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Fibroids and female reproduction: a critical analysis of the evidence

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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 the fibroids interfere with fertility. First, in IVF cycles, the delivery rate is reduced in patients with fibroids but is not affected in patients who have undergone myomectomy. Second, even if randomized studies are lacking, surgical treatment appears to increase the pregnancy rate: ~50% women who undergo myomectomy for infertility, subsequently conceive. Available evidence also suggests that submucosal, intramural and subserosal fibroids interfere with fertility in decreasing order of importance. Although more limited, some data supports an impact of the number and dimension of the lesions. Drawing clear guidelines for the management of fibroids in infertile women is difficult due to the lack of large randomized trials aimed at elucidating which patients may benefit from surgery. At present, physicians should pursue a comprehensive and personalized approach clearly exposing the pros and cons of myomectomy to the patient, including the risks associated with fibroids during pregnancy on one hand, and those associated with surgery on the other hand.

Keywords: fibroids; myomas; infertility

Introduction

The incidence and natural history of uterine fibroids remain not fully understood (Meyers *et al.*, 2002). The prevalence varies with age, being increased in the late reproductive period, and with ethnic origin, with African American women being disproportionately affected (Payson *et al.*, 2006). The reported frequency of the disease varies widely due to differences in study design. The best designed studies aimed at determining the prevalence of fibroids should apply ultrasound diagnosis in a randomly sampled population (Payson *et al.*, 2006). Few studies have used this methodology. A large US survey included 1364 women aged 35–49 years who were randomly selected from an urban health plan. All recruited women underwent a transvaginal sonography. The cumulative incidence of fibroids at 50 years of age was 70 and 80% for whites and African Americans, respectively (Baird *et al.*, 2003). An incidence rate of 34 cases per 1000 woman-years in US reproductive aged black women has been recently reported (Wise *et al.*, 2005). Women were recruited among subscribers to Essence magazine and data were collected through a questionnaire. Although that study has the merit of recruiting a large cohort of unselected women, the presence of fibroids was however not systematically investigated through ultrasonography. The prevalence of the disease is lower in Europe, although still remarkable from a healthcare point of view (Borgfeldt and Andolf, 2000; Heinemann *et al.*, 2003). 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 years (Marino *et al.*, 2004). 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 (Borgfeldt and Andolf, 2000).

Fortunately, despite this impressive epidemiological burden, the vast majority of fibroids are asymptomatic and do not require treatment. When symptomatic, the most common symptom is menorrhagia or hypermenorrhea (Marino *et al.*, 2004). Less frequently, women present because they feel a lump or a 'pelvic fullness'. This latest situation is generally determined by large fibroids (Hart, 2003). Rarely, urinary

symptoms can arise from anterior myomas, constipation can occur with those that are posterior and acute pain can result when degeneration or torsion of a pedunculated fibroid occurs (Stewart, 2001).

In asymptomatic cases, an expectant management is suitable considering that no effective medical options have been identified and that clinically relevant growth of the lesions is uncommon and unpredictable (Stewart, 2001). Whereas medical therapies may be of value in the short-term treatment of fibroids-associated abnormal bleeding, a long-term benefit on the dimension of the lesions has not been documented (Stewart, 2001; Mayonda *et al.*, 2004). Overall, there is a general consensus that the surgical approach is a more realistic alternative. If the fibroids are mainly intracavitary (submucosal), they can be effectively resected hysterocopically. Conversely, intramural or subserosal lesions should be treated by laparotomy or laparoscopy (Donnez and Jadoul, 2002; Mayonda *et al.*, 2004). Long-term results of these techniques are good even if recurrences are not rare. In recent years, alternative treatments such as bilateral uterine artery embolization (fibroid embolization), laparoscopic myolysis and resonance magnetic imaging (RMI)-guided focused ultrasound have gained some favour in the management of fibroids (Donnez *et al.*, 2000; Pron *et al.*, 2003; Olive *et al.*, 2004; Wallach and Vlahos, 2004; Worthington-Kirsch *et al.*, 2005; Goldberg and Pereira, 2006; Smart *et al.*, 2006; Stewart *et al.*, 2006). Data on pregnancy outcome following these procedures are however still scanty.

Childlessness is a life crisis and impaired fertility has been reported to affect 10–15% of couples (Evers, 2002). A critical and still unsolved question in this field is the relationship between fibroids and infertility. This issue is assuming increasing relevance considering that, in the developed world, there is the tendency to start a family at an age when natural female fertility is in decline and the incidence of fibroids is increasing. As a consequence, the proportion of infertile women diagnosed with fibroids is expected to rise and, if a detrimental effect on fertility could be definitively held, affected women would have to be treated. This may have important economic and clinical consequences considering in particular costs and possible complications associated with treatment. Given this scenario, we believe that it is essential to clarify whether these tumours affect fertility and, if so, which kind of lesions deserves treatment. Therefore, we performed a systematic literature review in order to define rational and effective therapeutic options in different clinical conditions.

Materials and Methods

We identified all English language medical papers published in the period 1990–2006 by means of the PubMed electronic database using the following search terms; myoma, myomata, leiomyoma, leiomyomata, fibroid, fertility, infertility, IVF, *in vitro* fertilization, ICSI, intracytoplasmatic sperm injection, ART, assisted reproductive technology, pregnancy, miscarriage, abortion, delivery and implantation. Cross-references picked up during the review search were also selected if they were not included initially. Both prospective and retrospective articles were considered. Studies presented at meetings or congresses, with only abstracts available, were not included. Data pooling was performed using the Statistics Package for Social Sciences (SPSS 14.0, Chicago, IL, USA).

Diagnosis and classification of fibroids

The diagnosis of fibroids is generally suspected on the basis of palpation of an enlarged irregular uterine contour on pelvic examination. Ultrasonography is typically used to confirm the diagnosis. Several publications have shown that ultrasound detection of myomas is highly sensitive (90–100%) and that it also has good specificity (87–98%), positive predictive value (81–93%) and negative predictive value (98–100%) (Fedele *et al.*, 1991; Cicinelli *et al.*, 1995; Indman, 1995; Becker *et al.*, 2002). Even if sonography is generally performed using transvaginal probes, a complementary transabdominal evaluation may be of value in selected cases such as in large-volume uteri (Vitiello and McCarthy, 2006). When the relationship between the myoma and the uterine cavity is unclear, a fluid-contrast ultrasound (sonohysterogram) can generally distinguish submucosal from intramural lesions (Cohen and Valle, 2000).

