Human Reproduction Vol.17, No.6 pp. 1424–1430, 2002

DEBATE

What are the implications of myomas on fertility?

A need for a debate?

J.Donnez[1] and P.Jadoul

Department of Gynecology, Catholic University of Louvain, Cliniques Universitaires St-Luc, Avenue Hippocrate 10, 1200 Brussels, Belgium

[1]To whom correspondence should be addressed. E-mail: donnez@gyne.ucl.ac.be

In order to evaluate the relationship between leiomyomas and infertility, which remains a subject of debate, we have tried to evaluate the impact of myomas on fertility and pregnancy outcome in different conditions where myomas are implicated. Medline research was conducted of publications appearing between January 1988 and August 2001 on the subjects of myomas and myomectomy and their impact on fertility and pregnancy outcome in infertile women. A total of 106 manuscripts were consulted. The incidence of myomas in infertile women without any obvious cause of infertility is estimated to be 1–2.4%. The relationship between leiomyomas and infertility remains a subject of debate. The question is: do myomas influence fertility? We are obliged to conclude that the question remains. The absence of an answer to this crucial question is probably due to the fact that we have not yet conducted the appropriate prospective studies required to obtain any clear results.

Key words: fertility/hysteroscopy/laparoscopy/myomas

Introduction

Leiomyomas of the uterus are the most common solid pelvic tumours found in women and are estimated to occur in 20–50% of women with increased frequency during the late reproductive years (Verkauf, 1992). The incidence of myomas in infertile women without any obvious cause of infertility is estimated to be between 1 and 2.4% (Robert *et al*., 1974; Buttram and Reiter, 1981; Verkauf, 1992). The relationship between leiomyomas and infertility remains a subject of debate. To address this issue, we have tried to evaluate the impact of myomas on fertility and pregnancy outcome in different conditions where myomas are implicated. In an era of evidence-based medicine, we need a clear analysis of the literature. Can we draw any conclusions from what has been published or do we need to reconsider the whole problem?

Materials and methods

A Medline search was conducted for publications appearing between January 1988 and August 2001 on the subjects of myomas and myomectomy and their impact on fertility and pregnancy outcome in infertile women. A total of 106 manuscripts were consulted. All were included, even if the methodology was questionable. In our opinion, including and scrutinizing questionable articles is necessary to have total perspective on the debate.

Myomas and infertility

The central question in this debate is the following: 'Do women with myomas suffer from decreased fertility?' To put it in more practical terms we should ask: 'If we find a myoma in a woman with an infertility problem, can we conclude that there is a direct link between the myoma and the infertility and can we hope to improve fertility by removing the myoma?'

Different theories have been proposed to explain the effects of myomas on fertility. What are the mechanisms involved? It is generally accepted that the anatomical location of a fibroid is an important factor, with submucous, intramural and subserosal fibroids implicated, in decreasing order of importance, in causing infertility. Myomas may cause dysfunctional uterine contractility which may interfere with sperm migration, ovum transport or nidation (Hunt and Wallach, 1974; Buttram and Reiter, 1981; Vollen-Hoven *et al*., 1990). Myomas may also be associated with implantation failure or gestation discontinuation due to focal endometrial vascular disturbance, endometrial inflammation, secretion of vasoactive substances or an enhanced endometrial androgen environment (Deligdish and Lowenthal, 1970; Buttram and Reiter, 1981).

Ideally, to prove a relationship between fibroids and infertility, prospective randomized studies should be performed comparing women desiring pregnancy with and without myomas, in order to compare pregnancy rates and possibly the time needed to achieve pregnancy. Such studies were not encountered in our review. Another possibility would be to compare pregnancy rates between infertile women with and without myomas in whom other infertility factors have been excluded.

There is only one publication (Bulletti *et al.*, 1999) that compares spontaneous conception in infertile women with and

© European Society of Human Reproduction and Embryology

Table I. Pregnancy rate (PR) in women with fibroids distorting the cavity, in women with fibroids not distorting the cavity and in a control group (women without myomas)

	Distorted cavity		Not distorted cavity		Control group	
	PR%	*n*	PR%	*n*	PR%	*n*
Eldgar-Geva *et al.*, 1998	10	1/10	16.4	9/55	30	98/318
Stovall *et al.*, 1998	37	34/91	53	48/91		
Farhi *et al.*, 1995	9	5/55	29	25/88	25	32/127
Ramzy *et al.*, 1998	39	15/39	34	123/367		
Surrey *et al.*, 2001	50.7	37/73	58.4	191/327		
Jun *et al.*, 2001	30.5	43/141	41.6	169/406		
Total	9	6/65	33.5	163/487	40.4	661/1636

without myomas in whom andrological and tubal infertility factors have been excluded. The authors found a significant difference ($P < 0.002$) in pregnancy rates between infertile women with and without myomas (11 versus 25%). It is the only randomized prospective study to date and if it is to be believed, infertile women with myomas have better pregnancy rates after myomectomy (42%) than infertile women without myomas (25%), who in turn have better pregnancy rates than infertile women with untreated myomas (11%).

The methodology of this article is questionable as the follow-up is limited to 9 months. Moreover, the different groups are too small to draw any conclusion and the influence of the location and size of the myoma cannot be evaluated.

Myomas and IVF

Another way to approach the issue of the relationship between myomas and infertility is to assess the influence of myomas on implantation rates. IVF provides a good model to assess this influence, excluding other factors such as tubal or andrologic factors and allowing investigation of the influence of myomas on embryo implantation for embryos of the same 'quality'. One should note that IVF cannot assess the impact of myomas on sperm migration and ovum transport.

