Human Reproduction Vol.16, No.11 pp. 2411–2417, 2001

A prospective controlled study of the effect of intramural uterine fibroids on the outcome of assisted conception

Roger Hart[1], Yacoub Khalaf[1,3], Cheng-Toh Yeong[1], Paul Seed[2], Alison Taylor[1] and Peter Braude[1]

[1]Guy's and St Thomas' Assisted Conception Unit, St Thomas' Hospital, London and [2]Fetal Health Research Group, Department of Obstetrics and Gynaecology, Guy's, King's and St Thomas' School of Medicine, King's College, London, UK

[3]To whom correspondence should be addressed at: Guy's and St. Thomas' Assisted Conception Unit, St Thomas' Hospital, Lambeth Palace Road, London SE1 7EH, UK. E-mail yakoub.khalaf@kcl.ac.uk

BACKGROUND: Although uterine fibroids occur in 30% of women and are associated with a degree of subfertility, the effect of intramural fibroids on the outcome of IVF or ICSI treatment has not been prospectively studied. METHODS: Data were prospectively collected on 434 women undergoing IVF/ICSI in the assisted conception unit of an inner London teaching hospital. Patients were assessed for the presence of fibroids by transvaginal ultrasound and hysterosonography or hysteroscopy where appropriate. RESULTS: During the study period, 112 women with (study), and 322 women without (controls), intramural fibroids were treated. Patients were similar regarding the cause and duration of their infertility, number of previous treatments, and basal serum FSH concentration. Women in the study group were on average 2 years older (36.4 versus 34.6 years; $P < 0.01$). There was no significant difference in the duration of ovarian stimulation or gonadotrophin requirement, number of follicles developed, oocytes collected, embryos available for transfer or replaced. When analysing only women with intramural fibroids of ≤5 cm in size ($n = 106$) pregnancy, implantation and ongoing pregnancy rates were significantly reduced: 23.3, 11.9 and 15.1 respectively compared with 34.1, 20.2 and 28.3% in the control group ($P = 0.016$, $P = 0.018$ and $P = 0.003$). The mean size of the largest fibroids was 2.3 cm (90% range 2.1–2.5 cm). Logistic regression analysis demonstrated that the presence of intramural fibroids was one of the significant variables affecting the chance of an ongoing pregnancy, even after controlling for the number of embryos available for replacement and increasing age, particularly age ≥40 years, odds ratio 0.46 (CI 0.24–0.88; $P = 0.019$). CONCLUSION: This study demonstrated that an intramural fibroid halves the chances of an ongoing pregnancy following assisted conception.

Keywords: assisted conception/ICSI/intramural fibroid/IVF/leiomyoma

Introduction

Uterine fibroids occur in up to 30% of women (Verkauf, 1992; Wallach, 1992), and are more common among Afrocarribean women. Although fibroids are implicated as a possible cause of subfertility (Buttram and Reiter, 1981; Hasan *et al.*, 1991), this is not accepted universally (Vellenhoven *et al.*, 1990). The mechanism by which the association with subfertility occurs may depend on the size and location of the fibroids. The association of submucosal fibroids with subfertility is well recognized, and pregnancy rates of up to 43% have been achieved following hysteroscopic resection (Goldenberg *et al.*, 1995; Hart *et al.*, 1999; Bernard *et al.*, 2000).

However, debate persists as to whether intramural fibroids can cause infertility (Verkauf, 1992), and the evidence for an effect on embryo implantation in cycles of assisted conception remains unclear. Studies to date have been retrospective, with small patient numbers and little distinction being made between intramural and subserosal fibroids (Seoud *et al.*, 1992; Farhi *et al.*, 1995; Eldar-Geva *et al.*, 1998; Ramzy *et al.*, 1998; Stovall *et al.*, 1998).

A prospective study was performed of all patients being treated in our unit in order to assess the effect of intramural fibroids on the outcome of their assisted reproduction cycles.