In recent years, magnetic resonance imaging (MRI) has gained popularity. However, it does not add clinically relevant information in most cases. Ultrasonography appears to be as efficient as MRI in fibroid detection and essentially as good for assessing their size and location if uteri have less than five lesions (Dueholm *et al.*, 2002). Conversely, when the number of lesions is higher, MRI exceeds ultrasound's technical limitation in precise fibroid mapping and characterization.

A significant issue in the field of fibroid identification is related to the necessity of ruling out a diagnosis of adenomyoma. Even if this condition is uncommon in women younger than 40 years old (Vercellini *et al.*, 2006), the differential diagnosis with fibroids is crucial since the treatment and prognosis of the two conditions may differ (Farquhar and Brosens, 2006). Ultrasonography is generally used for the differential diagnosis. Several publications have shown that ultrasound detection of adenomyomas is adequately sensitive (65–87%) and that it also has good specificity (88–98%), positive predictive value (74–93%) and negative predictive value (88–99%) (Fedele *et al.*, 1992; Huang *et al.*, 1995; Botsis *et al.*, 1998; Bazot *et al.*, 2001). The main sonographic markers for the differentiation of an adenomyoma from a fibroid are the absence of a lesion margin and the presence of lacunae (Botsis *et al.*, 1998). When doubts persist, however, MRI may reliably discriminate between the two conditions (Farquhar and, Brosens, 2006; Tamai *et al.*, 2006).

Fibroids are traditionally classified according to their anatomical location and are divided in submucous, intramural or subserosal locations (Bajekal and Li, 2000). Unfortunately, there is a lack of consensus as to the precise definition of these categories. This renders comparison among studies an arduous task. In a review of the literature, Bejakal and Li (2000) support the following definitions: submucous fibroids are those that distort the uterine cavity and are further divided into three subtypes: pedunculated (type 0), sessile with intramural extension of fibroid $<50\%$ (type I) and sessile with intramural extension $\geq 50\%$ (type II) (Wamsteker *et al.*, 1993). Intramural fibroids are those which do not distort the cavity and with $<50\%$ of the tumour protruding into the serosal surface of the uterus. Fibroids protruding $\geq 50\%$ out of the serosal surface are considered subserosal. They are further divided into sessile or pedunculated (Bajekal and Li, 2000).

Regardless of the precise definitions used, two major limits of this anatomic classification should be considered. First, the focus

is on the 'lesion' rather than on the 'uterus'. Fibroids are not always isolated as there are often several coexistent lesions. In case of multiple myomas, a detailed 'mapping' of each lesion is valuable from a surgical point of view, but may not always define a precise clinical situation. Moreover, this classification does not take into consideration the dimension of fibroids. This is an important limitation, since the size of the lesions varies widely and it is reasonable to assume that this may have a clinical impact. Since the thickness of a normal uterine wall is ~15–20 mm, it is expected that all fibroids which do not distort the uterine cavity and with a mean diameter of >40 mm should be classified as subserosal. Thus, even if a lesion takes up the entire uterine wall, it would have to be defined as subserosal, a category that is believed to have little impact on fertility.

Rationale of the association between fibroids and infertility

Associations that are not supported by a clear biological rationale are generally explained by biases rather than by causality. Unfortunately, poor attention has been paid to the mechanisms through which fibroids may determine subfertility. Moreover, results from experimental studies are sometimes conflicting. Despite these limitations, several mechanisms by which fibroids may reduce fertility have been proposed. It is generally believed that fibroids may interfere with sperm migration, ovum transport and embryo implantation (Richards *et al.*, 1998). Detrimental effects on these phenomena may be mediated by alteration of the uterine cavity contour causing mechanical pressure or by the occurrence of abnormal uterine contractility. In addition, local inflammation associated with the presence of submucosal fibroids may result in a hostile endometrial environment that impairs sperm transport and embryo implantation (Richards *et al.*, 1998). An inadequate blood supply to the endometrium has also been advocated to explain reduced embryo implantation (Ng and Ho, 2002). If fibroids are localized near the cervix or near the tubal ostia, the anatomical distortion may reduce access to the tubes by ejaculated sperm, whereas large corneal lesions might impair ovum retrieval by the tubes (Oliveira *et al.*, 2004).

Case series: a misleading estimation of the problem

Recent reviews focusing on the relationship between fibroids and infertility reported that these lesions may be responsible for only 2–3% of infertility cases (Donnez and Jadoul, 2002; Manyonda *et al.*, 2004; Benecke *et al.*, 2005; Rackow and Arici, 2005; Practice Committee of the ASRM, 2006). The paper that is generally cited to give an epidemiological estimate of the impact of fibroids on infertility is the review published by Buttram and Reiter (1981) more than 25 years ago. In this study, indications for surgery of 1698 patients operated for fibroids were examined and a history of infertility was present in 464 (27%) of them. However, this rate was not used to evaluate the impact of fibroids on infertility. The authors stated that the rate of myomectomy among major operations specifically performed for enhancement of fertility would be more appropriate to assess this impact. From their personal experience, it emerged that of 677 of such operations performed over a 10-year period only 16 (2.4%) involved myomectomy in patients in whom no other cause for infertility was found. Based on this rate, the authors concluded that uterine leiomyoma alone are an infrequent cause of infertility. In line with this finding, Verkauf (1992) successively reported that only 1% of 339 infertility laparotomies between 1981 and 1990 required myomectomy for otherwise unexplained infertility.