Seven manuscripts (Farhi *et al.*, 1995; Eldgar-Geva *et al.*, 1998; Ramzy *et al.*, 1998; Stovall *et al.*, 1998; Healy, 2000; Jun *et al.*, 2001; Surrey *et al.*, 2001) have compared the results of IVF in women with untreated myomas and without myomas. They showed a significant decrease in pregnancy rates in patients with a distorted uterine cavity (9% pregnancy rate) compared with patients without distortion of the cavity (29.1%) and patients without myomas (25.1%).

In a retrospective comparative study of patients with uterine fibroids and those without fibroids, Eldar-Geva *et al.* and Healy concluded that pregnancy and implantation rates were significantly lower in the groups of patients with intramural and submucosal fibroids, even when there was no deformation of the uterine cavity (pregnancy rate: 16.4 and 10% respectively versus 30% in the control group), but pregnancy and implantation rates were not influenced by the presence of subserosal fibroids (Eldar-Geva *et al.*, 1998; Healy, 2000).

In a non-randomized prospective case–control study, Stovall *et al.* concluded that myomas had a negative effect on implantation and pregnancy rates (37 versus 53%) (Stovall *et al.*, 1998).

Ramzy *et al.* concluded that the presence of a myoma up to 7 cm, which does not distort the uterine cavity, does not affect pregnancy rates in IVF (39 versus 34%) (Ramzy *et al.*, 1998).

Jun *et al.* found no significant differences in implantation rates and pregnancy outcome between women with myomas measuring <7 cm not distorting the uterine cavity and women without myomas (30.5 versus 41.6%) (Jun *et al.*, 2001). Surrey *et al.* concluded from their retrospective case–control study that live birth rates were not affected by the presence of intramural leiomyomas in IVF patients with hysteroscopically normal endometrial cavities (Surrey *et al.*, 2001).

When we compare these results, we can see that authors come to opposing conclusions. For some authors, myomas do not influence pregnancy rates if they have no repercussions on the uterine cavity (Farhi *et al.*, 1995; Ramzy *et al.*, 1998; Jun *et al.*, 2001; Surrey *et al.*, 2001). For others, the presence of a myoma, even one not distorting the cavity, decreases pregnancy rates (Edgar-Geva *et al.*, 1998; Stovall *et al.*, 1998; Healy, 2000).

How can we explain these differences? First of all, one should note the differences in pregnancy rates in the control groups between the different teams. Secondly, in our opinion, retrospective studies of small series have no medical value. If we conduct a meta-analysis of these studies (Table I), the pregnancy rate in women with fibroids distorting the cavity is 9%, while it is respectively 33.5 and 40% in women with fibroids not distorting the cavity and the control groups. Thirdly, the important differences observed between the different series raise the question of proper evaluation of the cases. In some series, the classification and the exact location of myomas is not clearly defined, casting doubts on the true value of the studies. Nevertheless, it seems reasonable to conclude that submucosal and intramural myomas distorting the uterine cavity impair implantation and pregnancy rates in women undergoing IVF.

Myomectomy and fertility outcome in infertile patients

The impact of fibroids on fertility was mainly evaluated indirectly by assessment of fertility after myomectomy. Does myomectomy improve pregnancy rates? Forty-six studies on fertility outcome after myomectomy in infertile patients have been published (Table II). Most of them are retrospective analyses. Some focus on a particular location of the myoma,

Table II. Pregnancy rates (PRs) after myomectomy

Author	Study	*n*	Myoma	Treatment	PR%	
					Lps/Lpt	Hsc
Starks, 1988	Prospective	32	SS, IM, SM	Lpt	62.5	
Brooks *et al*, 1989	Retrospective	t15	SM	Hsc		33.3
Gatti *et al*., 1989	Retrospective	30	–	Lpt	43.3	
Egwuatu, 1989	Retrospective	52	SS, IM, SM	Lpt	9.6	
Prien-Larsen and Kjer, 1989	Retrospective	33	–	Lpt	31	
Loffer, 1990	Retrospective	12	SM	Hsc		58.3
Vollen-Hoven *et al*., 1990	Prospective	13	–	Lpt	46	
Donnez *et al*., 1990	Retrospective	24	SM	Hsc		67
Valle, 1990	Retrospective	16	SM	Hsc		62
Corson and Brooks, 1991	Retrospective	13	SM	Hsc		76.9
Hucke *et al*., 1992	Retrospective	14	SM	Hsc		28.6
Verkauf, 1992	Retrospective	24	SS, IM, SM	Lpt	58.3	
Liu *et al*., 1993	Prospective	8	IM, SM	Lpt	75	
Gehlbach *et al*., 1993	Retrospective	37	SS, IM, SM	Lpt	57	
Tulandi *et al*., 1993	Prospective	26	SS, IM	Lpt	61.5	
Fayez and Dempsy, 1993	Retrospective	38	SS, IM, SM	Lpt	63	
Abramovici *et al*., 1994	Prospective	10	–	Lpt	50	
Nehzat *et al*., 1994	Retrospective	14	SS, IM, SM	LAM	28.3	
Sirjusingh *et al*., 1994	Retrospective	38	SS, IM, SM	Lpt	37	
Goldenberg *et al*., 1995	Retrospective	15	SM	Hsc	46.6	
Hallez, 1995	Retrospective	32	SM	Hsc	56	
Cravello *et al*., 1995	Retrospective	16	SM	Hsc	25	
Darai *et al*., 1996	Retrospective	52	SS, IM	Lpt, Lps	30.8	
Dubuisson *et al*., 1996	Prospective	21	>50 mm	Lps	33.3	
Ancien and Querada, 1996	Retrospective	20	SS, IM, SM	Lpt	15	
Hasson *et al*., 1992	Retrospective	17	SS, IM, SM	Lps	71	
Miller *et al*., 1996	Prospective	41	–	Lps	73.1	
Sudik *et al*., 1996	Retrospective	67	–	Lpt, Lps	58.2	
Darai *et al*., 1997	Retrospective	29	SS, IM, SM	Lps	48.2	
Kuhlman *et al*., 1997	Retrospective	41	–	Lpt, Lps	61	
Seineira *et al*., 1997	Retrospective	30	SS, IM, SM	Lps	16.7	
Preutthipan and Theppisai, 1998	Retrospective	12	SM	Hsc	16.7	
Campo and Garcea, 1999	Prospective	24	SS, IM	Lps	54.1	
Vercellini *et al*., 1999a	Retrospective	138	SS, IM	Lpt	55	
Vercellini *et al*., 1999b	Retrospective	40	SM	Hsc	37.5	
Giatras *et al*., 1999	Retrospective	41	SM	Hsc	60.9	
Varasteh *et al*., 1999	Retrospective	36	SM	Hsc	53	
Li *et al*., 1999	Retrospective	30	SS, IM	Lpt	43	
Ribeiro *et al*., 1999	Retrospective	28	>50 mm	Lps	64.3	
Serrachioli *et al*., 2000	Prospective	115	>50 mm	Lpt, Lps	54.8	
Dubuisson *et al*., 2000b	Retrospective	81	SS, IM	Lps	53	
Bernard *et al*., 2000	Retrospective	31	SM	Hsc	35.5	
Fernandez *et al*., 2001	Retrospective	59	SM	Hsc	27.1	
Dessolle *et al*., 2001	Retrospective	88	SS, IM	Lps	47.7	
Zollner *et al*., 2001	Retrospective	49	SS, IM, SM	Lpt, Lps, Hsc	41	
Rossetti *et al*., 2001	Retrospective	29	SS, IM	Lps	65.5	
Total		1631			49 (615/1255)	45 (168/376)
					48 (783/1631)	