Materials and methods

Study population

All women undergoing either IVF or intracytoplasmic sperm injection (ICSI) at the authors' institutions between August 1, 1999 and July 31, 2000 were enrolled into the study. Before their assisted reproduction cycle, each patient provided a complete history and underwent a physical examination, including a vaginal ultrasound scan. All patients were actively screened for the presence or absence of uterine fibroids by vaginal ultrasound at the initial visit and again during the course of their treatment to ensure that no patients were overlooked. Patients about to embark on an assisted reproduction cycle using cryopreserved embryos or donated oocytes were excluded. Only the first cycle that the patient embarked on during the study period was analysed, and only women with fibroids ≤5 cm were included in the final analyses. In order to have 90% power to detect a fall in conception rates from 30 to 15% between women without and those with fibroids, with a 3:1 prevalence of fibroids it was calculated that 116 women would be needed in the fibroid group.

Uterine evaluation

All patients in whom a uterine fibroid was reported were evaluated for its exact position. If it appeared in proximity to the endometrial cavity, the patient underwent saline hysterosonography or hysteroscopy. Hysterosonography was performed after premedication with 1 g rectal metronidazole (Flagyl; Rhone-Poulenc Rorer), diclofenac (Voltarol; Novartis) 100 mg rectally, and after commencement of a 5-day course of oral doxycycline 100 mg twice daily. Saline infusion into the uterine cavity was performed in the follicular phase of the cycle under ultrasound control via a hysterosalpingogram catheter (Cook balloon catheter; Limerick, Ireland). Hysteroscopy was performed as described either with local or general anaesthesia (Ruach *et al.*, 1998). Those patients found to have a submucosal fibroid were referred for hysteroscopic resection (Hart *et al.*, 1999) prior to embarking on assisted reproduction, and were excluded from the study. If the fibroid did not encroach on the endometrial cavity, the patient was entered into the study. A fibroid was considered subserosal if >50% of its volume protruded from the serosal surface of the uterus, as previously described (Li *et al.*, 1999).

Treatment protocol

Ovarian stimulation was performed using a protocol as previously described (Khalaf *et al.*, 2000). In summary, oocytes were obtained from cycles in which pituitary desensitization was achieved with the gonadotrophin-releasing hormone (GnRH) agonist buserelin (Suprefact; Hoechst, Hounslow, UK or Suprecur; Shire, Andover, UK) in the midluteal long protocol. This was followed by ovarian stimulation with recombinant or urinary FSH (Gonal F or Metrodin HP; Serono, Welwyn Garden City, UK). Transvaginal ultrasound was performed on day 9 or 10 after starting stimulation. Oocyte retrieval was planned after three or more follicles had reached 18 mm in diameter, and 10 000 units of human chorionic gonadotrophin (HCG) (Profasi; Serono or Pregnyl; Organon, Cambridge, UK) was used to induce oocyte maturation. Oocytes were aspirated transvaginally with ultrasound guidance 34–38 h later.

IVF

Fertilization of recovered oocytes was assessed 18 h after insemination. Cleavage-stage embryos were assigned quality grades on the second day after oocyte retrieval as described previously (Steer *et al.*, 1992). The highest grade embryos were selected for replacement, and cryopreservation was offered where there were three or more excess high-grade embryos.

ICSI

Following removal of cumulus/corona cells using hyaluronidase, the oocytes were examined for their nuclear maturity using an inverted microscope (Nikon Diaphot with Hoffmann modulation contrast optics). ICSI was carried out on all oocytes that had extruded the first polar body. Following sperm injection, the oocytes were transferred to 100 µl droplets of IVF medium under oil and incubated overnight at 37°C under 5% CO_2. On the following day (16 h after injection), the oocytes were checked for survival and fertilization. Normal fertilization was scored when two pronuclei were clearly visible.

Embryo transfer

It is our routine practice to advocate replacement of two embryos, except when the couple have had repeated failed cycles, or where the woman is over 38 years of age. Uterine embryo transfer was performed 2 days after oocyte retrieval using an Edwards-Wallace embryo replacement catheter (Sims Portex Ltd, Hythe, Kent, UK) replacing the best grade cleavage-stage embryos under abdominal ultrasound control to ensure their correct placement.

Statistical analysis

Patients were grouped as to whether they had fibroids. Only the first treatment cycle that they underwent during the treatment period was included, and only patients with fibroids ≤5 cm in size were included in the analysis of pregnancy rates. Data were summarized as mean (± SD) or *n* (%) as appropriate. Log transformations and geometric means were used for FSH concentrations.

Pregnancy rates were analysed using logistic regression. Implantation rates were analysed using Poisson regression, exposure being the numbers of embryos transferred (Rogers, 1991); 18 analyses were performed using Stata version 6 (StataCorp, College Station, Texas, USA).