We are not convinced that these studies provide a reliable estimate of the real relationship between fibroids and infertility. Routine diagnostic evaluations performed in subfertile couples were not listed and criteria used to include a couple in a specific diagnostic group were not specified. This may significantly impact the frequency of patients in whom 'no other causes for infertility was found'. It is noteworthy that the predictive value of infertility assessments is low. In a provocative study, Guzick *et al.* (1994) performed a standardized infertility evaluation in 32 fertile and 32 age-matched infertile couples. At least one 'abnormal' infertility test was found in 69% of fertile and 84% of infertile couples. A further limitation of the results reported by Buttram and Reiter (1981) and by Verkauf (1992) is that the rate was calculated in a group of patients undergoing surgery for infertility. The belief of involved physicians regarding the possible association between fibroids and infertility is expected to strongly influence this rate. In other words, the more physicians consider fibroids a cause of infertility, the highest is the rate of myomectomy performed to improve fecundity. Finally, the use of epidemiological data obtained prior to 1990 on the relationship between fibroids and infertility is debatable because the scenario has changed since the eighties. The advent of new instruments such as transvaginal sonography and the widespread diffusion of endoscopic procedures such as laparoscopy or hysteroscopy has improved our diagnostic ability and modified surgical indications.

The use of care-seeking populations to infer the impact of fibroids on infertility is overall deleterious as selection biases may play a crucial role. More reliable insights may be obtained by cross-sectional studies in unselected patients who were prescribed transvaginal sonography. However, this study design has been performed rarely (Borgfeldt and Andolf, 2000; Wegienka *et al.*, 2003; Marino *et al.*, 2004) and infertility was unfortunately never assessed.

Case-control and cohort studies: the need to consider infertility as the illness and fibroids as a risk factor

The two keystone observational study designs currently used to investigate causal associations are case-control and cohort studies. In an effort to clarify the relationship between fibroids and infertility, insights from studies aimed at assessing the association between these two conditions should be considered. Studies which have evaluated parity and history of infertility in patients with and without fibroids will be discussed first.

A decreased risk of fibroids in parous women when compared with nulliparous has been repeatedly reported (Ross *et al.*, 1986; Parazzini *et al.*, 1988, 1996, 2004; Lumbiganon *et al.*, 1996; Marshall *et al.*, 1998; Sato *et al.*, 2002; Van Voorhis *et al.*, 2002; Chen *et al.*, 2003; Wise *et al.*, 2004). Inconsistent findings have been reported by a few authors but this may have been due by type II errors since their studies were underpowered to evaluate this specific issue (Samadi *et al.*, 1996; Luoto *et al.*, 2000; Faerstein *et al.*, 2001; Marino *et al.*, 2004). Results from studies focusing on the relationship between fibroids and parity are

Table 1: Main results from selected studies investigating the association between fibroids and parity

Study	Study design	Number of cases	Parity	History of infertility
Ross *et al.* (1986)	Case-control	535	0.5 (0.3–0.8)	
Parazzini *et al.* (1988)	Case-control	275	0.6 (0.4–0.9)	
Lumbiganon *et al.* (1996)	Case-control	910	0.8 (0.7–0.8)	
Parazzini *et al.* (1996)[a]	Case-control	621	0.6 (0.4–0.7)	2.0 (1.1–3.7)
Samadi *et al.* (1996)	Case-control	201	0.8 (0.5–1.4)	
Marshall *et al.* (1998)	Cohort	3006	0.7 (0.6–0.7)	1.3 (1.2–1.4)
Luoto *et al.* (2000)	Case-control	100	1.3 (0.6–2.7)	
Chen *et al.* (2001)	Case-control	317	0.3 (0.2–0.5)	
Faerstein *et al.* (2001)	Case-control	318	1.1 (0.7–1.8)	1.2 (0.8–1.8)
Sato *et al.* (2002)	Case-control	144	0.3 (0.2–0.5)	
Van Voorhis *et al.* (2002)	Case-control	169	0.8 (0.6–1.0)	
Marino *et al.* (2004)	Cohort	73	1.3 (0.6–2.6)	
Wise *et al.* (2004)	Cohort	2279	0.7 (0.6–0.8)	0.9 (0.8–1.1)
Parazzini *et al.* (2004)[a]	Case-control	843	0.7 (0.6–0.9)	

Data are reported as OR, RR or IRR (95% CI). [a]The study from Parazzini *et al.* (2004) is an extension of the one published in 1996.

summarized in Table 1. It is noteworthy that the four largest investigations on this topic lead to extremely similar results. In a prospective cohort study recruiting >3000 patients, Marshall *et al.* (1998) documented a relative risk (RR) for fibroids in parous women of 0.7 (95% confidence interval, CI, 0.6–0.7). In another prospective cohort study including 2279 cases, Wise *et al.* (2004) showed an incidence rate ratio (IRR) of 0.7 (95% CI 0.6–0.8) in parous when compared with nulliparous women. The results of the two largest case-control studies are in line with these findings. Lumbiganon *et al.* (1996) observed that parity was associated with an odds ratio (OR) for the presence of fibroids of 0.8 (95% CI 0.7–0.8). Parazzini *et al.* (2004) documented that the OR for fibroids progressively decreases with parity, being 0.7 (95% CI, 0.5–0.9) in women with one child and 0.5 (95% CI 0.4–0.7) in those with 3 or more children.

The observation that parity is associated with a reduction in the risk of fibroids may 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 a history of infertility may be of help in clarifying this issue. Unfortunately, evidence on this regard is scarce. Results from studies investigating this association are also summarized in Table 1. Of note, none of these studies has adequately controlled for other possible causes of infertility. Even if there is a *prima facies* care for an increased frequency of infertility among cases, results are not consistent. In particular, the two largest available cohort studies showed conflicting results. While Marshall *et al.* (1998) observed a RR for fibroids of 1.3 (95% CI 1.2–1.4) in patients reporting a history of infertility, Wise *et al.* (2004) failed to confirm this association (IRR = 0.9; 95% CI 0.8–1.1). Nevertheless, when restricting the analysis to hysterectomy-confirmed cases, a positive albeit not statistically significant association emerged (IRR = 1.3; 95% CI 0.9–1.8). Further, properly designed studies are required to definitively clarify this aspect.

