Article

Do uterine fibroids affect IVF outcomes?

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Abstract

The effect of myomectomy on implantation and pregnancy rates prior to assisted reproduction treatments is controversial. This study was designed to assess clinical outcomes of IVF cycles in women with uterine fibroids. A retrospective single-centre assessment of clinical outcomes of IVF/intracytoplasmic sperm injection (ICSI) treatments in infertile women in a 4-year span was carried out. All patients underwent detailed transvaginal ultrasound and hysteroscopy to precisely identify presence, location and intracavitary growth of uterine fibroids. Cumulative pregnancy, ongoing pregnancy and live birth rates were considered primary outcome measurements. Fifty-one women with fibroids (97 treatment cycles), 63 patients with previous myomectomy (127 cycles), and 106 infertile women who did not demonstrate fibroids anywhere in the uterus (215 cycles) were considered for the analysis. No significant difference was found for pregnancy and live birth rates between groups. Women with fibroids >4 cm required an increased number of cycles to obtain an ongoing pregnancy, compared with the other groups. The data do not support pre-IVF myomectomy in women with small-to-moderate uterine fibroids, regardless of their location. This represents valuable information in the counselling of women with fibroids before reproductive assisted cycles.

Keywords: *assisted reproductive technology procedures*, *ICSI*, *IVF*, *myomectomy*, *uterine fibroids*

Introduction

Uterine fibroids are the most common benign pelvic tumours of the female genital tract during reproductive age, and are generally thought to contribute to infertility (Casini *et al*., 2006). Although mechanisms underlying the relationship between fibroids and infertility are still poorly understood (interference with sperm or ovum migration, endometrial vascular disturbance, inflammation, production of vasoactive substances) (Donnez and Jadoul, 2002), a surgical approach is widely accepted (Campo *et al*., 2003; Olive *et al*., 2004; Benecke *et al*., 2005). Only fibroids that distort the endometrial cavity seem to impair fertility (Bulletti *et al*., 2004), and their removal is recommended before undergoing assisted reproduction techniques (Rackow and Arici, 2005).

At present there is no consensus about the 'optimal' approach to fibroids for those women scheduled for assisted reproduction cycles. Many variables have been assessed over the years, such as the size of the myoma, location, compression of the uterine cavity, medical therapy, timing of surgery and surgical technique (Oliveira *et al*., 2004; Rackow and Arici, 2005). While it is easy to counsel women with large uterine fibroids before starting an assisted reproduction programme, appropriate counselling in cases of small fibroids is complex and difficult. The impact of small myomas that do not encroach upon the endometrium on outcomes of assisted reproduction cycles is far less clear than large submucosal fibroids (Check *et al*., 2002; Oliveira *et al*., 2004). This study was carried out to elucidate this clinical issue further. Women with a history of myomectomy and normal controls with no sonographic evidence of fibroids were considered as comparison groups.

Materials and methods

Study subjects

This study was based on data retrieved from medical records of all patients who underwent IVF and intracytoplasmic sperm injection (ICSI) treatments between September 2002 and September 2006 at the Centre of Pathophysiology of Human Reproduction and Gametes Cryopreservation, University of Bari. The study included 51 women with fibroids (97 treatment cycles performed, group A), 63 women with previous myomectomy (127 cycles, group B) and 106 normal controls without fibroids (215 cycles, group C). Group A consisted of women who had other plausible causes of infertility than myomas (male factor, tubal diseases, endometriosis, anovulatory cycles) and those who, fully informed of benefits and possible complications of myomectomy prior to IVF, refused the surgical treatment. Study subjects in group B underwent surgery at least 1 year before starting IVF procedures. No difference in IVF and ICSI procedures was found between groups.

All patients underwent physical examination and baseline transvaginal sonography and hysteroscopy in early follicular phase 1 month before treatment. Ultrasound was performed using a 4–7 MHz transvaginal transducer on Acuson 128/XP (Mountain View, California) or Aloka ProSound alpha5 machines. Office hysteroscopy was carried out in all patients to evaluate the uterine cavity.

Presence and classification of uterine fibroids was achieved by ultrasound and hysteroscopy. Location (submucous, intramural with or without cavity distortion and subserous), number, and size of fibroids was recorded. Fibroids were classified as submucous when they abutted the endometrial cavity with more than 50% covered by the mucosa (**Figure 1a**), intramural when more than 50% of the fibroid developed in the uterine wall (**Figure 1b**), and subserous when more than 50% was covered by the serosal layer. Moreover, patients with myomas were further classified as with ‘cavity distortion’ when the endometrium–myometrium transition was clearly seen as a line with deformation of its contours by the presence of the fibroids in both sagittal and transverse sections of the uterus. Intramural fibroids with cavity distortion (at ultrasound and confirmed by hysteroscopy) were enclosed in the group of submucous fibroids. The dimension of each fibroid was determined as the mean value (cm) of the two largest diameters.