All results were presented as estimates with 95% confidence intervals (CI). Significance at $P < 0.05$ was claimed when 'no effect' (difference in means = 0 or odds ratio = 1) was not in the interval.

Results

During the study period, 322 women without fibroids (control group) and 112 women with fibroids (study group) were treated. In the latter group, six women had fibroids ≥5 cm in size and were excluded from the analysis of pregnancy rates. Patients in both groups were similar with regard to duration of their infertility, number of previous treatment cycles, and FSH concentration before treatment (Table I). Age was significantly different between the two groups, being on

Table I. Demographic data[a]

Parameter	Control patients (n = 322)	Fibroid patients (n = 112)	Difference	P
Age at time of treatment (years)	34.6 ± 3.9	36.4 ± 3.9	+1.8	< 0.0001
Duration of infertility (years)	3.2 ± 3.7	3.6 ± 3.5	+0.4	0.38
No. of previous IVF/ICSI treatment cycles	0.7 ± 1.1	0.6 ± 1.2	−0.1	0.26
Pretreatment basal FSH (IU/l)	7.9 ± 10.8	7.6 ± 10.7	−0.3	0.84

[a]Values are mean ± SD.

average 2 years greater in the study group (36.4 versus 34.6 years; $P < 0.0001$). Indeed, 20.9% of the study patients were aged ⩾40 years compared with only 8.8% in the control group ($P = 0.0012$). The causes of infertility were similar in both groups (Table II). There was no inter-group difference in the duration of ovarian stimulation required before oocyte retrieval, the amount of gonadotrophins required to effect ovarian stimulation, the number of follicles developed, or the number of oocytes collected (Table III). There was also no inter-group difference in the number of embryos available on the day of embryo transfer; in total, 290 women in the control group had at least one embryo replaced, whilst the corresponding number was 86 of 106 potential patients in the fibroid group (Table III). The pregnancy, implantation and ongoing pregnancy rates per embryo transfer were significantly reduced in the study group; 23.3, 11.9 and 15.1% respectively compared with 34.1, 20.2 and 28.3% in the control group. The odds ratio for conception with IVF or ICSI for a patient with an intramural fibroid compared to a patient without was 0.51 (CI 0.30–0.90).

Pregnancy rates per embryo transfer in women by age after the exclusion of women with fibroids >5 cm in size are listed in Table IV. The descriptive data of fibroids in the study group are recorded in Table V. After exclusion of fibroids >5 cm, the mean size of fibroids was 2.3 cm (90% range 2.1–2.5 cm).

Logistic regression analysis was performed in order to clarify the influence of fibroids on the outcome of IVF/ICSI treatment. Variables analysed included the presence of an intramural fibroid, age as a continuous variable, age ⩾40 years, serum FSH concentration, gonadotrophin requirement to effect stimulation, number of oocytes collected, and number of embryos available for transfer. Logistic regression analysis showed that the most significant factor with regard to a successful treatment cycle was the number of embryos available for transfer (odds ratio 1.12, $P < 0.001$, CI 1.05–1.19), thereby confirming the data of others (Templeton and Morris, 1998). The effect of age was largely limited to a reduced chance of pregnancy in women aged ⩾40 years (Table IV). In view of this, age ⩾40 years was included into the logistic regression, as well as using age as a continuous variable. After adjusting for the number of embryos available for replacement, the only significant variables were the presence of intramural fibroids, age and age ⩾40 years. After a further correction for age, and then those patients ⩾40 years, the presence of intramural fibroids reduced the chance of a positive pregnancy test (0.32–1.03, P = not significant and 0.32–1.04, P = not significant respectively), although not reaching significance at the 95th CI (Table VI). By performing logistic regression analysis for the outcome variable ‘ongoing pregnancy’, and also controlling for the number of embryos available for replacement and age, and then age ⩾40 years, it could be shown that fibroids significantly reduced the chance of an ongoing pregnancy by a factor of 0.46 (0.24–0.88, $P = 0.020$) and 0.46 (0.24–0.88, $P = 0.019$) respectively (Table VII). Poisson regression analysis for the outcome variable ‘embryo implantation’, when controlled for the number of embryos available for transfer and age, then age ⩾40 years showed there to be a trend towards a reduction in implantation in women with intramural fibroids; odds ratio 0.65 (0.41–1.05, $P = 0.076$) and 0.63 (0.39–1.01, $P = 0.055$) respectively (Table VIII).