Overall, the question remains about causality of the association. Does pregnancy protect from fibroid development or, conversely, do fibroids negatively affect fertility? In this context, it is mandatory to underline that from our perspective, fibroids would have to be considered as a risk factor whereas infertility would represent the illness. Observational studies focusing on fibroids as an illness are inevitably less informative. The demonstration that nulliparity or a history of infertility is associated with the presence of fibroids would not definitively support that these lesions can cause infertility for two reasons. First, selection bias may play a crucial role. How were patients selected? Since infertility is a strong determinant for seeking care, the proportion of infertile patients among cases is expected to be higher even if fibroids do not influence fertility. Second, the demonstration of an association between fibroids and a history of infertility cannot be used to support causality. This is a common problem in studies investigating associations, but this point represents a major concern in this context since it is more difficult to assess whether the exposure (fibroids) precedes the illness (infertility) or vice versa.

In order to gain insights into the association between fibroids and infertility, a more appropriate study design would be a case-control study where infertile women are cases, whereas fertile women are controls. Cohort studies comparing fertility in women with and without fibroids would also be of value even if, for obvious reasons, this type of study is difficult to carry out and it has thus not yet been performed in unselected women seeking conception. There is only one study that has investigated the chances of pregnancy in a series of 168 patients with anovulatory dysfunction undergoing ovarian hyperstimulation. The cumulative delivery rate in women with fibroids ($n = 34$) and in controls ($n = 130$) did not differ significantly (33 and 44%, respectively) (Wang *et al.*, 2001). However, selection biases and the relatively small sample size do not allow definite conclusions.

The IVF model: a surrogate but precious tool

The advent of assisted reproductive techniques (ART) and in particular of IVF has offered a useful tool to elucidate the relationship between fibroids and infertility. Indeed, results from IVF cycles may provide precious information on the impact of myomas on embryo implantation.

To our knowledge, 17 studies have investigated the outcome of IVF–ICSI cycles in women with and without fibroids (Seoud *et al.*, 1992; Farhi *et al.*, 1995; Eldar-Geva *et al.*, 1998; Ramzy *et al.*, 1998; Stovall *et al.*, 1998; Dietterich *et al.*, 2000; Healy, 2000; Hart *et al.*, 2001; Jun *et al.*, 2001; Surrey *et al.*, 2001; Check *et al.*, 2002; Ng and Ho, 2002; Yarali and Bukulmez, 2002; Oliveira *et al.*, 2004; Wang and Check, 2004; Gianaroli *et al.*, 2005; Ng *et al.*, 2005; Khalaf *et al.*, 2006). From a methodological point of view, these studies should be considered cohort studies where fibroids represent the exposure (risk factor) and failure to achieve pregnancy is the illness. However, results from these studies are not consistent. This may be related to differences in study design. Indeed, inclusion and exclusion criteria,

Table 2: Selected studies evaluating the influence of fibroids on IVF outcome

Study	Study design	Number of cases	Number of controls	Fibroid dimension (cm)	Number of fibroids	Fibroid localization	Data presented separately for			
							SM	IM	SS	SS-IM
Seoud *et al.* (1992)	Retrospective	24	124	3.0 ± 1.5	n.r.	SS-IM				X
Farhi *et al.* (1995)	Retrospective	172	127	n.r.	n.r.	SM-IM-SS	X			X
Eldar-Geva *et al.* (1998)	Retrospective	106	318	2.6 ± 0.7	1.7 ± 0.4	SM-IM-SS	X	X	X	X
Stovall *et al.* (1998)	Retrospective	91	91	n.r.	n.r.	IM-SS				X
Ramzy *et al.* (1998)	Retrospective	39	367	3.5 ± 0.9	1.1 ± 0.5	IM-SS				X
Dietterich *et al.* (2000)	Prospective	9	11	n.r.	2.8 ± 1.4	IM-SS				X
Hart *et al.* (2001)	Prospective	112	322	2.3 ± 1.1	1.8 ± 0.8	IM		X		
Jun *et al.* (2001)	Retrospective	114	406	Median 1.5 (IQR = 1.0–2.3)	n.r.	SM-IM-SS				
Surrey *et al.* (2001)	Retrospective	73	327	n.r.	n.r.	IM		X		
Check *et al.* (2002)	Prospective	61	61	1.5 ± 0.7	2.1 ± 1.4	IM		X		
Ng and Ho (2002)	Prospective	77	312	Median 2.1 (range 1.0–6.1)	n.r.	IM-SS				X
Yarali and Bukulmez (2002)	Retrospective	77	271	Range: 0.5–10.0	Range: 1–8	IM-SS		X	X	X
Oliveira *et al.* (2004)	Retrospective	245	245	1.9 ± 1.3	2.0 ± 0.4	IM-SS		X	X	X
Wang and Check (2004)	Prospective	49	73	Below 30 mm	n.r.	IM-SS				X
Ng *et al.* (2005)	Prospective	48	47	Median 2.4 (range: 1.8–6.1)	n.r.	IM-SS				X
Gianaroli *et al.* (2005)	Retrospective	129	129	1.8 ± 1.4	2.5 ± 2.8	IM		X		

IM, intramural; IQR, interquartile range; SM, submucosal; SS, subserosal; n.r., not reported.

characteristics of myomas (size, number and precise location), diagnostic instruments used to determine site of fibroids, control group and study power all differ.

To our knowledge, three meta-analyses that have aimed to assess the impact of fibroids in IVF cycles are reported in the literature. Pritts (2001) documented a significant negative impact of submucosal fibroids on pregnancy rate (RR = 0.3; 95% CI 0.1–0.7) but failed to observe any relevant impact of fibroids located at other sites. Results from Donnez and Jadoul (2002) are in line with these findings. Conversely, Benecke *et al.* (2005) reported a negative impact also for intramural fibroids with an OR of 0.7 (95% CI 0.5–0.9). We performed an updated meta-analysis of studies investigating the influence of fibroids located at different sites in IVF cycles. Two studies on this topic were excluded since they reported a re-analysis of the same cases (Healy, 2000; Khalaf *et al.*, 2006). Included studies are shown in Table 2. We considered two outcomes: clinical pregnancy rate and delivery rate. Results from this meta-analysis are shown in Table 3. Overall, the results support the opinion that myomas negatively affect pregnancy rate. Although based on a small number of studies, submucosal lesions appear to strongly interfere with the chance of pregnancy: the common OR (95% CI) for conception and delivery is 0.3 (0.1–0.7) and 0.3 (0.1–0.8), respectively. The impact of intramural myomas is less dramatic even if also statistically significant: the common OR (95% CI) for conception and delivery is 0.8 (0.6–0.9) and 0.7 (0.5–0.8), respectively. In general, these effects appear to be more relevant when considering the delivery rate rather than the clinical pregnancy rate. Conversely, subserosal lesions do not seem to play a role.