SS = subserosal; IM = intramural; SM = submucosal; Lpt = laparotomy; Lps = laparoscopy; Hsc = hysteroscopy; LAM = laparoscopy-assisted myomectomy; – = not mentioned.

while others do not distinguish the type of myoma. The global pregnancy rate after myomectomy in infertile women, regardless of the kind of surgery undertaken, varies between 9.6 and 76.9%.

How can we explain this discrepancy? Considerable differences in results persist even when the different kinds of surgery are considered separately. After hysteroscopic myomectomy, pregnancy rates are between 16.7 and 76.9% and after laparoscopic or laparotomic myomectomy, between 9.6 and 75%.

On the other hand, the global pregnancy rate found in these 46 studies is 48% (783 pregnancies in 1631 subjects). The pregnancy rate after hysteroscopic myomectomy is 45% (168/376) and after laparoscopic or abdominal myomectomy, 49% (615/1255). The differences found with the same surgical approach show the influence of different factors on pregnancy rates: (i) age and other infertility factors; (ii) factors related to the myoma(s); and (iii) technical factors.

Age and other infertility factors

Factors not directly related to the technique used could interfere with pregnancy rates. Age >35 years and an association with other infertility factors decrease pregnancy rates (Ramzy *et al*.,

1998; Li *et al*., 1999; Vercellini *et al*., 1999a; Fauconnier *et al*., 2000; Zollner *et al*., 2001). In Fauconnier's study, fertility was found to be reduced in women who had associated tubal pathology, male or ovulatory factors (Fauconnier *et al.*, 2000). In this study, fertility only slightly declined in the group of women aged ⩾40 years. Other authors found no relationship between age and fertility after myomectomy (Gatti *et al.*, 1989; Gehlbach *et al.*, 1993). Vercellini *et al.* showed decreased pregnancy rates after myomectomy in women >35 years of age and when the duration of infertility before myomectomy exceeded 2 years (Vercellini *et al.*, 1999a).

Factors related to the myomas (number, volume, location)

With regard to the number of myomas, some authors showed a lower pregnancy rate when more fibroids were removed (Sudik *et al*., 1996; Dessolle *et al*., 2001), while others noted no difference (Vercellini *et al*., 1999a; Fauconnier *et al*., 2000; Rossetti *et al*., 2001). For Sudik *et al*. pregnancy rates were better after removal of myomas with a volume of >100 ml (±8 cm diameter) (Sudik *et al*., 1996). However, others found no difference according to myoma size (Vercellini *et al*., 1999a; Fauconnier *et al*., 2000; Rossetti *et al*., 2001).

Ancien and Querada, and Sudik *et al*. demonstrated no influence of myoma location (Ancien and Querada, 1996; Sudik *et al*., 1996). Fauconnier *et al*. found a lower pregnancy rate with posterior myomas (Fauconnier *et al*., 2000). Dessolle *et al*. showed better results when there was distortion of the uterine cavity before myomectomy (Dessolle *et al*., 2001). According to Fauconnier *et al*. prior deformation of the cavity did not influence pregnancy rates after myomectomy, but the presence of menometrorrhagia before myomectomy seemed to be associated with better results of myomectomy on fertility outcome (Fauconnier *et al*., 2000).

Altogether, the conclusions on the influence on pregnancy rates of the number, size and location of myomas and their capacity for distorting the cavity are somewhat contradictory. These contradictions and the influence of a patient's age and associated fertility factors, together with the probable role of technical factors, can lead us to question the real impact of myomas on fertility.

When we analyse the global results, the pregnancy rate after myomectomy in these 46 studies is 48%, without any significant difference between hysteroscopic myomectomy (45%) and laparoscopic and abdominal myomectomy (49%). In order to be able to interpret these figures, we need control groups of infertile women with myomas, to whom surgery was not proposed. Such groups were not found in these 46 manuscripts. Another important factor required to interpret these figures is the duration of infertility before myomectomy and the time taken to achieve pregnancy after myomectomy. Pregnancies seem to occur quite soon after myomectomy, 7.5 ± 2.6 months in Dessolle's review (Dessolle *et al.*, 2001). No extensive figures on pregnancy rates relating to infertility duration were encountered.

