

# Fibroids, infertility and pregnancy wastage

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**Uterine fibroids are often found in women of reproductive age. Different types of fibroids may affect reproductive outcome to a different extent, with submucous, intramural and subserosal fibroids being (in decreasing order of importance) a cause of infertility and pregnancy wastage. Fibroids may also produce a number of complications during pregnancy. Women who are scheduled for assisted conception should be advised to have submucous and possibly intramural fibroids removed prior to IVF. Large fibroids (>5 cm), wherever their location, should be considered individually, with the reproductive history being an important consideration. Miscarriage rates are significantly reduced following myomectomy. Open myomectomy should be the route of choice when there are large subserosal or intramural fibroids, multiple fibroids or entry into the uterine cavity is to be expected. Proper assessment of the benefits and risks of surgery for individual patients should be carefully considered before offering a procedure.**

*Key words:* assisted reproduction/fibroids/infertility/myomectomy/reproductive outcome

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## Introduction

Uterine fibroids (leiomyomata, myomata) are a fairly frequent occurrence in a woman in the reproductive age group. Various prevalence rates have been quoted in literature ranges from 20–50%, based on post-mortem studies (Novak and Woodruff, 1979). Therefore, it is not surprising to detect uterine fibroids in women with a history of infertility or reproductive wastage from time to time. Whether this represents an incidental finding or a cause of reproductive failure will be discussed in this article.

## Classification of fibroids

Different types of fibroids may affect reproductive outcome to a different extent and the results of surgical intervention for each type of fibroid may vary. Fibroids may be classified as submucous, intramural or subserous (Tindall, 1987).

Unfortunately, there is a lack of consensus in the literature as to exactly how these categories are defined. A suggested classification for fibroids, according to location in the uterus is as follows:

### **Submucosal**

The European Society of Hysteroscopy has agreed on a classification for submucous fibroids (Wamsteker *et al.*, 1993). A submucous fibroid is one that distorts the uterine cavity. It is further divided into three subtypes: type 0 = pedunculated fibroid without intramural extension, type I = sessile with intramural extension of fibroid <50% and type II = sessile with an intramural extension of  $\geq 50\%$ . The degree of intramural extension can be assessed by ultrasonography, or by hysteroscopy by observing the angle between the fibroid and the endometrium at the attachment to the uterine wall.

### **Intramural**

A fibroid which does not distort the uterine cavity and with <50% of its protruding into the serosal surface of the uterus is considered to be an intramural fibroid.

### **Subserosal**

A fibroid is considered subserosal if >50% of the fibroid protrudes out of the serosal surface of the uterus. A subserosal fibroid may be sessile or pedunculated.

## Fibroids and infertility

The degree to which fibroids contribute to infertility is controversial. Fibroids were implicated as the sole factor of infertility in <10% of infertility cases (Wallach and Vu, 1995). It is well accepted that the anatomical location of the fibroid is an important

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factor, with submucous, intramural and subserosal fibroids being in decreasing order of importance, in causing infertility. Fibroids of >5 cm and, those located near the cervix or near the tubal ostia, are more likely to pose a problem (Ubaldi *et al.*, 1995). Submucous or intramural myomata may cause dysfunctional uterine contractility which may interfere with sperm migration, ovum transport or nidation (Hunt and Wallach, 1974; Buttram and Reiter, 1981; Vollenhoven *et al.*, 1990). In addition, uterine myomata may be associated with pre-conception (implantation) failure or gestation discontinuation due to focal endometrial vascular disturbance as well as endometrial inflammation, secretion of vasoactive substances, or an enhanced endometrial androgen environment (Deligdisch and Lowenthal, 1970; Buttram and Reiter, 1981)

### Fibroids and reproductive outcome

It has been observed that ~1–4% of pregnancies are associated with fibroids (Muram *et al.*, 1980; Rice *et al.*, 1988; Exacoustos and Rosati, 1993). Overall, 80% of uterine fibroids observed during pregnancy remain the same size or become smaller during the course of pregnancy (Muram *et al.*, 1980; Lev-Toaff *et al.*, 1987).