Whereas previous meta-analyses consistently showed a detrimental effect of submucosal but not subserosal fibroids, conclusions regarding intramural lesions have been conflicting. The two initial meta-analyses failed to document a harmful effect (Pritts, 2001; Donnez and Jadoul, 2002). The Practice Committee of the American Society for Reproductive Medicine (2006) recently supports this conclusion. On the contrary, results from the meta-analysis of Benecke *et al.* (2005) are in line with our findings showing a lower pregnancy rate in women with intramural fibroids. Discrepancies are due to the higher number of studies included in this latter study and in our analysis. By improving the statistical power, the mild but significant detrimental effect of intramural fibroids has emerged.

Two limitations of studies focusing on IVF should be considered. First, they can do no more than evaluate the impact of fibroids on embryo implantation. Possible detrimental effects on tubal transport of oocytes and/or embryos are overcome by the technique. Second, recent findings suggest that the size of the fibroids is positively related to implantation failure, in particular when the diameter of the lesion exceeds 4 cm (Oliveira *et al.*, 2004). The mean or median diameter of the fibroids included in

Table 3: Meta-analyses on the influence of fibroids on IVF outcome according to the localization of the lesions

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

[a] Included studies are reported in Table 2.

studies on IVF and fibroids is rarely above 3 cm (Table 2). Indeed, the policy of the units reporting on the influence of fibroids on IVF outcome is generally to recommend surgery for lesions exceeding 5 cm in diameter. Thus, it may be speculated that the detrimental effect that emerges from studies investigating pregnancy rate in women undergoing IVF is an underestimation of the real impact of fibroids.

Fertility after myomectomy

Since epidemiological evidence on the relationship between fibroids and infertility remains nebulous, some authors have tried to disentangle this issue focusing on the pregnancy rate following myomectomy. Although this approach is scientifically flawed, it has the merit to be easily performed. As a consequence, it has been used in a large number of studies. The success rate however has varied widely among series. This may be related to differences in the characteristics of the myomas (size, number and precise location), the presence of other causes of infertility, the sample size and the duration of follow-up.

Several reviews of the literature on the pregnancy rate following myomectomy have been published and may be helpful in estimating the real rate of success of the intervention. Focusing on studies published between 1933 and 1980, Buttram and Reiter (1981) reported a 40% pregnancy rate following abdominal myomectomy (480 out of 1202 cases). This rate increased to 54% when patients in whom all other causes of infertility were ruled out. A more recent comprehensive review of articles published between 1982 and 1996 on the success rate after abdominal myomectomy confirmed this rate of success. The post-surgical pregnancy rate across prospective studies was 57% (95% CI 48–65). When focusing on women with otherwise unexplained infertility, this rate was 61% (95% CI 51–70) (Vercellini *et al.*, 1998). The advent of endoscopic surgery does not seem to have modified this result. Donnez and Jadoul (2002) recently performed a literature review on both prospective and retrospective studies published between 1988 and 2001. The pregnancy rate in patients undergoing hysteroscopic and laparoscopic/abdominal myomectomy was 45% (95% CI 40–50) and 49% (95% CI 46–52), respectively. More recent large series have confirmed these findings (Di Gregorio *et al.*, 2002; Campo *et al.*, 2003; Damiani *et al.*, 2003; Landi *et al.*, 2003; Soriano *et al.*, 2003; Liu *et al.*, 2004; Marchionni *et al.*, 2004; Kumakiri *et al.*, 2005). Considering hysteroscopic myomectomy, there is one study that also included a control group of infertile women with a normal cavity. A significant increased pregnancy rate was observed in patients who underwent resection of fibroids >2 cm (Varesteh *et al.*, 1999). Laparoscopic and laparotomic surgeries appear to have a similar rate of success but larger studies are warranted before drawing definite conclusions (Seracchioli *et al.*, 2000; Landi *et al.*, 2003; Malzoni *et al.*, 2003; Hurst *et al.*, 2005; Griffiths *et al.*, 2006).

Despite a large number of series reporting on the pregnancy rate after myomectomy, randomized studies are lacking. A recent cochrane review on this issue failed to identify any randomized trial comparing surgery to expectant management (Griffiths *et al.*, 2006). To our knowledge, there is only one comparative study investigating the chances of pregnancy in women undergoing laparoscopic myomectomy and in a control group of unoperated patients (Bulletti *et al.*, 1999). Inclusion criteria were recurrent miscarriage and/or infertility. Patients with causes of infertility other than fibroids were excluded. Allocation was done using stratification criteria for myoma dimension and location in order to ensure similar distribution of cases in the two study groups. There were 106 women who underwent myomectomy and 106 who did not receive treatment. Patients were followed for nine months after allocation. A higher delivery rate was observed in the surgical group (42 versus 11%, $P < 0.001$). It is noteworthy that the pathological condition of the recruited patients was remarkable, with the vast majority of patients (76%) having three or more myomas, with at least one larger than 6 cm. Unfortunately, the study was not randomized and the authors did not report the proportion (and pregnancy rate) of women complaining about infertility in the two groups. Firm conclusions therefore cannot be drawn.

IVF outcome after myomectomy

While there is a consistent body of literature on the influence of fibroids on IVF outcome, the impact of previous myomectomy has been less extensively investigated. This point may be of interest for at least two reasons. First, it may indirectly provide further evidence on the influence of fibroids on fertility. Based on the previously-mentioned observation that the presence of fibroids negatively affect pregnancy rate, the documentation that previous myomectomy is associated with an outcome similar to that of women without fibroids would constitute further evidence supporting a negative impact of these lesions. Second, the demonstration that previous myomectomy does not negatively affect pregnancy rate would support the notion that surgery *per se* is not detrimental.