Technical factors

Technical factors, such as the surgeon's skill and experience and the material and techniques used surely play a role. We tried to analyse the impact of the different surgical techniques on pregnancy rates.

Hysteroscopic myomectomy

For submucosal myomas, transhysteroscopic removal is the standard approach (Donnez *et al.*, 1996). Different techniques can be used such as the resectoscope or the Nd:YAG laser (Donnez and Nisolle, 1993). Depending on the size of the intramural part of a submucosal myoma, one- or two-step surgery is required (Donnez *et al*., 1989, 1995, 2001). GnRH agonists have proved useful in reducing myoma size and expelling the myoma inside the uterine cavity (Donnez *et al*., 1992; Nisolle *et al*., 1994).

After hysteroscopic myomectomy in infertile women, pregnancy rates vary from 16.7 to 76.9%, with a mean value of 45% (Brooks *et al*., 1989; Donnez *et al*., 1990; Loffer, 1990; Corson and Brooks, 1991; Valle, 1991; Hucke *et al*., 1992; Cravello *et al*., 1995; Goldenberg *et al*., 1995; Hallez, 1995; Preutthipan and Theppisai, 1998; Giatras *et al*., 1999; Varasteh *et al*., 1999; Vercellini *et al*., 1999b; Bernard *et al*., 2000; Fernandez *et al*., 2001).

Only one study (Varasteh *et al*., 1999) included a control group of infertile women with a normal uterine cavity at hysteroscopy, and showed a significant benefit of removing submucosal myomas of >2 cm in size. Fernandez *et al*. also described better pregnancy rates after the removal of larger myomas, although the difference was not statistically significant (Fernandez *et al*., 2001). Indeed, the pregnancy rate after the removal of myomas >5 cm in size was 57%, while it was 23% for myomas <5 cm. Besides myoma size, no other myoma characteristics were examined to explain the differences in pregnancy rates.

Laparoscopic and laparotomic myomectomy

For intramural and subserosal myomas, laparoscopic and abdominal removal can be considered. The pregnancy rates after laparoscopic myomectomy vary between 16.7 and 73.1% and after abdominal myomectomy between 9.6 and 75%.

Are there any indications that one of these two techniques should be preferred? Seracchioli *et al*. published the only randomized study comparing pregnancy rates after laparoscopic and laparotomic myomectomy (Seracchioli *et al*., 2000). The authors showed no statistically significant difference between the cumulative pregnancy rates after 2 years (41.75% in the laparoscopy group and 47.07% in the laparotomy group). The myoma recurrence rate did not differ in the two groups (21.4 versus 20.3%).

Studies on the risks of adhesions (Mais *et al*., 1995; Bulletti *et al*., 1996; Diamond *et al*., 1996; Dubuisson *et al*., 2000a) and the risks of recurrence (Nehzat *et al.*, 1998; Fauconnier *et al.*, 2000) have tried to find arguments in favour of one of the two techniques. Unfortunately, they only compared the severity of adhesions evaluated by second-look laparoscopy and the number of recurrences, but we have no idea of their true impact on pregnancy rates.

Other techniques: embolization and myolysis

Ravina *et al*. first proposed uterine artery embolization as an alternative to surgical treatment of uterine fibroids (Ravina *et al*., 1995). However, this technique is still very young, so

follow-up with respect to pregnancy rates after embolization is limited and few conclusions can be drawn. Can embolization be considered when pregnancy is desired? In Forman's series, only 17 women out of 192 who wished to become pregnant after embolization, conceived (Forman *et al*., 1999). After treatment, significant complications occurred in six patients, which were expected to reduce fertility. Other reports of pregnancies after fibroid embolization remain anecdotal (Bradley *et al*., 1998; Hutchins *et al*., 1999; Nicholson and Ettles, 1999; Pron *et al*., 1999). We agree with Forman that embolization should be avoided in women who desire pregnancy. Fertilization and delivery rates after uterine fibroid embolization are a matter of speculation for the moment.

In the late 1980s, techniques of laparoscopic myolysis were developed. Nd:YAG laser (Goldfarb, 1992; Nisolle *et al*., 1993; Donnez *et al*., 1999), bipolar needles (Goldfarb, 1995; Phillips, 1995), diathermy (Chapman, 1993) and cryomyolysis (Zreik *et al*., 1998) were proposed. More recently, myoma interstitial thermo-therapy (Donnez *et al*., 2000) was described. No data are available on pregnancy rates after this technique.

In conclusion, data available in the literature do not allow us to propose the techniques to young women with myomas because of the absence of evidence in the results, in terms of fertility, for those who wish to become pregnant. So far, we have no idea about adhesions or subsequent infertility. In the absence of conclusive data, it seems logical to propose uterine embolization or myolysis to women who do not desire pregnancy.

Myomectomy and pregnancy outcome

Do myomectomy and the resulting uterine scars impair pregnancy outcome? According to Li *et al*. and Vercellini *et al*. miscarriage rates are significantly reduced after myomectomy (Li *et al*., 1999; Vercellini *et al*., 1999a). Uterine scars are associated with a risk of vicious placental implantation (acreta, increta, percreta, praevia) and a risk of uterine rupture. In Seracchioli's randomized study comparing laparoscopic and abdominal myomectomies, no uterine rupture occurred (Seracchioli *et al.*, 2000). There were no significant differences between the percentages of vaginal births (35 versus 22%) and Caesarean sections (65 versus 78%).

Of the 145 pregnancies in Dubuisson's follow-up after laparoscopic myomectomy, 38 (26.2%) resulted in miscarriage, 58 in vaginal deliveries and 42 in Caesarean sections (Dubuisson *et al.*, 2000c). Dubuisson describes three uterine ruptures, all occurring before labour, one attributed to the laparoscopic myomectomy.

