may interfere with fertility secondary to anatomical distortion and alterations to the uterine environment. For those women afflicted with fibroids the risks of pregnancy wastage are also increased.

Fibroids and infertility

Whilst fibroids are associated with infertility in 5-10% of cases, they are estimated to be the sole cause of infertility in 2-3% of cases 10. The mechanism by which fibroids have a detrimental effect on fertility remains controversial with various theories being postulated. It has been suggested that the mechanism by which fibroids cause infertility are mechanical in nature. The tumours, if subendometrial or tubal in position, may directly block the passage of spermatozoa. Any tumour that distorts the shape or elongates the endometrial cavity may affect the establishment and maintenance of early pregnancy. Subendometrial tumours are capable of causing endometrial erosion with subsequent inflammation. This state alters the biochemical nature of intrauterine fluid and thus results in hostile environment for the spermatozoa. Alternatively, the subendometrial tumours may disrupt the endometrial blood supply, thus affecting nidation and sustenance of the early embryo. It has also been suggested that the hyperoestrogenic environment associated with fibroids may impair fertility. The effect of fibroids on fertility is dictated largely by the location and size of the fibroid. A decreased risk of fibroids in parous women when compared with nulliparous women has been repeatedly reported. The observation that parity is associated with a reduction in the risk of fibroids could be interpreted in two ways. Parity may be a protective factor or, alternatively, fertility may be partly compromised in women with fibroids. Studies investigating the association between fibroids and history of infertility may be of help in clarifying this issue, but unfortunately evidence on this regard is scarce. Overall, the question therefore remains about causality of the association. Does pregnancy protect from fibroid development or, conversely, do fibroids affect fertility.

Fibroids and IVF treatment outcome

The advent of assisted reproductive techniques (ART) and in particular of in vitro fertilisation (IVF) treatment has offered a useful tool to elucidate the relationship between fibroids and fertility. Results from IVF treatment provide precious information on the impact of uterine fibroids on embryo implantation.

There have been meta-analyses that have aimed to assess the impact of fibroids in IVF cycles. Somigliana et al (2007) published a meta-analysis of studies investigating the influence of fibroids located at different sites in IVF cycles11. Overall, their results showed that myomas negatively affect pregnancy rates. Although based on a small number of studies, submucous fibroids appeared to strongly interfere with the chance of pregnancy: OR (95% CI) for conception and delivery being 0.3 (0.1-0.7) and 0.3 (0.1-0.8) respectively. The impact of intramural fibroids was less dramatic although still statistically significant: OR (95% CI) for conception and delivery being 0.8 (0.6-0.9) and 0.7 (0.5-0.8) respectively. In a follow up study, intramural fibroids were shown to have an adverse effect on live birth rate after three consecutive cycles of IVF treatment 12. In general, these effects appeared to be more relevant when considering the delivery rate compared to the clinical pregnancy rate. Conversely, subserosal fibroids did not seem to affect pregnancy rates.

A recent updated systematic review by Pritts et al (2009)

results were consistent in showing that women with submucous fibroids, compared with infertile women without fibroids, demonstrated a significantly lower clinical pregnancy rate (RR 0.36; 95% CI 0.17-0.73), implantation rate (RR 0.28; 95% CI 0.12-0.64), and ongoing pregnancy/ live birth rate (RR 0.31; 95% CI 0.11-0.85) and a significantly higher spontaneous abortion rate (RR 1.67; 95% CI 1.37-2.05). Women with intramural fibroids also produced significantly lower clinical pregnancy rate, implantation rate and ongoing pregnancy/ live birth rate and a significantly higher spontaneous abortion rate. When women with subserous fibroids were compared with women without fibroids, no difference was observed for any outcome measure.

There is controversy on the impact of intramural fibroids that do not distort the uterine cavity on IVF treatment outcome. The first prospective observational study to report an adverse effect of such fibroids on outcome of IVF was reported by Hart et al (2001)14. However other studies failed to reproduce this significant effect. This was addressed in a recent systematic review Sunkara et al (2010) that looked at 19 observational studies comprising a total of 6087 IVF cycles15. Meta-analysis of these studies showed a significant decrease in live birth (RR 0.79; 95% CI 0.70-0.88) and clinical pregnancy rates (RR 0.85; 95% CI 0.77-0.94) in women with non-cavity distorting intramural fibroids compared to those without fibroids, following IVF treatment. However there is currently lack of evidence from randomised controlled trials whether any intervention in this group of women would improve the outcome of IVF treatment and restore live birth rates to the levels expected in women without fibroids.

Fibroids and Miscarriage

Buttram and Reiter (1981) in their review of published reports from 1957 to 1980 identified a reduction in miscarriage from 41% to 19%, in a cohort of women with symptomatic fibroids who underwent myomectomy10. Women in these studies had symptomatic palpable fibroids which differ to most infertility patients who have asymptomatic fibroids diagnosed on ultrasound examination. Li et al (1999) in a small uncontrolled series of 19 asymptomatic women who conceived with fibroids reported a reduction in miscarriage post myomectomy compared to the pre myomectomy rate (24% vs 60%) 16.