The interpretation of this analysis means that, apart from the number of embryos available for replacement, both the presence of an intramural fibroid and age ⩾40 years were independently significantly associated with a marked reduction in the chance of an ongoing pregnancy after a cycle of IVF/ICSI, by factors of 0.46 and 0.32 respectively. Intramural fibroids may have a strong influence on the conception and implantation rates, although not reaching significance at the 95th CI.

Table II. Causes of infertility

Cause of infertility	Control patients (n = 322)	Study patients (n = 112)
Anovulatory	15 (4.6)	2 (1.7)
Endometriosis	1 (0.4)	0 (0)
Male factor	126 (39.0)	39 (34.8)
Unexplained	64 (19.8)	19 (17.0)
Tubal damage	78 (24.1)[a]	34 (30.4)[a]
Not recorded	39 (12.7)	18 (16.1)

Values in parentheses are percentages.
[a]Fisher’s Exact test, P = not significant for difference.

Table III. Ovarian stimulation profile of the patients and pregnancy and implantation rates

	Control patients (n = 322)	Study patients (n = 112)	Difference	P
No. of follicles on day of oocyte collection[a]	11.7 ± 6.0	12.1 ± 6.6	+0.4	NS
No. of oocytes collected[a]	9.3 ± 5.5	10.1 ± 6.3	+0.8	NS
No. of embryos suitable for replacement[a]	4.4 ± 3.8	4.5 ± 4.4	+0.1	NS
No. of embryos replaced[a]	2.1 ± 0.6	2.0 ± 0.8	−0.1	NS
Implantation rate (%)[b]	20.2 (16.8–24.2)*	11.9 (7.7–18.2)[+]	−8.3	0.018
Pregnancy rate (%)[b]	34.1 (28.7–39.9)*	23.3 (14.8–33.6)[+]	–10.8	0.016
Ongoing pregnancy rate (%)[b]	28.3 (23.1–33.8)*	15.1 (8.3–24.4)[+]	–13.2	0.003

[a]Values are mean ± SD.
[b]Values are mean (range).
*n = 290 patients achieved embryo transfer.
[+]n = 86 of the 106 patients with fibroids ⩽5 cm in size achieved embryo transfer.
NS = not significant.

In order to analyse the effect of replacing three as opposed to two embryos in women with fibroids, logistic regression analysis was performed after adjustment for FSH concentration >10 IU/l and age ⩾40 years. This showed a less favourable outcome with three-embryo replacement when compared with two embryos ($P = 0.04$) for the chance of an ongoing pregnancy.

Discussion

This is the first large prospective controlled study of the effect of fibroids on the outcome of assisted conception. The results showed that small intramural fibroids present in 25.7% of the patients reduced the chance of an embryo implanting by half. After allowing for the patient's age and the number of embryos available for transfer, the presence or absence of an intramural fibroid was a significant factor influencing a woman's chance of having an ongoing pregnancy after a cycle of assisted reproduction. However, the effect of intramural fibroids on pregnancy and implantation rates did not reach significance at the 95th CI. This may be due to insufficient numbers of women with fibroids in the study group, since by analysing the pregnancy rates per embryo transfer the power of the study was reduced to 77%. In order to allow for the confounding variables in a prospective study in assisted reproduction, logistic regression provided the best means of excluding these 'nuisance variables' as opposed to matching patients.

The mechanisms by which fibroids may reduce the implantation potential of an embryo are unclear, but proposed theories include local conditions (such as vascular changes), hyperplasia, atrophy or inflammation of the endometrium, or the presence of local transmitter substances in the myometrium (Bernard *et al.*, 2000).

Both groups had similar pretreatment serum FSH concentrations, but the study group were on average 2 years older than the controls, and both such factors are known to influence the success of a treatment cycle (Toner *et al.*, 1991). Thus, logistic regression analysis was performed in order to remove the effect of age as a confounding variable for the chance of an ongoing pregnancy. It was not possible to demonstrate any effect of intramural fibroids on the outcome of ovarian stimulation, as both groups of patients produced similar numbers of follicles, oocytes and embryos available for transfer.