A few case reports were found in the literature on uterine rupture after laparoscopic myomectomy (Harris, 1992; Mecke *et al*., 1995; Friedman *et al*., 1996; Pelosi and Pelosi, 1997; Dubuisson *et al*., 2000c; Foucher *et al*., 2000; Hockstein, 2000). However, they do not allow us to draw any conclusions on the relative risk compared with abdominal myomectomy. Moreover, we found no recent reports at all on the risk of uterine rupture after abdominal myomectomy.

For some authors, the presence of a uterine scar is an indication for Caesarean section (Friedman *et al*., 1996; Seineira *et al*., 1997); for others, it is not systematically required (Darai *et al*., 1997; Ribeiro *et al*., 1999; Dubuisson *et al*., 2000c). Reports remain anecdotal, especially reports on the risks for the newborn.

Conclusion

The role of uterine fibroids in infertility remains unknown. A causal relationship between fibroids and infertility has not been definitively demonstrated. Ideally, a comparison of pregnancy rates should be made between women with known fibroids and women without fibroids. Such studies have not been conducted, so our knowledge of the relationship between infertility and myomas results from indirect studies. The IVF model appears to indicate that pregnancy rates only decrease when myomas are submucosal.

The only study comparing infertile women without tubal and andrological infertility factors, with and without myomas and after myomectomy, seems to suggest that the presence of myomas decreases pregnancy rates, while their removal increases pregnancy rates.

The favourable pregnancy rates obtained after myomectomy lead us to believe that myomas influence fertility. Surprisingly, the global pregnancy rates are the same after hysteroscopic, laparoscopic and abdominal myomectomy. However, we have no control groups of women who did not undergo surgery.

So the question remains: do myomas influence fertility? The absence of response to this crucial question is probably due to the fact that we have not yet conducted the appropriate prospective studies required to obtain any clear answers. Meanwhile, every situation has to be judged separately and efforts must be made to develop the best technique, that is to say, the technique with the least risk of impairing fertility or causing complications during pregnancy. At the same time, more fundamental research must be carried out to detect the mechanisms of infertility and understand the genetic basis for fibroid development and the molecular and hormonal mechanisms of myometrial proliferation (Nisolle *et al*., 1999). In the future, this approach will allow the development of an effective prevention strategy in genetically predisposed individuals and provide strategies to slow the growth of myomas.

References

Abramovici, H., Dirnfeld, M., Auslander, R., Bornstein, J., Blumenfeld, Z. and Sorokin, Y. (1994) Pregnancies following treatment by GNRH-a and myomectomy in infertile women with uterine leiomyomata. *Int. J. Fertil. Menopausal Stud*., **39**, 150–155.

Ancien, P. and Querada, F. (1996) Abdominal myomectomy: results of a simple operative technique. *Fertil. Steril*., **65**, 41–51.

Bernard, G., Darai, E., Poncelet, C., Benifla, J.L. and Madelenat, P. (2000) Fertility after hysteroscopic myomectomy: effect of intramural myomas associated. *Eur. J. Obstet. Gynecol. Reprod. Biol*., **88**, 85–90.

Bradley, E.A., Reidy, J.F., Forman, R.G., Jarosz, J. and Braude, P.R. (1998) Transcatheter uterine artery embolization to treat large uterine fibroids. *Br. J. Obstet. Gynaecol*., **105**, 235–240.

Brooks, P.G., Loffer, F.D. and Serden, S.P. (1989) Resectoscopic removal of symptomatic intrauterine lesions. *J. Reprod. Med*., **34**, 435–437.

Bulletti, C., De Ziegler, D., Polli, V., Diotallevi, L., Del Ferro, E. and Flamigni, C. (1999) The role of leiomyomas in infertility. *J. Am. Assoc. Gynecol. Laparosc*., **6**, 441–445.

Bulletti, C., Polli, V., Negrini, V., Giacomucci, E. and Flamigni, C. (1996) Adhesion formation after laparoscopic myomectomy. *J. Am. Assoc. Gynecol. Laparosc*., **3**, 533–536.

Buttram, V.C. and Reiter, R.C. (1981) Uterine leiomyomata: etiology, symptomatology, and management. *Fertil. Steril.*, **36**, 433–445.

Campo, S. and Garcea, N. (1999) Laparoscopic myomectomy in premenopausal women with and without preoperative treatment using gonadotrophin-releasing hormone analogues. *Hum. Reprod*., **14**, 44–48.

Chapman, R. (1993) Treatment of uterine myomas by interstitial hyperthermia. *Gynecol. Endosc*., **2**, 227.

Corson, S.L. and Brooks, P.G. (1991) Resectoscopic myomectomy. *Fertil. Steril.*, **55**, 1041–1044.

Cravello, L., D'Ercole, C., Azoulay, P., Boubli,1 L. and Blanc, B. (1995) Hysteroscopic treatment of uterine fibromas. *J. Gynecol. Obstet. Biol. Reprod*., **24**, 374–380.

Darai, E., Deval, B. and Darles, C. (1996) Myomectomie: coelioscopie ou laparotomie? *Contracep. Fertil. Sex*., **24**, 751–756.

Darai, E., Dechaud, H., Benifla, J.L., Renolleau, C., Panel, P. and Madelenat, P. (1997) Fertility after laparoscopic myomectomy: preliminary results. *Hum. Reprod*., **12**, 1931–1934.

Deligdish, L. and Lowenthal, M. (1970) Endometrial changes associated with myomata of the uterus. *J. Clin. Pathol*., **23**, 676–680.

Dessolle, L., Soriano, D., Poncelet, C., Benifla, J.L., Madelenat, P. and Darai, E. (2001) Determinants of pregnancy rate and obstetric outcome after laparoscopic myomectomy for infertility. *Fertil. Steril*., **76**, 370–374.

Diamond, M.P. (1996) Reduction of adhesions after uterine myomectomy by Seprafilm membrane (HAL-F): a blinded, prospective, randomized, multicenter clinical study. *Fertil. Steril*., **66**, 904–910.