Ovarian stimulation protocol

The ovarian stimulation protocol used has been described previously (Lorusso *et al.*, 2005). Briefly, all patients received the same ovarian stimulation protocol after suppression with long acting gonadotrophin-releasing hormone (GnRH) agonists.

The luteal phase was supplemented with progesterone in oil 50 mg/day (Amsa, Rome, Italy) starting on the day after oocyte retrieval and continuing until 7 weeks’ gestation if pregnancy was achieved. The pregnancy was tested 14 days after embryo transfer by quantitative definition of serum β-HCG, while implantation was defined on ultrasound as number of fetal sacs per number of transferred embryos 4 weeks after transfer. Clinical pregnancy was defined as fetal cardiac activity on transvaginal sonography. Pregnancy progressing beyond week 12 of gestation was considered to be ongoing.

Statistical analysis

Categorical variables were compared with two-tailed chi-squared test with Yates correction or Fisher’s Exact test, as appropriate. Continuous variables were assessed by the one-way analysis of variance between groups (ANOVA) and the Gaussian distribution was tested using the method of Kolmogorov and Smirnov. Differences among subgroups were evaluated with Tukey–Kramer multiple comparisons test. Data were analysed using GraphPad InStat (version 3.00, GraphPad Software Inc., San Diego, California, USA) and significance set at a P-value of <0.05.

Results

Demographic characteristics and baseline clinical data of patients are displayed in **Table 1**. The groups were homogeneous for age, incidence of primary infertility, duration of infertility, number of IVF treatment cycles, and cause of infertility. Ovarian response to stimulation with gonadotrophins was similar in the three groups (**Table 2**).

Reproductive outcomes are reported in **Table 3**. Implantation rates were comparable in the three groups. Clinical and ongoing pregnancy rates were significantly higher in group B compared with group A ($P < 0.05$). No differences were found in the miscarriage, ectopic and multiple pregnancy rates for embryo transfer. Finally, preterm delivery and delivery at term were comparable among the groups.

Further analysis was carried out in the group of patients with fibroids (group A). Clinical outcomes were related to number, location and size of fibroids over all IVF/ICSI attempts in the study period. Overall, 13 women had submucous or intramural fibroids with cavity distortion (25.5%), 18 (35.3%) had intramural fibroids without cavity distortion, and 20 (39.2%) had subserous fibroids. No statistical difference was found in implantation, miscarriage and pregnancy rates (**Table 4**). No association was observed comparing the number of cycles required to achieve an ongoing pregnancy with type (submucous or intramural with cavity distortion, intramural and subserous) and number of fibroids (1, 2 or >2), whereas large myomas significantly impaired fertility ($P <$ 0.05, **Figure 2**).

Finally, clinical outcomes of laparotomic (n = 15, 23.8%) versus laparoscopic/hysteroscopic myomectomy (n = 48, 76.2%) were compared in group B (previous myomectomy). A nearly significant higher pregnancy rate (41.7 versus 20.0%) was observed in the group with previous laparoscopic myomectomy, though not statistically significant ($P = 0.08$).

Figure 1. Submucosal (**A**) and intramural (**B**) fibroids that encroach the uterine cavity. Evidence of intracavitary pregnancy in a patient with two uterine fibroids after an IVF cycle (**C**).

Table 1. Demographic characteristics and clinical data of patients.

	Group A, n = 51	*Group B, n = 63*	*Group C, n = 106*
Age (years)	34.8 ± 5.3	35.5 ± 3.9	33.8 ± 4.5
Primary infertility (*n*, %)	33 (64.7)	39 (61.9)	72 (67.9)
Duration of infertility (years)	4.5 ± 2.1	5.1 ± 3.5	4.8 ± 3.5
Number of cycles	1.9 ± 0.8	2.0 ± 0.9	2.0 ± 1.0
Male factor (*n*, %)	9 (17.6)	13 (20.6)	22 (20.8)
Tubal factor (*n*, %)	17 (33.3)	20 (31.7)	38 (35.8)
Endometriosis (*n*, %)	13 (25.5)	14 (22.2)	27 (25.5)
Anovulatory (*n*, %)	12 (23.5)	12 (19.0.)	17 (16.0)
Unexplained (*n*, %)	0 (0.0)	4 (6.3)	2 (1.9)

There were no statistically significant differences between groups.