Fibroids may produce a number of complications during pregnancy. Firstly, it may result in a miscarriage. The miscarriage rate is likely to be higher if implantation occurs over a submucous fibroid. Fibroids in close proximity to the placenta are more likely to be associated with early pregnancy bleeding and spontaneous miscarriage. The location of a fibroid in relation to the placenta appears to be more important than the size (Muram *et al.*, 1980; Rosati *et al.*, 1989). Intramural and subserosal fibroids of <3 cm are often considered to be not clinically significant (Rice *et al.*, 1988; Rosati *et al.*, 1989). However, we have observed a first trimester miscarriage rate of 40% and a second trimester miscarriage rate of 17% with intramural and subserosal fibroids (Li *et al.*, 1999).

A recent study suggested that a previous myomectomy increased the incidence of ectopic pregnancy following IVF (Strandell *et al.*, 1999). Apart from miscarriage and ectopic pregnancy, fibroids may also produce a number of other complications during pregnancy: preterm labour, abdominal pain due to degeneration, abruptio, intrauterine growth retardation, obstructed labour and post-partum haemorrhage.

Several mechanisms have been postulated to explain the pregnancy wastage associated with fibroids (Te Linde, 1985; Wallach and Vu, 1995). In a study which examined the ultrastructure of the host myometrium of fibromyomatous uteri (Richards *et al.*, 1998), the sacrolemmal dense bands of host myometrial myocytes were found to be of significantly greater length than that of normal myometria with a corresponding decrease in the number of caveolae, making the host myometria structurally abnormal. This specific abnormality may affect calcium metabolism in these tissues, which in turn may cause abnormal contractions leading to reproductive wastage or infertility.

### Impact of fibroids on assisted conception

There are altogether five retrospective cohort studies that examined the impact of fibroids on the results of assisted conception. The results for each type of fibroid are separately

analysed in Table I. The pregnancy rate per embryo transfer in submucous, intramural and subserosal fibroids were 9, 16 and 37% respectively, compared with an average of 30% in control subjects. The results are consistent with the commonly held view that submucous fibroids have the most detrimental effect on pregnancy rate, intramural fibroids a modest impact and subserosal fibroids have the least impact on pregnancy rate.

The miscarriage rate in the various types of fibroids were: submucous, 40% (two out of five cases), intramural, 33% (three out of nine cases), and subserosal, 33% (eight out of 24 cases) compared with a total of 183/1115 (16.4%) among all the control subjects in all five series. Whilst it appears to show, once again, a trend similar to that of pregnancy rate, i.e. in descending order of importance: submucous, intramural and subserosal fibroid, the numbers are too small on the whole for a firm conclusion to be made.

It is not possible, from the available literature data, to analyse the impact of the size and number of fibroids on the outcome of assisted conception because the information was not clearly described in the reported series.

From the above data, it appears that patients should be advised to have submucous and possibly intramural fibroids removed prior to IVF, whereas those with subserosal fibroids may be reassured that it is unlikely to have an adverse impact on the implantation rate and live birth rate. However, large fibroids (>5 cm) should be considered individually, with the reproductive history, e.g. miscarriage, being an important consideration (Li *et al.*, 1999).

### Factors affecting conception and reproductive outcome following myomectomy

#### Age of patient

Age was found to have a clinically significant impact on pregnancy rate, with a lower spontaneous or assisted conception pregnancy rate when the woman is >35 years (Ramzy *et al.*, 1998; Li *et al.*, 1999). It is well accepted that older women are less likely to conceive when compared with younger women (Berkeley *et al.*, 1983; Acien and Quereda, 1996).

#### History of infertility

Some authors (Acien and Quereda, 1996; Li *et al.*, 1999) have found that a history of infertility negatively affected the conception rate following myomectomy. The pregnancy rate was reduced by as much as 20% in the presence of additional infertility factors (Vercellini *et al.*, 1998).