Three studies have evaluated the impact of previous myomectomy on IVF outcome (Seoud *et al.*, 1992; Narayan *et al.*, 1994; Surrey *et al.*, 2005). Seoud *et al.* (1992) compared cycles in patients with previous myomectomy ($n = 121$) to controls without myomas ($n = 2018$). The delivery rate in the two groups was 16 and 24%, respectively ($P = 0.08$). Narayan *et al.* (1994) investigated the effect of myomectomy in a small group of patients operated on for submucosal fibroids ($n = 27$). The delivery rate was not significantly different when compared with a group of unoperated patients without fibroids (37 versus 22%, $P = 0.13$). Finally, Surrey *et al.* (2005) recently report IVF outcome in patients operated for submucosal fibroids. The pregnancy rate in operated patients and in the control group was 68 (69/101) and 62% (900/1448), respectively ($P = 0.24$). Overall, even if the available evidence is still scanty, previous myomectomy does not appear to negatively affect the chances of pregnancy in IVF cycles.

A recent comparative study has provided further evidence on the effectiveness of myomectomy prior to IVF (Bulletti *et al.*, 2004). Patients selected for the procedure who were diagnosed with intramural-subserosal fibroids with at least one lesion with a mean diameter >5 cm were informed about the pros and cons of myomectomy. Patients decided on their own whether to undergo surgery and were divided into two groups ($n = 84$ each) with similar characteristics. The cumulative delivery rates in women who did and did not undergo surgery was 25 and 12%, respectively ($P = 0.01$) (Bulletti *et al.*, 2004).

Expectant management versus myomectomy: clinical aspects

An important albeit poorly considered issue is related to the complications that may be associated with the presence of fibroids during pregnancy on one hand and to the intervention of myomectomy on the other hand. This information may play a critical role in guiding clinical decisions.

Fibroids and pregnancy

It has been claimed that the hormonal milieu of pregnancy can determine a rapid growth of fibroids and increased symptoms (Muram *et al.*, 1980). However, one prospective study showed that growth is usually seen only in the first trimester, and many uterine myomas, particularly larger ones, often get smaller late in pregnancy (Lev-Toaff *et al.*, 1987). More recently, a prospective and properly designed study documented that only in a minority of patients (15%) did fibroids grow during pregnancy (Strobelt *et al.*, 1994). Overall, the clinical importance of the influence of pregnancy on the growth of myomas seems to be limited (Ouyang *et al.*, 2006).

It is commonly believed that fibroids increase the miscarriage rate. In case-control studies, a history of miscarriage is more frequently reported by affected patients (Lumbiganon *et al.*, 1996; Sheiner *et al.*, 2004). However, as previously discussed, this study design may be misleading in this context. Data from cohort studies may be more informative. Two large controlled cohort studies have investigated the association between fibroids and miscarriage (Exacoustos and Rosati, 1993; Benson *et al.*, 2001). In the first study, the abortion rates in the fibroid ($n = 492$) and in the control groups ($n = 12216$) were 7.7 and 6.8%, respectively (not significant) (Exacoustos and Rosati, 1993). Conversely, the second study, which was specifically designed to address this issue, documented a rate of spontaneous pregnancy loss in women with fibroids ($n = 143$) that was almost twice the rate of loss in the control group ($n = 715$) (14.0 versus 7.6%, $P < 0.05$) (Benson *et al.*, 2001). It is noteworthy that none of these studies recruited patients prior to conception. It may thus be speculated that, if fibroids actually increase the rate of abortion, a consistent proportion of cases are not included in studies recruiting women who were still pregnant since patients with an early miscarriage may not refer. These studies would thus underestimate the association. The relatively low rates of miscarriage reported in the two above-mentioned cohort studies support this criticism.

Two further indirect evidences sustain a possible increased risk of abortion in women with fibroids. First, as previously mentioned, insights from IVF cycles suggest that the negative impact of fibroids is more important when considering the delivery rate rather than the pregnancy rate (Table 3). Second, a strong reduction of the miscarriage rate has been documented after myomectomy (Buttram and Reiter, 1981; Li *et al.*, 1999; Vercellini *et al.*, 1999; Campo *et al.*, 2003; Marchionni *et al.*, 2004; Skokeir, 2005). These studies are discussed in the following section.

There is a general consensus that fibroids lead to pelvic pain in a consistent proportion of pregnant patients. Available cohort controlled studies strongly confirmed this opinion. Rice *et al.* (1989) reported that this complaint occurred in 15.1% of women with fibroids, while no cases were described in the control group ($P < 0.001$). Similarly, Exacoustos and Rosati (1993) reported an incidence of pain in 12.6 and 0.1% in women with and without fibroids, respectively ($P < 0.001$).

Fibroids may also increase the rate of several pregnancy complications during the second and third trimesters (Ouyang *et al.*, 2006). We identified seven retrospective controlled cohort studies reporting on this point (Rice *et al.*, 1989; Davis *et al.*, 1990; Exacoustos and Rosati, 1993; Vergani *et al.*, 1994; Coronado *et al.*, 2000; Sheiner *et al.*, 2004; Qidwai *et al.*, 2006). Evaluated outcomes and reported results were not consistent. This might be related to differences in study design and statistical power. The most relevant complications and the relative entity of the association are illustrated in Table 4. The study from Davis *et al.* (1990) was not included in this table since it was underpowered to provide meaningful information. Overall, even if most pregnancies are unaffected by fibroids, there is a general consensus that their presence is associated with a higher rate of complications. In particular, the most convincing evidence is in favour of an association with placental abruption, placenta

Table 4: Selected controlled cohort studies on the incidence of obstetric complications in pregnant women with fibroids