Table 2. Response to ovarian stimulation.

	Group A, cycles = 97	*Group B, cycles = 127*	*Group C, cycles = 215*
Amount of rFSH (IU)	2195 ± 846	2020 ± 975	2295 ± 1179
Total no. of follicles, HCG day	11.9 ± 7.3	13.1 ± 6.4	10.5 ± 7.1
No. of follicles ≥18 mm, HCG day	7 ± 3.9	8 ± 3.6	7.4 ± 2.9
Oestradiol concentrations, HCG day (pg/ml)	1707 ± 915	1731.7 ± 887	1669 ± 841
No. of retrieved oocytes	9.9 ± 4.8	8.6 ± 5.6	9.5 ± 5.7
No. of fertilized oocytes[a]	5.6 ± 4.4	5.5 ± 4.6	3.6 ± 4.6
No. of embryos transferred[a]	2.2 ± 1.0	2.8 ± 0.8	2.0 ± 1.3
No. of IVF cycles with embryo transfer (%)	92 (94.8)	121 (95.3)	205 (95.3)

There were no statistically significant differences between groups.
[a]Values referred to IVF cycles with embryo transfer.

Table 3. Clinical outcomes in the three groups.

	Group A, cycles = 97	*Group B, cycles = 127*	*Group C, cycles = 215*	*P-value*
Transferred embryos (mean, SD)	2.2 ± 1.0	2.8 ± 0.8	2.0 ± 1.3	NS
Implantation rate (%)	10.1 (21/207)	13.5 (47/347)	14.9 (62/416)	NS
Clinical pregnancy rate/patient (%)	33.3 (17/51)	65.1 (41/63)[a]	53.8 (57/106)[a]	<0.05
Clinical pregnancy rate/transfer (%)	18.5 (17/92)	33.9 (41/121)[a]	27.8 (57/205)	<0.05
Miscarriage rate/transfer (%)	2.1 (2/92)	2.5 (3/121)	0.9 (2/205)	NS
Ectopic pregnancy rate/transfer (%)	1.1 (1/92)	0	0	NS
Multiple pregnancy rate/transfer (%)	1.1 (1/92)	2.5 (3/121)	1.4 (3/205)	NS
Ongoing pregnancy rate/patient (%)	18.5 (17/92)	33.9 (41/121)[a]	27.8 (57/205)	<0.05
Preterm delivery (%)[b]	0	2.4 (1/41)	1.7 (1/57)	NS
Delivery at term (%)[b]	100 (17/17)	97.6 (40/41)	98.3 (56/57)	NS

[a]Significantly different to corresponding value for Group A.
[b]Percentage of ongoing pregnancies.

Table 4. Clinical outcomes in the fibroid group. Submucous group includes also patients with intramural fibroids that encroach on the uterine cavity.

	Location			*Size*		
	Submucous, cycles = 24	*Intramural, cycles = 31*	*Subserous, cycles = 40*	*<2 cm, cycles = 55*	*2–4 cm, cycles = 33*	*>4 cm, cycles = 9*
IVF cycles with embryo transfer (*n*)	23	31	38	52	31	9
Implantation rate (%)	16.6(9/54)	6.9 (5/72)	8.6 (7/81)	11.4 (13/114)	9.8 (7/71)	4.5 (1/22)
Clinical pregnancy rate/transfer (%)	30.4 (7/23)	13 (4/31)	15.8 (6/38)	19.2 (10/52)	19.3 (6/31)	11.1 (1/9)
Miscarriage rate/transfer (%)	4.3 (1/23)	0	2.6 (1/38)	1.9 (1/52)	3.2 (1/31)	0
Ectopic pregnancy rate/transfer (%)	4.3 (1/23)	0	0	1.9 (1/52)	0	0
Multiple pregnancy rate/transfer (%)	0	3.2 (1/31)	0	1.9 (1/52)	0	0
Ongoing pregnancy rate (%)	30.4 (7/23)	13 (4/31)	15.8 (6/38)	19.2 (10/52)	19.3 (6/31)	11.1 (1/9)

Rates calculated per transfer.
There were no significant differences between the size groups or the location groups.