#### Miscarriage

Whilst uterine fibroids are associated with an increased rate of first and mid-trimester pregnancy loss, this rate is significantly reduced following a myomectomy (Li *et al.*, 1999; Vercellini *et al.*, 1999a).

#### Size of fibroid

An earlier review (Buttram and Reiter, 1981) suggested that a uterine size of >10 weeks prior to the operation was associated with a poorer reproductive outcome after myomectomy. One group (Sudik *et al.*, 1996) found that the pregnancy rate after myomectomy for fibroids with a volume of >100 ml (~8 cm

**Table I.** Outcome of assisted conception treatment in women with fibroids

Author	Subjects with submucous fibroids (n)	Embryo transfer	PR	LB	MR	Control subjects (n)	Embryo transfer	PR	LB	MR
Farhi <i>et al.</i> (1995)	18	55	5/55 (9)	3/5 (60)	2/5 (40)	50	127	32/127 (25)	24/32 (75)	8/32 (25)
Eldar Geva <i>et al.</i> (1998)	9	10	1/10 (10)	NS	NS	249	318	98/318 (30)	78/98 (80)	20/98 (20)
Total	27	65	6/65* (9.2)	3/5 (60)	2/5 (40)	299	445	130/445 (29.2)	102/130 (78.5)	28/130 (21.5)
Subjects with subserosal fibroids						Control subjects				
Eldar Geva <i>et al.</i> (1998)	46	55	9/55* (16)	6/9 (67)	3/9 (33)	249	318	98/318 (30)	78/98 (80)	20/98 (20)
Subjects with intramural fibroids						Control subjects				
Seoud <i>et al.</i> (1992)	11	24	10/24 (42)	5/10 (50)	5/10 (50)	1357	2018	586/2018 (29)	484/586 (83)	102/586 (17)
Eldar Geva <i>et al.</i> (1998)	33	41	14/41 (34)	11/14 (79)	3/14 (21)	249	318	98/318 (30)	78/98 (80)	20/98 (20)
Total	44	65	24/65 (37)	16/24 (67)	8/24 (33)	1606	2336	684/2336 (29)	562/684 (82)	122/684 (18)
Subjects with intramural subserosal fibroids						Control subjects				
Ramzy <i>et al.</i> (1998)	39	39	15/39 (39)	9/15 (60)	6/15 (40)	367	367	123/367 (34)	104/123 (85)	19/123 (15)
Stovall <i>et al.</i> (1998)	91	91	34/91 (37)	30/34 (88)	4/34 (12)	91	91	48/91 (53)	44/48 (92)	4/91 (4.4)
Farhi <i>et al.</i> (1995)	28	86	25/86 (29)	15/25 (60)	10/25 (40)	50	127	32/127 (25)	24/32 (75)	8/32 (25)
Total	158	216	74/216 (34)	54/74 (73)	20/74 (27)	508	585	203/585 (35)	172/203 (85)	31/203 (15)

PR=pregnancy rate; LB=livebirth rate (per pregnancy); NS=not specified; MR=miscarriage rate.

\*Statistically different from controls.

diameter) were significantly higher than those of smaller fibroids. They suggested that larger fibroids are more likely to interfere with fertility than smaller ones, hence removal of a large fibroid could result in restoration of fertility. A more recent review of 27 studies (Vercellini *et al.*, 1998) could find no conclusive evidence either way on whether number, size or location of fibroids prior to myomectomy influenced post-operative pregnancy rates. Uterine size was not considered to be a factor in determining reproductive outcome in two other studies (Rosenfield, 1986; Smith and Uhler, 1990).

#### Number of fibroids

The pregnancy rate was significantly lower in women when more than five fibroids were removed (Sudik *et al.*, 1996). This reduction may be attributed to the increased number of incisions and subsequent adhesions. In a study of 50 patients desiring pregnancy (Berkeley *et al.*, 1983), it was found that women who

had multiple fibroids removed had difficulty in conceiving post-operatively. On the other hand other authors (Rosenfield, 1986; Li *et al.*, 1999; Vercellini *et al.*, 1999a), noted no difference in pregnancy rate after myomectomy, irrespective of the size or number of fibroids removed.