Previous studies analysing the effect of intramural fibroids on the outcome of assisted conception have been retrospective, and have not demonstrated any clear effect. In one study (Farhi *et al.*, 1995), 46 women with documented uterine leiomyomas were compared with a control group with 'mechanical' infertility; implantation and abortion rates were both similar in the two groups. An analysis of IVF results showed that impaired implantation was associated with leiomyomas only where uterine intracavitary abnormalities co-existed. Patients with submucosal fibroids had a significantly lower implantation rate than those without myomas. One group (Stovall *et al.*, 1998) demonstrated a negative effect of the presence of fibroids

Table IV. Pregnancy rates by age

Age group (years)	Pregnancy rate (%)
20–<25	33.3
25–<30	32.5
30–<35	35.4
35–<40	33.1
⩾40	13.6[a]

[a]$P = 0.009$ for effect of age ⩾40 years on pregnancy rate.

Table V. Descriptive data on fibroids (all fibroids were intramural, or subserosal element was <50%)

	Fibroid patients ($n = 112$)
Incidence of secondary infertility	56 (50.0%). One patient had a previous late miscarriage
Outcome of previous IVF/ICSI ($n = 39$)	Six women conceived
Route of previous myomectomy ($n = 20$)	12 hysteroscopic (three were repeat procedures)[a] Eight laparotomies[b] (one subsequent hysteroscopic resection) One laparoscopic One vaginal
Mean (± SD) dimensions of uterus ($n = 85$)	7.5 ± 2.1 cm (length of uterus from internal os to fundus) 4.5 ± 1.6 (width of uterus across maximum diameter)
Mean (± SD) number of fibroids	1.8 ± 0.8 (range: 1–4)
Mean (± D) size of largest fibroid (cm), excluding women with fibroids >5 cm as excluded from final analysis ($n = 106$)	2.3 ± 1.1 cm (median 2.0 cm; 90% range 2.1–2.5 cm)[c]
No. of patients who underwent saline sonography/hysteroscopy due to proximity of intramural fibroid to endometrial cavity	65 (58%)
Pregnancy outcome in patients who conceived ($n = 20$)	13 ongoing singleton pregnancies Two early miscarriages One late miscarriage of twins One late miscarriage of a singleton Three biochemical pregnancies

[a]Two patients conceived in this treatment cycle.
[b]One patient conceived in this treatment cycle.
[c]Two women with fibroids of 4 cm in size conceived.

Table VI. Odds ratios with 95% confidence intervals by logistic regression analysis for a positive pregnancy test in women who have an embryo replaced: unadjusted, adjusted for the number of embryos available only and age (either as a continuous variable or age ⩾40 years) on the chance of positive pregnancy test

Predictor	Unadjusted	Adjusted for embryos available	Adjusted for embryos available and age	Adjusted for embryos available and age ⩾40 years
No. of embryos available	1.12 (1.05–1.19) $P < 0.001$ ——	Unchanged – ——	1.12 (1.06–1.20) $P = 0.001$	1.12 (1.05–1.20) $P = 0.001$
Maternal age	0.94 (0.89–0.99) $P = 0.023$ ——	0.93 (0.88–0.99) $P = 0.054$	Unchanged	–
Maternal age ⩾40 years	0.31 (0.13–0.75) $P = 0.009$ ——	0.36 (0.15–0.91) $P = 0.03$	–	Unchanged
FSH concentration	0.93 (0.84–1.03) $P = 0.159$	–	–	–
No. of ampoules	0.98 (097–1.00) $P = 0.034$ ——	0.98 (0.97–1.00) NS	–	–
No. of oocytes retrieved	1.07 (1.03–1.11) $P = 0.001$ ——	0.99 (0.92–1.95) NS	–	–
Intramural fibroid ⩽5 cm in size	0.51 (0.30–0.90) $P = 0.019$ ——	0.49 (0.28–0.88) —— –	0.57 (0.32–1.03) $P = 0.062$ (NS)	0.58 (0.32–1.04) $P = 0.067$ (NS)

—— If factor is a significant influence on pregnancy rate it is used in the next regression analysis.
NS = not significant.