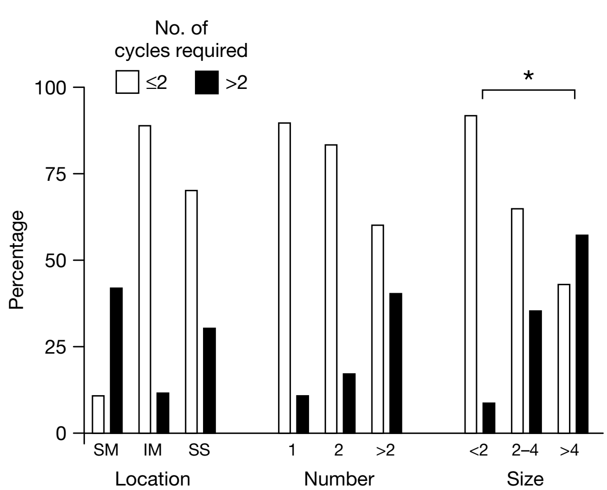

Figure 2. Number of cycles required to achieve an ongoing pregnancy in the group of patients with fibroids in regard to location (SM submucosal; IM intramural; SS subserosal), number of fibroids and their size (cm). *$P < 0.05$.

Discussion

The presence of uterine fibroids in women undergoing assisted reproduction cycles seems to affect outcomes, especially if these myomas are larger than 4 cm. Submucosal fibroids apparently have a relative effect on clinical outcomes compared with women with previous myomectomy or controls.

Uterine fibroids are associated with different gynaecological symptoms, including menorrhagia, pelvic pain or pressure, and they are thought to be associated with infertility, although many women with uterine myomas are asymptomatic and fertile. Focal vascular disorders in the endometrium overlaying submucosal fibroids, local production of inflammatory and vasoactive cytokines that alter the endometrial environment have been supposed to impair a woman's fertility (Deligdish and Loewenthal, 1970; Miura *et al.*, 2006). Therefore, removal of uterine fibroids seems a logical consequence of these findings to improve fertility, although myomectomy of medium–small fibroids that do not compress the uterine cavity is controversial (Pritts, 2001; Oliveira *et al.*, 2004). Surgical (laparotomic, laparoscopic, and hysteroscopic) removal (Griffiths *et al.*, 2006) or selective embolization (Goldberg and Pereira, 2006) have been proposed in subfertile women.

This study compared clinical outcomes in assisted reproduction treatments in women with evidence of fibroids compared with two control groups. These consisted of women with previous myomectomy (laparotomic or laparoscopic/hysteroscopic) and infertile patients with no evidence of uterine fibroids. Small-to-moderate sized fibroids seem not to impact assisted reproduction outcomes regardless of location. The data suggest that the number of cycles required to obtain an ongoing pregnancy in women with submucosal myomas is slightly higher than in intramural/subserosal fibroids. Therefore, it seems wise to propose a hysteroscopic removal of small fibroids that encroach the uterine cavity in subfertile women. Office operative hysteroscopy may represent a suitable approach in these cases (Bettocchi *et al.*, 2002).

This is a retrospective study, which brings some limitation with its own nature (Rackow and Arici, 2005). The bias of selection of patients was overcome by including all patients referred to the authors' centre in an arbitrarily defined period, ensuring a sufficient study population, without any exclusion criteria. In the present study, ultrasound and hysteroscopy were used to ensure the correct visualization of fibroids. The correct size, localization and intracavitary growth of fibroids allow proper labelling and classification (subserosal, intramural, and submucous), this being the main point at issue (Pritts, 2001). Transvaginal ultrasound is highly accurate for measurements of tumour size, and hysteroscopy can precisely identify intracavitary growth and location (Cicinelli *et al.*, 1995). Moreover, in retrospective analyses on laparoscopic versus laparotomic approach to uterine fibroids, it is important to consider the size of fibroids. Laparotomy is generally preferred for large fibroids, and this can affect the interpretation of results. A detailed meta-analysis revealed the relevance of this information, especially for the interpretation of findings (Pritts, 2001). In this study, no difference was found for size and location of fibroids between laparotomic and laparoscopic myomectomy groups (data not shown).

So far as is known, this is the first study reporting outcomes of assisted reproduction treatments in women with uterine fibroids compared with two control groups, namely patients with previous myomectomy and those with no evidence of fibroids. Check and co-workers (Check *et al.*, 2002) published the only prospective randomized trial on myomectomy before IVF cycles so far. They failed to demonstrate significant improvements in outcomes by surgical removal of small fibroids (<5 cm) before assisted reproduction treatments. All the other studies have a retrospective approach comparing either fibroids versus myomectomy or fibroids versus patients who did not demonstrate fibroids (Pritts, 2001; Olive *et al.*, 2004; Benecke *et al.*, 2005; Rackow and Arici, 2005; Griffiths *et al.*, 2006).