#### Location of fibroids

The location of the fibroid did not appear to affect the pregnancy rate after the operation, whether or not it was submucous in location and regardless of whether or not the uterine cavity was entered (Berkeley *et al.*, 1983; Rosenfield, 1986; Acien and Quereda, 1996; Sudik *et al.*, 1996).

#### Operation to conception interval

Most women who conceive, do so within 1 year after a myomectomy (Berkeley *et al.*, 1983; Rosenfield, 1986; Sudik *et al.*, 1996). This is an important consideration when the clinician

**Table II.** Reproductive outcome after myomectomy via laparotomy in women with infertility/pregnancy wastage

Author	Subjects <i>n</i>	Size cm/g	Site <i>n</i> (%)	Number (per pregnancy)	Pregnancy rate <i>n</i> (%)	Livebirths
Berkeley <i>et al.</i> (1983)	50	average 283 g	any	average 4.6	25/50 (50)	20/25 (80)
Garcia and Tureck (1984)	15	≥5 cm	SM	≥1	8/15 (53)	7/8 (88)
Rosenfield (1986)	23	3–14 cm	IM/SS	≥1	15/23 (65)	13/15 (57)
Smith and Uhler (1990)	32	average 284 g	any	average 5	16/32 (50)	12/16 (75)
Verkauf (1992)	26	>3	SS/IM	≥1	16/26 (62)	10/16 (63)
Gehlbach <i>et al.</i> (1993)	37	6–9	any	average 3	19/37 (51)	14/19 (65)
Sudik <i>et al.</i> (1996)	67	<5 (64) >5 (36)	SM (20) SS/IM (80)	<5 (65) ≥5 (35)	39/67 (58)	31/51 (61)
Acien and Quereda (1996)	40	2–16	any	1–14	27/40 (68)	25/27 (93)
Li <i>et al.</i> (1999)	51	<5 (20) >5 (80)	SS (20) IM (80)	<4 (82) >5 (12)	29/51 (57)	25/33 (76)
Vercellini <i>et al.</i> (1999a)	174	3–5 (27) >5 (73)	IM (78) SS (22)	<5 (86) >5 (14)	85/174 (49)	92/104 (88)
Total	465				279/465 (60)	249/314 (79)

SM = submucous; IM = intramural; SS = subserosal fibroids.

has to decide whether to operate on an asymptomatic woman who is not considering a pregnancy in the immediate future.

### Open myomectomy

Open myomectomy, i.e. removal of fibroid via laparotomy should be the route of choice when there are large subserosal or intramural fibroids (>7 cm), when multiple fibroids (more than five) are to be removed and when entry into the uterine cavity is to be expected.

The pregnancy rate after myomectomy reported in various retrospective studies (Table II) was 50–68%, with a spontaneous miscarriage rate of 6–40%, and a live birth rate of 57–93%, calculated as a percentage of the total number of pregnancies, rather than the number of subjects. Caesarean section was the mode of delivery in nearly 50% of women following a myomectomy (86/177). Two comprehensive reviews (Verkauf, 1992; Vercellini, 1998) suggest that >50% of women with infertility/reproductive wastage conceive after myomectomy. The short interval time between surgery and conception suggests that myomectomy has an important value in treatment of patients with fibroids and otherwise unexplained infertility (Verkauf, 1992).

### Hysteroscopic myomectomy

Neuwirth and Amin first suggested that hysteroscopic myomectomy may be the procedure of choice for treating submucosal myomata (Neuwirth and Amin, 1976). Of all myomata, ~5% were submucosal (Novak and Woodruff, 1979), although in selected groups this may be as high as 18% (Fedele *et al.*, 1991).