Study	Rice *et al.* (1989)	Exacoustos and Rosati (1993)	Vergani *et al.* (1994)	Coronado *et al.* (2000)	Sheiner *et al.* (2004)	Qidway *et al.* (2006)
Number of cases	93	492	183	2065	690	401
Preterm delivery	4.0 (2.4–6.7)	1.0 (0.8–1.4)	0.9 (0.5–1.5)	1.5 (1.2–1.9)	1.4 (1.1–1.7)	1.5 (1.1–2.0)
PROM		1.0 (0.7–1.4)	0.5 (0.2–1.4)	1.8 (1.2–2.7)	1.8 (1.4–2.4)	1.1 (0.7–1.8)
IUGR	0.8 (0.2–3.2)	1.3 (1.0–1.7)	0.7 (0.3–1.6)	2.0 (1.5–2.6)	3.7 (2.6–5.3)	
Chorioamnionitis						0.8 (0.5–1.3)
Placenta previa			1.0 (0.1–7.0)	1.8 (1.1–3.2)	3.9 (1.9–8.0)	1.9 (1.0–3.4)
Placental abruption	16.5 (8.1–33.7)	8.9 (6.1–13.1)	2.6 (0.6–10.9)	3.9 (1.6–9.2)	2.6 (1.6–4.2)	0.8 (0.3–2.7)
Fetal malpresentation	2.0 (1.0–3.7)			4.0 (3.1–5.2)	5.0 (4.0–6.4)	1.6 (1.1–2.4)
Cesarean delivery	2.5 (1.6–3.7)	1.1 (0.9-1.3)	2.0 (1.4–2.8)	6.4 (5.5–7.5)	6.7 (5.5–8.1)	1.6 (1.3–2.1)
Post-partum hemorrhage			0.7 (0.4–1.2)	1.6 (0.8–3.3)	1.5 (0.5–4.5)	2.6 (1.5–4.3)
Retained placenta			0.8 (0.1–5.6)		2.7 (1.2–6.0)	2.7 (1.2–6.0)
Malformation				1.9 (1.3–2.8)		
Infant/perinatal death				1.2 (0.8–1.8)	1.4 (0.7–2.8)	
Puerperal infection		8.9 (5.1–15.5)				1.1 (0.6–2.1)

Data are reported as OR (95% CI). PROM, premature rupture of membranes; IUGR, intra-uterine growth restriction.

previa, intrauterine growth restriction (IUGR) and fetal malpresentation. Not surprisingly, a higher rate of caesarean section has also been repeatedly reported.

A role of fibroids in the determinism of pregnancy complications is also supported by the demonstration that the dimension and location of the lesions play a role in this regard (Rice *et al.*, 1989; Exacoustos and Rosati, 1993; Vergani *et al.*, 2004; Qidway *et al.*, 2006). In particular, the location of the myomas in relation to the placental site has been reported to be a significant clue to the outcome of pregnancy (Muram *et al.*, 1980; Rice *et al.*, 1989; Exacoustos and Rosati, 1993).

Myomectomy and pregnancy

No controlled study has been published regarding obstetric outcome in patients who have undergone myomectomy. A consistent number of case series on this topic has been reported but the lack of a control group does not allow reliable conclusions.

The risk of miscarriage does not appear to be increased in patients who have undergone myomectomy. On the contrary, several studies support the concept that the rate of pregnancy wastage significantly decreases after surgery. In a review of 1941 patients who underwent myomectomy, the spontaneous abortion rate improved from 41% prior to surgery to 19% following myomectomy (Buttram and Reiter, 1981). More recently, four independent studies used a similar study design to investigate the impact of intramural and/or subserosal fibroids in the miscarriage rate. Results from all these studies tend to confirm a strong benefit of surgery. In a series of 51 patients, Li *et al*. (1999) observed a significant reduction in the abortion rate from 60 to 24%. For a group of 36 women who underwent abdominal myomectomy with miscarriage as the only or main indication, Vercellini *et al.* (1999) similarly reported a relevant decreased rate of pregnancy loss after surgery (from 73 to 13%). Additionally, Campo *et al.* (2003) and Marchionni *et al.* (2004) observed a significant reduction in the abortion rate from 57 to 14% ($n = 41$) and from 69 to 25% ($n = 72$), respectively, after myomectony. Similar results have been reported after hysteroscopic myomectomy of submucosal fibroids. In a series of 29 women, the abortion rate decreased from 62 to 26% (Skokeir, 2005). Unfortunately, due to the lack of a control group, the study design of all these reports is inadequate to provide a definite answer to the question.

In a large retrospective study aimed at determining risk factors for extrauterine pregnancy during IVF cycles, Strandell *et al.* (1999) documented an increased risk of ectopic pregnancy (OR = 1.7) in women with previous myomectomy. Further evidence is however required prior to draw definite conclusions considering that this is an isolated report and the strength of the association is modest.

One of the major concerns about myomectomy is the low, albeit clinically relevant, risk of uterine rupture during pregnancy or labour. This complication has been repeatedly reported for myomectomy at both laparoscopy and laparotomy, but studies aimed at precisely quantifying this risk are scanty and controversial (Roopnarinesingh *et al.*, 1985; Dubuisson *et al.*, 2000; Hurst *et al.*, 2005; Serrachioli *et al.*, 2006). In a retrospective study carried out at the Trinidad Maternity, the rate of rupture observed at birth after myomectomy at laparotomy was 5.3% (95% CI 0.5–14.8) (Roopnarinesingh *et al.*, 1985). Whether or not the laparoscopic approach increases this risk is a matter of debate. While there are several case reports of uterine rupture after laparoscopic myomectomy, the precise entity of this risk is difficult to determine as these reports generally do not describe the incidence per number of procedures performed (Hurst *et al.*, 2005). Dubuisson *et al.* (2000) reported one case of uterine rupture out of 100 patients who delivered (1.0%, 95% CI 0.0–5.5), while Damiani *et al.* (2003) and Seracchioli *et al.* (2006) failed to document this complication in a series of 48 and 108 women, respectively. Regardless of the surgical approach, fear about the risk of uterine rupture certainly leads to a high rate of cesarean section in pregnant patients who previously underwent myomectomy.