Table VII. Simple odds ratios (OR) by logistic regression analysis for outcome variable: ‘ongoing pregnancy’ after embryo transfer, adjusted for embryos available for transfer and age or age ⩾40 years on the chance of an ongoing pregnancy in women with an intramural fibroid ⩽5 cm in size

	OR	*P*	(95% CI)
Uncontrolled effect of intramural fibroid ⩽5 cm in size	0.40	0.006	0.21–0.77
Effect of intramural fibroid ⩽5 cm in size controlled for the number of embryos available and age	0.46	0.020	0.24–0.88
Effect of intramural fibroid ⩽5 cm in size controlled for the number of embryos available and age ⩾40 years	0.46	0.019	0.24–0.88

Simple OR by logistic regression analysis for outcome variable: ‘ongoing pregnancy’ after embryo transfer, adjusted for embryos available for transfer and the presence of an intramural fibroid for age as a continuous variable or age ⩾40 years

	OR controlled for the number of embryos available and the presence of an intramural fibroid	*P*	95% CI
Age	0.94	0.042	0.88–1.00
Age ⩾40 years	0.32	0.039	0.11–0.94

Table VIII. Poisson regression analysis for outcome variable: embryo implantation, exposure being the number of embryos replaced in women with intramural fibroids ⩽5 cm in size

	Odds ratio	*P*	95% CI
Uncontrolled effect of intramural fibroid ⩽5 cm in size	0.59	0.025	0.37–0.94
Controlled for embryos available and age as a continuous variable	0.65	0.076	0.41–1.05
Controlled for embryos available and age ⩾40 years	0.63	0.055	0.39–1.01

Poisson regression analysis for outcome variable: embryo implantation for age as a continuous variable and age ⩾40 years, exposure being the number of embryos replaced, controlled by the number of embryos available for transfer and the presence of an intramural fibroid ⩽5 cm in size

	OR controlled for the number of embryos available and the presence of an intramural fibroid	*P*	95% CI
Age	0.95	0.024	0.91–0.99
Age ⩾40 years	0.64	0.178	0.33–1.23

on the outcome of assisted conception, although intramural and subserosal fibroids were analysed together. In a small study (Ramzy *et al.*, 1998), no effect of uterine fibroids was noted on treatment outcome. However, others (Eldar-Geva *et al.*, 1998) stratified patients according to the position of the myomas and reported implantation rates in controls as 15.8% compared with 15.7% in patients with subserosal fibroids, 6.4% in patients with intramural myomas, and 4.3% in the group of patients with submucosal fibroids. These results are similar to findings in the present prospective study. Interestingly, this study also assessed the effect of fibroids on miscarriage, the authors reporting miscarriage rates of 33.3% in the fibroid group and 16.3% in the control group; however, this difference did not reach significance due to small patient numbers. Confirmatory evidence of the influence of an intramural fibroid reducing the ongoing pregnancy rate can be inferred from a more recent study (Bernard *et al.*, 2000). This showed that women who undergo hysteroscopic resection of a solitary submucous myoma have a significantly higher live birth rate than those who undergo resection who have a co-existing intramural myoma.

The fact that patients with small intramural fibroids who undergo assisted reproduction have a reduced ongoing pregnancy rate has major implications for the practice of assisted conception. These patients might consider a myomectomy, or perhaps opt to have more embryos replaced than their counterparts without fibroids. Convincing evidence of any benefit of myomectomy before embarking on a cycle of assisted reproduction is lacking. In a study of myomectomy at laparotomy using microsurgical techniques for infertility patients, 57% conceived after surgery but only 10 of the patients studied had fibroids <5 cm in size (Li *et al.*, 1999). In a meta-analysis of 23 studies assessing fertility after myomectomy at laparotomy, one group (Vercellini *et al.*, 1998) reported an overall conception rate of 61% (95% CI 51–70%), but pointed out that the details of the number and size of the fibroids was scanty or absent in most of the reports analysed.

Laparoscopic myomectomy in properly selected infertile women resulted in a 2-year spontaneous cumulative conception rate of 51.2%, although the mean size of the main fibroid in this study was 4.5 cm (Dubuisson *et al.*, 2000a). There is also the concern of a potential risk of uterine rupture in a subsequent pregnancy after laparoscopic myomectomy, although this risk is known to be small (Dubuisson *et al.*, 2000b). Thus, there is no current evidence to advocate routine myomectomy on patients with small intramural fibroids undergoing assisted conception, notwithstanding the practical difficulties of attempting to locate such small myomas at the time of laparotomy or laparoscopy.