Donnez, J. and Nisolle, M. (1993) Nd-YAG laser hysteroscopic surgery: endometrial ablation, partial endometrial ablation and myomectomy. *Reprod. Med. Rev.*, **2**, 63–71.

Donnez, J., Schrurs, B., Gillerot, S., Sandow, J. and Clerckx, F. (1989) Treatment of uterine fibroids with implants of gonadotrophin releasing-hormone agonist: assessment by hysterography. *Fertil. Steril.*, **51**, 947–950.

Donnez, J., Gillerot, S., Bourgonjon, D., Clerckx, F. and Nisolle, M. (1990) Neodymium: YAG laser hysteroscopy in large submucous fibroids. *Fertil. Steril.*, **54**, 999–1003.

Donnez, J., Nisolle, M., Grandjean, P., Gillerot, S. and Clerckx, F. (1992) The place of GnRH agonist in the treatment of endometriosis and fibroids by advanced endoscopic techniques. *Br. J. Obstet. Gynaecol.*, **99**, 31–33.

Donnez, J., Polet, R., Smets, M., Bassil, S. and Nisolle, M. (1995) Hysteroscopic myomectomy. *Curr. Opin. Obstet. Gynecol.*, **7**, 311–316.

Donnez, J., Mathieu, P.E., Bassil, S., Smets, M., Nisolle, M. and Berlière, M. (1996) Fibroids: management and treatment: the state of the art. *Hum. Reprod.*, **11**, 1837–1840.

Donnez, J., Polet, R. and Squifflet, J. (1999) Laparoscopic myolysis. *Gynecol. Endosc.* (Proceedings of the ESGE meeting, Stockholm), p.112.

Donnez, J., Squifflet, J.L., Polet, R., Nisolle M. (2000) Laparoscopic myolysis. *Hum. Reprod. Update*, **6**, 609–613.

Donnez, J., Nisolle, M., Smets, M. and Squifflet, J.L. (2001) Hysteroscopic myomectomy. In Donnez, J., Nisolle, M. and Carnforth, (eds) *An Atlas of Operative Laparoscopy and Hysteroscopy.* Parthenon Publishing, pp. 483–493.

Dubuisson, J.B., Chapron, C., Chavet, X. and Gregorakis, S.S. (1996) Fertility after laparoscopic myomectomy of large intramural myomas: preliminary results. *Hum. Reprod.*, **11**, 518–522.

Dubuisson, J.B., Fauconnier, A., Babaki-Fard, K. and Chapron, C. (2000a) Laparoscopic myomectomy: a current review. *Hum. Reprod. Update*, **6**, 588–594.

Dubuisson, J.B., Fauconnier, A., Chapron, C., Kreiker, G. and Nordgaard, C. (2000b) Reproductive outcome after laparoscopic myomectomy in infertile women. *J. Reprod. Med*., **45**, 23–30.

Dubuisson, J.B., Fauconnier, A., Deffarges, J.V., Noordgaard, C., Kreiker, G. and Chapron C. (2000c) Pregnancy outcome and deliveries following laparoscopic myomectomy. *Hum. Reprod*., **15**, 869–873.

Egwuatu, V.E. (1989) Fertility and fetal salvage among women with uterine leiomyomas in a Nigerian leasing hospital. *Int. J. Fertil*., **34**, 341–346.

Eldgar-Geva, T., Meagher, S., Healy, D.L., MacLachlan, V., Breheny, S. and Wood, C. (1998) Effect of intramural, subserosal and submucosal uterine fibroids on the outcome of assisted reproductive technology treatment. *Fertil. Steril*., **70**, 687–691.

Farhi, J., Ashkenazi, J., Feldberg, D., Dicker, D., Orvieto, R. and Ben Rafael, Z. (1995) Effect of uterine leiomyomata on the results of *in vitro* fertilization treatment. *Hum. Reprod*., **10**, 2576–2578.

Fauconnier, A., Chapron, C., Babaki-Fard, K. and Dubuisson, J.B. (2000) Recurrence of leiomyomata after myomectomy. *Hum. Reprod. Update*, **6**, 595–602.

Fayez, J.A. and Dempsy, R.A. (1993) Short hospital stay for gynecologic reconstructive surgery via laparotomy. *Obstet. Gynecol*., **81**, 598–600.

Fernandez, H., Sefrioui, O., Virelizier, C., Gervaise, A., Gomel, V. and Frydman, R. (2001) Hysteroscopic resection of submucosal myomas in patients with infertility. *Hum. Reprod.*, **16**, 1489–1492.

Forman, R.G., Reidy, J. and Nott, V. (1999) Fibroids and Fertility. SMIT/CIMIT 11th annual scientific meeting. Sept 1999, Boston.

Foucher, F., Leveque, J., Le-Bouar, G. and Grall, J. (2000) Uterine rupture during pregnancy following myomectomy via coelioscopy. *Eur. J. Obstet. Gynecol. Reprod. Biol*., **92**, 279–281.

Friedman, W., Maier, R.F. and Luttkus, A. (1996) Uterine rupture after laparoscopic myomectomy. *Acta Obstet. Gynecol. Scand.*, **75**, 683–684.

Gatti, D., Falsetti, L., Viani, A. and Gastaldi, A. (1989) Uterine fibromyoma and sterility: role of myomectomy. *Acta Eur. Fertil*., **20**, 11–13.

Gehlbach, D.L., Sousa, R.C., Carpenter, S.E. and Rock, J.A. (1993) Abdominal myomectomy in the treatment of infertility. *Int. J. Gynaecol. Obstet*., **40**, 45–50.

Giatras, K., Berkeley, A.S., Noyes, N., Licciardi, F., Lolis, D. and Grifo, J.A. (1999) Fertility after hysteroscopic resection of submucous myomas. *J. Am. Assoc. Gynecol. Laparosc.*, **6**, 155–158.