On the other hand, surgery is not without complications. Even if very rare, major intraoperative and post-operative complications may occur. The former include bladder, bowel and ureteral injury, bleeding requiring transfusion and unintended conversion to hysterectomy. Major post-operative complications include hemorrhage requiring treatment, fistula, thrombosis and embolism (Altgassen *et al.*, 2006). Of relevance here is that the operation can be potentially harmful to reproductive capacity, owing to the risk of adhesion formation and endometrial cavity distortion (Tulandi *et al.*, 1993; Dubuisson *et al.*, 1998). Adhesions form in >90% of the cases at abdominal myomectomy. The incidence is highest with posterior uterine incisions and lower with fundal or anterior incisions (Tulandi *et al.*, 1993; Hurst *et al.*, 2005). The laparoscopic approach may reduce this complication but definite evidence is still lacking (Hurst *et al.*, 2005).

Alternative treatments for fibroids

The traditional treatment of fibroids has been surgery. Over the last several years, however, non-surgical approaches have begun to emerge. Medical therapies as well as radiological interventions have been proposed.

GnRH agonists, the mainstay of medical therapy for myomas, work by determining a hypogonadotropic hypogonadal state clinically resembling menopause. These agents produce a significant and rapid reduction in uterine size, generally by OR to 35–65%, but cannot be administered for more than 3–6 months (Stewart, 2001; Mayonda *et al.*, 2004). Their use in the context of infertility treatment is questionable since ovulation is generally impeded during treatment and the lesions resume their pretreatment dimension within few months after treatment suspension (Stewart, 2001; Mayonda *et al.*, 2004). Other medical options that may determine reduction in myoma size include the androgenic steroid danazol, the antiprogestagen mifepristone, the selective estrogen receptor modulator raloxifene and the aromatase inhibitor fadrozole (Olive *et al.*, 2004; Steinauer *et al.*, 2004; Bulun *et al.*, 2005; Ohara, 2005; Fiscella *et al.*, 2006). Again, the value of these therapies is questionable in the context of infertility treatment. The use of these agents interferes with fertility mechanisms and fibroids tend to resume their pretreatment dimension after suspension. There is no clinical data on the potential benefits of these therapies on pregnancy rate after suspension of treatment.

Non-medical alternative options have been developed over the recent past. They include fibroid embolization, laparoscopic myolysis and RMI-guided focused ultrasound (Donnez *et al.*, 2000; Olive *et al.*, 2004; Goldberg and Pereira, 2006; Smart *et al.*, 2006 Stewart *et al.*, 2006). Due to safety concerns, women who

desire to retain fertility are generally excluded from these treatments. As a consequence, data regarding pregnancy outcome is scanty. In particular, information on laparoscopic myolysis and RMI-guided focused ultrasound is absolutely insufficient and thus the effects of these techniques on pregnancy outcome remain unknown (Wallach and Vlahos, 2004). Conversely, more evidence has been recently cumulating regarding the effects of fibroid embolization. Overall, there are some concerns on this issue. In a large survey of 1200 patients, Walker and McDowell (2006) recorded 108 women who attempted to become pregnant, of whom 33 were successful (31%). This rate appears to be lower when compared with surgery but the study was not controlled and it is difficult to draw definite conclusions. Data regarding pregnancy outcome tends to support a detrimental effect of fibroid embolization. Specifically, an increased risk of miscarriage, preterm delivery, IUGR, abnormal placentation, malpresentation and post-partum hemorrhage has been reported (Fauconnier *et al.*, 2004; Olive et al., 2004; Pron *et al.*, 2005; Goldberg and Pereira, 2006; Walker and McDowell, 2006). However, results are controversial, as studies are generally underpowered and not controlled. Larger series are warranted prior to draw definite conclusions. Overall, fibroid embolization cannot be recommended in everyday clinical practice in women who desire to retain fertility.

Conclusions

Epidemiological evidence on the relationship between infertility and fibroids is not conclusive due to methodological limitations. Conversely, two main pieces of clinical evidence support the vision that fibroids may interfere with fertility. First, insights from the IVF model suggest a detrimental effect on implantation: the delivery rate is reduced in patients with fibroids, while it is not affected in patients who had undergone myomectomy. Second, even if randomized studies are lacking, surgical treatment appears to increase the pregnancy rate: about one of two women undergoing myomectomy for infertility subsequently conceives.

A major point to be considered in this area is related to the severity of the disease. Uterine leiomyomata is a heterogeneous condition varying from a small single subserosal fibroid to multiple large lesions that radically distort pelvic anatomy. Whereas the effect on fertility of the former is irrelevant, the latter strongly impairs the probability of conception. Available evidence suggests that submucosal, intramural and subserosal fibroids interfere with fertility in decreasing order of importance. Although more limited, some evidence also supports an impact of the number and the dimension of the lesions.

The notion that fibroids affect fertility has to be translated into clinical practice. Drawing clear guidelines for the management of fibroids in infertile women is however difficult due to the lack of large randomized trials aimed to elucidate which patients may benefit from surgery. The Practice Committee of the American Society for Reproductive Medicine (2006) recommends surgical treatment after complete evaluation of other potential factors of infertility. We believe that this view is somehow simplistic and we suggest to adopt a comprehensive and personalized approach in the decision-making process to identify the best option for the woman. At least four points have to be considered: (i) the age of the woman; (ii) the location, dimension and number of the fibroids; (ii) the concomitant presence of fibroids-related symptoms such as menorrhagia or hypermenorrhea and (iv) the presence of other causes of infertility and whether or not there is an indication to IVF. As previously underlined, in some cases the decision may be an easy task. In contrast, many women may fall in a 'grey' zone. In these cases, we suggest to adopt a personalized attitude clearly exposing the pros and cons of myomectomy to the patient, including risks associated to fibroids during pregnancy on one hand and those associated with surgery on the other hand (summarized in Table 5). The ultimate aim is to assume a shared decision with the patient.

Table 5: Summary of the main detrimental effects of myomas and myomectomy

Myomas	Myomectomy
Infertility	Surgical complications
Importance of location, dimension and number	Adhesion formation
Pregnancy complications	Uterine rupture during labour or pregnancy
Miscarriage	
Pelvic pain	
Placental abruption	
Placenta previa	
IUGR	
Malpresentation	

IUGR, intra-uterine growth restriction.

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