Compared with myomectomy via laparotomy, hysteroscopic myomectomy is associated with a lower risk of scar rupture during subsequent pregnancy and vaginal delivery, as any scar resulted does not involve the whole thickness of the uterine wall. Pelvic adhesions, which is a common occurrence following open myomectomy, is avoided.

The results of seven retrospective studies on the outcome of hysteroscopic myomectomy are summarized in Table III. The overall results, including conception rate (55%) and live birth rate (80%) are very similar to those of myomectomy via laparotomy. A significantly higher pregnancy and live birth rates were found when fibroids >2 cm were resected, compared with women who had fibroids <2 cm resected or women with normal uterine cavity (Varasteh *et al.*, 1999). In addition, a shorter interval from treatment to conception was noted in women with larger fibroids. No difference in spontaneous miscarriage rate was noted after treatment in these two groups. The pregnancy rate (10/22) was found to be highest when pedunculated submucous fibroids (Type 0) were resected (Vercellini *et al.*, 1999b). Large fibroids take longer to resect, require a very experienced surgeon and frequently require more than one operation to completely remove the fibroid. In their study, only one of six women with Type II submucous fibroids conceived (Vercellini *et al.*, 1999b). They suggested that an open myomectomy may be preferable to hysteroscopic resection when a predominantly intramural fibroid is to be removed.

Hysteroscopic myomectomy is a safe, effective and relatively simple surgical procedure for the restoration of fertility. However, large (>5 cm) Type II submucous fibroid may not be suitable for hysteroscopic surgery. If hysteroscopic surgery is considered in

**Table III.** Reproductive outcome after hysteroscopic myomectomy in women with infertility/pregnancy wastage

Author	Subjects <i>n</i>	Size cm	Pregnancy rate <i>n</i> (%)	Livebirths per pregnancy <i>n</i> (%)
Corson and Brooks (1991)	13	average <4	10/13 (77)	8/11 (73)
Valle (1990)	16	average 3.2	10/16 (63)	8/16 (80)
Goldenberg <i>et al.</i> (1995)	15	3–6	7/15 (47)	6/7 (86)
Hallez (1995)	32	1–6.5	18/32 (56)	21/23 (91)
Giatras <i>et al.</i> (1999)	41	average <4	25/41 (61)	23/25 (92)
Varasteh <i>et al.</i> (1999)	36	<4 <2 >2	19/36 (53) 4/12 (33) 15/24 (63)	13/19 (68) 3/4 (75) 10/15 (67)
Vercellini <i>et al.</i> (1999b)	45	<3.5	19/45(42)	14/21 (67)
Total	198		108/198 (55)	93/116 (80)

**Table IV.** Laparoscopic myomectomy: reproductive outcome in infertile women

Author	Subjects <i>n</i>	Size cm	Site	Number	Pregnancy rate <i>n</i> (%)	Live birth rate per pregnancy <i>n</i> (%)	Caesarean section rate <i>n</i> (%)
Dubuisson <i>et al.</i> (1996) <sup>a</sup>	21	5–10 (average 6.2)	IM	1–10 (average 2.2)	7/21(33.3)	5/7 (71)	4/5 (80)
Miller <i>et al.</i> (1996) <sup>a</sup>	40	4–10	IM/SS	<5	30/40 (75)	26/30 (87)	not stated
Darai <i>et al.</i> (1997) <sup>b</sup>	44	1–7	IM/SS (average 5.4)	1–7	17/44 (39) (average 1.5)	11/19 (58)	3/11 (27)
Seinera <i>et al.</i> (1997) <sup>b</sup>	34	3–8	IM/SS (average 4)	1–4	5/34 (15)	5/5 (100)	5/5 (100)
Ribeiro <i>et al.</i> (1999) <sup>b</sup>	28	4–13	IM (average 6)	≥1 =	18/26 (64)	14/18 (78)	8/14 (57)
Campo and Garcea (1999) <sup>a</sup>	24	3–10 (average 4.8)	IM/SS	1–8 (average 2.9)	13/24 (54)	11/13 (85)	5/11 (45)
Total	191	3–8			90/191 (47)	68/90 (76)	25/46 (54)

IM = intramural fibroid; SS = subserosal.