Benson et al (2001) reported a nearly two fold increase in miscarriage rate among 143 women with ultrasonographically identified fibroids in the first trimester, when compared to 715 age matched controls without fibroids (14% vs 7.6%, P<0.5)17. Although the fibroid size was not associated with the spontaneous loss rate, the presence of multiple fibroids was a significant predictor of spontaneous loss and among the 88 patients with only a single fibroid, there was no increased risk of spontaneous miscarriage compared with controls. A meta-analysis of controlled studies of intramural fibroids and IVF outcome which reported on spontaneous miscarriage showed a spontaneous miscarriage rate of 22% in women with intramural fibroids compared with 15.4% in the control group. Data are currently unavailable to evaluate the risk of miscarriage in women with submucosal fibroids. Casini et al (2006) reported miscarriages in five of nine (53%) pregnant women with submucosal fibroids and nine out of 21 women (43%) who underwent prior myomectomy18.

Fertility after myomectomy

Before the advent of less invasive options hysterectomy was the standard treatment for women troubled with fibroid associated symptoms. This option is understandably unacceptable for women wishing to conserve their fertility. Myomectomy which involves the removal of the fibroid with conservation of the uterus is the alternative surgical treatment option for women wishing to conceive. The procedure may be performed abdominally, laparoscopically or hysteroscopically. Several reviews of literature on pregnancy rates following myomectomy have been published. One of the early reviews focussing on studies published between 1933 and 1980 by Buttram and Reiter (1981) reported a 40% pregnancy rate following abdominal myomectomy (480 out of 1202 cases)10. This rate was 54% when patients with other causes of infertility were excluded. Another review by Vercellini et al (1998) confirmed this rate of success following myomectomy19. They reported a post surgical pregnancy rate of 57% across prospective studies. When including women with unexplained infertility, this rate was 61%. The advent of endoscopic surgery did not seem to modify this result. In a review by Donnez and Jadoul (2002) the pregnancy rate among women undergoing hysteroscopic and laparoscopic myomectomy was reported as 45% and 49% respectively20. These findings have further been confirmed by more recent and larger studies.

IVF outcome after myomectomy

Whilst there is a consistent body of literature on the adverse influence of fibroids on pregnancy outcome, the impact of myomectomy has been less extensively investigated. Narayan et al (1994) investigated the effect of myomectomy on a small group of women with submucosal fibroids (n=27)21. They found that the delivery rate was not significantly different in women who underwent myomectomy compared to women without fibroids (37% and 22% respectively, P=0.13). Surrey et al (2005) reported a pregnancy rate of 62% and 68% respectively in women operated for submucous fibroids and controls without fibroids following IVF treatment22. From these studies we can infer that although the overall evidence is scarce, previous myomectomy did not seem to negatively affect the pregnancy rate following IVF treatment.

A comparative study by Bulletti et al (2004) has provided further evidence on the effectiveness of myomectomy prior to IVF treatment23. Women with intramural and/ or subserosal fibroids with at least one lesion >5cm were allocated to myomectomy or no surgery based on their decision. They reported a live birth rate of 25% and 12% respectively in women who did and did not undergo surgery prior to IVF treatment.

Alternative treatments for fibroids

Several non-surgical approaches for the treatment of fibroid associated symptoms have emerged over the last several years with medical therapies as well as radiological interventions being proposed. GnRH agonists, the mainstay of medical therapy for fibroids, work by creating a hypogonadotrophic hypogonadal state and produce a significant reduction in uterine size. Their use in the context of infertility treatment remains questionable since ovulation is generally inhibited during treatment and the fibroids usually resume their pre-treatment dimension within a few months after stopping treatment. Other medical options that may reduce the size of fibroids include the androgenic steroid danazol, the antiprogestagen

mefipristone, the selective oestrogen receptor modulator raloxifene and the aromatase inhibitor fadrozole. Again because of reasons mentioned above their use in the context of infertility treatment remains questionable.

Non medical alternative treatment options for fibroids that have been developed over the recent past include fibroid embolisation, laparoscopic myolysis and MRI guided focused ultrasound. Data regarding pregnancy outcome with these interventions is scanty as most women who wish to conserve fertility have been excluded from these treatments due to safety concerns. Particularly, information on laparoscopic myolysis and MRI-guided focussed ultrasound are absolutely insufficient and the effect of these techniques on pregnancy therefore unknown. Recently, more evidence has been emerging on the effects of fibroid embolisation on pregnancy outcome. In a large survey of 1200 women, Walker and McDowell (2006) recorded 108 women who attempted to become pregnant of whom 31% were successful24. This rate appears to be lower than surgery, but it is difficult to draw definite conclusions as there was no control group. Data regarding pregnancy outcome following uterine artery embolisation tends to support a detrimental effect. An increased risk of miscarriage, preterm delivery, IUGR, abnormal placentation and postpartum haemorrhage has been reported. However, these results are controversial, as studies are underpowered. Based on present evidence fibroid embolisation cannot be recommended in daily clinical practice to women wishing to conserve their fertility.

Recently, uterine leiomyomas have become an attractive target for gene therapy. Gene therapy is the introduction of genetic material into patients' cells to achieve a therapeutic benefit. Gene therapy strategies include: mutation compensation of dysregulated genes; replacement of defective tumour-suppressor genes; inactivation of oncogenes; introduction of suicide genes; immunogenic therapy and anti angiogenesis based approaches. Preclinical studies of gene therapy have shown promising results in uterine leiomyomas and researchers are of the view that this approach is not far from becoming a medical reality.

Given the current evidence, clinicians should pursue a comprehensive and personalised approach taking into account the pros and cons of myomectomy, including the impact of fibroids on fertility, the risks associated with fibroids during pregnancy on one hand and the risks associated with surgery on the other hand.

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