Goldenberg, M., Sivan, E., Sharabi, Z., Mashiach, S., Lipitz, S. and Seidman, D.S. (1995) Reproductive outcome following hysteroscopic management of intrauterine septum and adhesions. *Hum. Reprod.*, **10**, 2663–2665.

Goldfarb, H.A. (1992) Nd: YAG laser laparoscopic coagulation of symptomatic myomas. *J. Reprod. Med*., **37**, 636.

Goldfarb, H.A. (1995) Bipolar laparoscopic needles for myoma coagulation. *J. Am. Assoc. Gynecol. Laparosc.*, **2**, 175–179.

Hallez, J.P. (1995) Single stage total hysteroscopic myomectomies: indications, techniques and results. *Fertil. Steril*., **63**, 703–708.

Harris, W.W.J. (1992) Uterine dehiscence following laparoscopic myomectomy. *Obstet. Gynecol.*, **80**, 545–546.

Hasson, H.M., Rotman, C., Rana, N., Sistos, F. and Dmowski, W.P. (1992) Laparoscopic myomectomy. *Obstet. Gynecol.*, **80**, 884–888.

Healy, D.L. (2000) Impact of uterine fibroids on ART outcome. *Environ. Health Perspect*., **108**, 845–847.

Hockstein, S. (2000) Spontaneous uterine rupture in the early third trimester after laparoscopically assisted myomectomy. *J. Reprod. Med*., **45**, 139–141.

Hucke, J., Campo, R.L., DeBruyne, F. and Freikha, A.A. (1992) Hysteroscopic resection of submucous myoma. *Geburtshilfe Frauenheilkd*., **52**, 214–218.

Hunt, J.E. and Wallach, E.E.(1974) Uterine factor in infertility: an overview. *Clin. Gynecol*., **17**, 44–64.

Hutchins, F.L. Jr, Worthington-Kush, R. and Berkowitz, R.P. (1999) Selective uterine artery embolization as primary treatment for symptomatic leiomyomata uteri. *J. Am. Assoc. Gynecol. Laparosc*., **6**, 279–284.

Jun, S.H., Ginsburg, E.S., Racowsky, C., Wise, L.A. and Hornstein, M.D. (2001) Uterine leiomyomas and their effect on *in vitro* fertilization outcome: a retrospective study. *J. Assist. Reprod. Genet*., **18**, 139–143.

Kuhlmann, M., Gartner, A., Schindler, E.M., Regidor, P.A., Buhler, K. and Schindler, A.E. (1997) Uterine leiomyomata and sterility: therapy with gonadotropin-releasing hormone agonists and leiomyomectomy. *Gynecol. Endocrinol.*, **11**, 169–174.

Li, T.C., Mortimer, R. and Cooke, I.D. (1999) Myomectomy: a retrospective study to examine reproductive performance before and after surgery. *Hum. Reprod*., **14**, 1735–1740.

Liu, C.H., Lin, Y.S., Lin, C.C., Tzeng, C.C. and Chou, C.Y. (1993) Medical treatment of uterine myoma with long-acting gonadotropin-releasing hormone agonist prior to myomectomy. *J. Formos. Med. Assoc*., **92**, 536–539.

Loffer, F.D. (1990) Removal of large symptomatic intrauterine growths by the hysteroscopic resectoscope. *Obstet. Gynecol.*, **76**, 836–840.

Mais, V., Ajossa, S., Piras, B., Guerriero, S., Marongiu, D. and Melis, G.B. (1995) Prevention of de-novo adhesion formation after laparoscopic myomectomy: a randomized trial to evaluate the effectiveness of an oxidized regenerated cellulose absorbable barrier. *Hum. Reprod.*, **10**, 3133–3135.

Mecke, H., Wallas, F. and Brocher, A. (1995) Pelviskopische Myomenukleation: Technik, Grenzen, Komplicationen. *Geburtsh Frauenheilk*., **55**, 374–379.

Miller, C.E., Johnston, M. and Rundell, M. (1996) Laparoscopic myomectomy in the infertile woman. *J. Am. Assoc. Gynecol. Laparosc*., **3**, 525–532.

Nehzat, C., Nehzat, F., Bess, O. and Mashiach, R. (1994) Laparoscopically assisted myomectomy: a report of a new technique in 57 cases. *Int. J. Fertil. Menopausal Stud.*, **39**, 39–44.

Nehzat, F.R., Roemisch, M., Nezhat, C.H., Seidman, D.S. and Nehzat, C.R. (1998) Recurrence rate after laparoscopic myomectomy. *J. Am. Assoc. Gynecol. Laparosc.*, **5**, 237–240.

Nicholson, A. and Ettles, D. (1999) Fibroid embolization: observations in 24 patients. SMIT/CIMIT 11th annual scientific meeting. Sept. 1999, Boston.

Nisolle, M., Smets, M. and Gillerot, S. (1993) Laparoscopic myolysis with the Nd: YAG laser. *J. Gynecol. Surg.*, **9**, 95–99.

Nisolle, M., Donnez, J., Casanas-Roux, F., Saussoy, P. and Gillerot, S. (1994) Advanced endoscopic techniques used in dysfunctional bleeding, fibroids and endometriosis, and the role of gonadotrophin-releasing hormone agonist treatment. *Br. J. Obstet. Gynaecol.*, **101**, 2–9.

Nisolle, M., Gillerot, S., Casanas-Roux, F., Squifflet, J., Berlière, M. and Donnez, J. (1999) Immunohistochemical study of the proliferation index, oestrogen receptors and progesterone receptors A and B in leiomyomata and normal myometrium during the menstrual cycle and under gonadotrophin-releasing hormone agonist therapy. *Hum. Reprod.*, **14**, 2844–2850.

Pelosi, M. and Pelosi, M.A. (1997) Spontaneous uterine rupture at thirty-three weeks subsequent to previous superficial laparoscopic myomectomy. *Am. Obstet. Gynecol.*, **177**, 1547–1549.