<sup>a</sup>Prospective study.

<sup>b</sup>Retrospective study.

this situation, laparoscopic control and the availability of a very experienced hysteroscopic surgeon is essential.

### Laparoscopic myomectomy

It is now possible to carry out laparoscopic myomectomy for subserosal or intramural fibroids. Whilst it is suggested that the laparoscopic approach is appropriate for pedunculated or subserosal fibroids (Nezhat, 1996), other authors (Wallach and Vu, 1995) commented that removal of asymptomatic pedunculated subserosal fibroids may not be justified, as these may not necessarily be the cause of infertility or recurrent miscarriage. Adequate closure of the myometrium is essential, to avoid the risk of uterine rupture in a future pregnancy (Dubuisson *et al.*, 1995). Laparoscopic myomectomy of an intramural fibroid requires a very experienced laparoscopic surgeon, otherwise intramural fibroids may be better

removed via laparotomy. In addition, uterine indentations at the sites of laparoscopic removal of intramural or deep subserosal myomata at second look laparoscopy have been reported (Nezhat *et al.*, 1991). Uterine fistulae have also been reported, in some cases, during follow-up of these patients (Nezhat *et al.*, 1992). This raised concerns about the potential compromise in the integrity of the uterine wall during subsequent pregnancies following laparoscopic myomectomy in infertile patients. There have been at least two reported cases of uterine rupture during the third trimester of pregnancy following the procedure (Harris, 1992; Dubuisson *et al.*, 1995). The reproductive outcome following laparoscopic myomectomy has been examined in six studies (Table IV). Pregnancy and live birth rates (47 and 76% respectively) are comparable with those after open and hysteroscopic myomectomy procedures. Once again, the majority (>80%) of women who conceive do so in the first year after myomectomy.

## Patient selection and counselling

It is important to carefully assess the benefits and risks of surgery before offering any procedure to a patient. A proper assessment of the patient is essential. A thorough work-up of the infertility/recurrent miscarriage problem should be carried out prior to the surgery. A detailed reproductive history and examination needs to be followed by investigations such as ultrasonography, laparoscopy, hysteroscopy and/or a hysterosalpingogram. This will help to ascertain the size, number and location of the fibroids in order to be able to arrive at the correct management option, including the choice of operation.

Women with infertility or a poor obstetric history are often desperate to consider any measure that may improve their reproductive outcome. Women should be thoroughly counselled and be fully informed about the various treatment options. Patient information leaflets should be readily available, to help reinforce verbal discussions. Clinicians should be able to discuss the expected success rates as well as possible complications.

## Conclusions

Fibroids are a fairly frequent occurrence in the reproductive age group and are exclusively responsible for both infertility and pregnancy wastage in a small (5%) but significant proportion of patients. Of women with infertility and uterine myomata, ~50% conceive after myomectomy. A slightly higher proportion of women with a history of recurrent pregnancy loss, conceive following myomectomy. More importantly, there is a highly significant reduction in early and mid trimester miscarriage rates. Evidence suggests that most women who wish to conceive are able to do so in the first year, with pregnancy rates dropping sharply after this time. If possible, therefore, the surgery should be timed to take place when a woman is ready to start a family. The site, number and size of the myomata as well as the expertise of the surgeon along with patient preference may all influence the management option. A submucous fibroid or an intramural fibroid distorting the uterine cavity, fibroids >5 cm and multiple fibroids are all indications for intervention in a woman considering a pregnancy. For relatively small (<5 cm) intramural or subserosal fibroids, the reproductive history is an important consideration in counselling the patient regarding the need for surgical intervention. Open myomectomy, i.e. removal of fibroid via laparotomy should be the route of choice when there are large subserosal or intramural fibroids (>7 cm), when multiple fibroids (>5) are to be removed and when entry into the uterine cavity is to be expected.

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