The data support a pre-IVF myomectomy in women with uterine fibroids especially if they are larger than 4 cm. Myomectomy may be considered in women who have been through several IVF cycles with good ovarian response, high quality of embryos and poor pregnancy outcomes. A conservative approach may be offered to women with small intramural/subserous fibroids. There are several reasons for avoiding laparoscopic or laparotomic myomectomy prior to IVF cycles. Secondary infection, iatrogenic damage to internal organs, formation of adhesions, and uterine scars can impair outcomes of assisted reproduction cycles (inseminations, IVF, ICSI) (Pritts, 2001). On the other hand, removal of small intracavitary fibroids using office hysteroscopy seems a safe option. These represent key aspects for counselling of infertile couples in cases of uterine fibroids.. A prospective matched-control study with appropriate study populations, evaluating options for optimal fibroid management in women undergoing assisted reproductive technology procedures is required to address this clinical issue.

References

Benecke C, Kruger TF, Siebert TI *et al.* 2005 Effect of fibroids on fertility in patients undergoing assisted reproduction. A structured literature review. *Gynecologic and Obstetric Investigation* **59**, 225–230.

Bettocchi S, Ceci O, Di VR *et al.* 2002 Advanced operative office hysteroscopy without anaesthesia: analysis of 501 cases treated with a 5 Fr. bipolar electrode. *Human Reproduction* **17**, 2435–2438.

Bulletti C, DE ZD, Levi SP *et al.* 2004 Myomas, pregnancy outcome, and in vitro fertilization. *Annals of the New York Academy of Sciences* **1034**, 84–92.

Campo S, Campo V, Gambadauro P 2003 Reproductive outcome before and after laparoscopic or abdominal myomectomy for subserous or intramural myomas. *European Journal of Obstetrics, Gynecology and Reproductive Biology* **110**, 215–219.

Casini ML, Rossi F, Agostini R *et al.* 2006 Effects of the position of fibroids on fertility. *Gynecological Endocrinology* **22**, 106–109.

Check JH, Choe JK, Lee G *et al.* 2002 The effect on IVF outcome of small intramural fibroids not compressing the uterine cavity as determined by a prospective matched control study. *Human Reproduction* **17**, 1244–1248.

Cicinelli E, Romano F, Anastasio PS *et al.* 1995 Transabdominal sonohysterography, transvaginal sonography, and hysteroscopy in the evaluation of submucous myomas. *Obstetrics and Gynecology* **85**, 42–47.

Deligdish L, Loewenthal M 1970 Endometrial changes associated with myomata of the uterus. *Journal of Clinical Pathology* **23**, 676–680.

Donnez J, Jadoul P 2002 What are the implications of myomas on fertility? A need for a debate? *Human Reproduction* **17**, 1424–1430.

Goldberg J, Pereira L 2006 Pregnancy outcomes following treatment for fibroids: uterine fibroid embolization versus laparoscopic myomectomy. *Current Opinion Obstetrics and Gynecology* **18**, 402–406.
Griffiths A, D'Angelo A, Amso N 2006 Surgical treatment of fibroids for subfertility. *Cochrane Database Systems Review b*, CD003857.
Lorusso F, Depalo R, Tsadilas S *et al*. 2005 Is the occurrence of the empty follicle syndrome a predictor that a subsequent stimulated cycle will be an unfavourable one? *Reproductive BioMedicine Online* **10**, 571–574.
Miura S, Khan KN, Kitajima M *et al*. 2006 Differential infiltration of macrophages and prostaglandin production by different uterine leiomyomas. *Human Reproduction* **21**, 2545–2554.
Olive DL, Lindheim SR, Pritts EA 2004 Non-surgical management of leiomyoma: impact on fertility. *Current Opinion in Obstetrics and Gynecology* **16**, 239–243.
Oliveira FG, Abdelmassih VG, Diamond MP *et al*. 2004 Impact of subserosal and intramural uterine fibroids that do not distort the endometrial cavity on the outcome of in vitro fertilization–intracytoplasmic sperm injection. *Fertility and Sterility* **81**, 582–587.
Pritts EA 2001 Fibroids and infertility: a systematic review of the evidence. *Obstetrical and Gynecological Survey* **56**, 483–491.
Rackow BW, Arici A 2005 Fibroids and in-vitro fertilization: which comes first? *Current Opinion in Obstetrics and Gynecology* **17**, 225–231.

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