Phillips, D. (1995) Laparoscopic leiomyomata coagulation-myolysis. *Gynecol. Endosc.*, **4**, 5–11.

Preutthipan, S. and Theppisai, U. (1998) Hysteroscopic resection of submucous myomas: results of 50 procedures at Ramathibodi hospital. *J. Med. Assoc. Thai.*, **81**, 190–194.

Prien Larsen, J.C. and Kjer, J.J. (1989) Myomectomy as a treatment of infertility in women with uterine fibromyoma. *Ugeskr. Laeger.*, **151**, 2584–2586.

Pron, G., Simons, M. and Common, A. (1999) Uterine artery embolization for symptomatic fibroids: sarcoma, pregnancy and other reasons for treatment relapse or failure. SMIT/CIMIT 11th annual scientific meeting. Sept. 1999, Boston.

Ramzy, A.M., Satta, M., Amin, Y., Mansour, R.T., Serour, G.I. and Aboulghar, M.A. (1998) Uterine myomata and outcome of assisted reproduction. *Hum. Reprod.*, **13**, 198–202.

Ravina, J.H., Herbreteau, D., Ciraru-Vigneron, N., Bouret, J.M., Houdart, E., Aymard, A. and Merland, J.J. (1995) Arterial embolisation to treat uterine myomata. *Lancet*, **346**, 671–672.

Ravina, J.H., Vigneron, N.C., Aymard, A., Le Dref, O. and Merland, J.J. (2000) Pregnancy after embolization of uterine myoma: report of 12 cases. *Fertil. Steril.*, **73**, 1241–1243.

Ribeiro, S., Reich, H., Rosenberg, J., Guglielminetti, E. and Vidali, A. (1999) Laparoscopic myomectomy and pregnancy outcome in infertile patients. *Fertil. Steril.*, **71**, 571–574.

Robert, H.G., Palmer, R. and Bouryheyler, C. (1974) *Précis de gynecologie*. Masson, Paris, France.

Rossetti, A., Sizzi, O., Soranna, L., Mancuso, S., and Lanzone, A. (2001) Fertility outcome: long-term results after laparoscopic myomectomy. *Gynecol. Endocrinol.*, **15**, 129–134.

Seinera, P., Arisio, R., Decko, A., Farina, C. and Crana, F. (1997) Laparoscopic myomectomy: indications, surgical technique and complications. *Hum. Reprod.*, **12**, 1927–1930.

Seracchioli, R., Rossi, S., Govoni, F., Rossi, E., Venturoli, S., Bulletti, C. and Flamigni, C. (2000) Fertility and obstetric outcome after laparoscopic myomectomy of large myomata: a randomized comparison with abdominal myomectomy. *Hum. Reprod.*, **15**, 2663–2668.

Sirjusingh, A., Bassaw, B. and Roopnarinesingh, S. (1994) The results of abdominal myomectomy. *West Indian Med. J.*, **43**, 138–139.

Starks, G.C. (1988) CO_2 laser myomectomy in an infertile population. *J. Reprod. Med.*, **88**, 184–186.

Stovall, D.W., Parrish, S.B., Van Voorhis, B.J., Hahn, S.J., Sparks, A.E. and Syrop, C.H. (1998) Uterine leiomyomas reduce the efficacy of assisted reproduction cycles: results of a matched follow-up study. *Hum. Reprod.*, **13**, 192–197.

Sudik, R., Husch, K., Steller, J. and Daume, E. (1996) Fertility and pregnancy outcome after myomectomy in sterility patients. *Eur. J. Obstet. Gynecol. Reprod. Biol.*, **65**, 209–214.

Surrey, E.S., Liez, A.K. and Schoolcraft, W.B. (2001) Impact of intramural leiomyomata in patients with a normal endometrial cavity on *in vitro* fertilization–embryo transfer cycle outcome. *Fertil. Steril.*, **75**, 405–410.

Tulandi, T., Muray, C. and Gurianick, M. (1993) Adhesion formation and reproductive outcome after myomectomy and second-look laparoscopy. *Obstet. Gynecol.*, **82**, 213–215.

Valle, R.F. (1990) Hysteroscopic removal of submucous leiomyomas. *J. Gynecol. Surg.*, **6**, 89–96.

Varasteh, N.N., Neuwirth, R.S., Levin, B. and Keltz, M.D. (1999) Pregnancy rates after hysteroscopic polypectomy and myomectomy in infertile women. *Obstet. Gynecol.*, **94**, 168–171.

Vercellini, P., Maddalena, S., De Giorgio, O., Pesole, A., Ferrari, L. and Crosignani, P.G. (1999a) Determinants of reproductive outcome after abdominal myomectomy for infertility. *Fertil. Steril.*, **72**, 109–114.

Vercellini, P., Zaina, B., Yaylayan, L., Pisacreta, A., De Giorgio, O. and Crosignani, P.G. (1999b) Hysteroscopic myomectomy: long-term on menstrual pattern and fertility. *Obstet. Gynecol.*, **94**, 341–347.

Verkauf, B.S. (1992) Myomectomy for fertility enhancement and preservation. *Fertil. Steril.*, **58**, 1–15.

Vollen-Hoven, B.J., Lawrence, A.S. and Healy, D.L. (1990) Uterine fibroids: a clinical review. *Br. J. Obstet. Gynaecol.*, **97**, 285–288.

Zollner, U., Classen, V. and Steck, T. (2001) Fertility and pregnancy outcome after myomectomy. *Geburtsh. Frauenheilk.*, **61**, 213–219.

Zreik, T., Rutherford, T. and Palter, S. (1998) Cryomyolysis: a new procedure for the conservative treatment of uterine fibroids. *J. Am. Assoc. Gynecol. Laparosc.*, **1**, 33–38.