Although laparoscopic myolysis has proved successful at shrinking fibroids, early reports suggest that the risk of uterine rupture in a subsequent pregnancy is substantial (Vilos *et al.*, 1998). Another potentially more appropriate procedure for women with small myomas is vaginal myomectomy, although this technique has not been fully evaluated in infertile women (Davies *et al.*, 1999). As there is no prospective evidence to advocate surgery for these patients, the only other strategy which could be used to improve pregnancy rates would be to lower the threshold for replacing three embryos in these women. However, after adjusting for age, serum FSH concentration and number of embryos available for transfer using logistic regression, replacing three embryos failed to improve the outcome in the study group. Advocating three-embryo replacement would be contrary to the current Royal College of Obstetricians and British Fertility Society guidelines, which advise strongly against the replacement of three embryos in order to avoid triplet pregnancies (Templeton, 2000). On the basis of the present data, it would appear that the replacement of three embryos is not a logical solution to counteract the effect of the intramural fibroid. Only a three-arm randomized trial comparing the *status quo*—routine myomectomy for small fibroids or replacement of three embryos, might provide the answer.

Although patients with fibroids may have an increased chance of having a miscarriage (Buttram and Reiter, 1981), the profound effect of small fibroids on the chance of an 'ongoing' pregnancy in the current study was surprising. Others (Eldar-Geva *et al.*, 1998) reported a miscarriage rate of 16.3% in control patients, and 33.3% in a group of patients with small intramural fibroids, though this difference did not reach statistical significance.

In conclusion, patients with small intramural myomas undergoing assisted conception have a significantly reduced 'ongoing' pregnancy rate when compared with patients without an intramural myoma. However, whether routine myomectomy or the replacement of a greater number of embryos offers a solution to this problem will need to be evaluated prospectively.

Acknowledgements

The authors acknowledge the assistance of the nurses, embryologists and other members of the medical team of the assisted conception unit for their help in this study.

References

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

Buttram, V.C. and Reiter, R.C. (1981) Uterine leiomyomata: etiology, symptomology and management. *Fertil. Steril.*, **36**, 433–435.

Davies, A., Hart, R. and Magos, A.L. (1999) The excision of uterine fibroids by vaginal myomectomy: a prospective study. *Fertil. Steril.*, **71**, 961–964.

Dubuisson, J.B., Fauconnier, A., Chapron, C. *et al.* (2000a) Reproductive outcome after laparoscopic myomectomy in infertile women. *J. Reprod. Med.*, **45**, 23–30.

Dubuisson, J.B., Fauconnier, A., Deffarges, J.-V. *et al.* (2000b) Pregnancy outcome and deliveries following laparoscopic myomectomy. *Hum. Reprod.*, **15**, 869–873.

Eldar-Geva, T., Meagher, S., Healy, D.L. *et al.* (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. *et al.* (1995) Effect of uterine leiomyomata on the results of in-vitro fertilization treatment. *Hum. Reprod.*, **10**, 2576–2578.

Goldenberg, M., Sivian, E., Sharabi, Z. *et al.* (1995) Outcome of hysteroscopic resection of submucous myomas for infertility. *Fertil. Steril.*, **64**, 714–716.

Hasan, F., Arumugam, K. and Sivanesaratnam, V. (1991) Uterine leiomyomata in pregnancy. *Int. J. Gynaecol. Obstet.*, **34**, 45–48.

Hart, R., Molnar, B.G. and Magos, A. (1999) Long term follow-up of hysteroscopic myomectomy assessed by survival analysis. *Br. J. Obstet. Gynaecol.*, **106**, 700–705.

Khalaf, Y., Taylor, A. and Braude, P. (2000) Low serum estradiol concentrations after five days of controlled ovarian hyperstimulation for *in vitro* fertilization are associated with poor outcome. *Fertil. Steril.*, **74**, 63–66.

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.

Ramzy, A.M., Sattar, M., Amin, Y. *et al.* (1998) Uterine myomata and outcome of assisted reproduction. *Hum. Reprod.*, **13**, 198–202.

Ruach, M., Hart, R. and Magos, A. (1998) Outpatient hysteroscopy. *Contemp. Rev. Obstet. Gynaecol.*, **8**, 51–54.

Rogers, W.H. (1991) Poisson regression with rates. *Stata Technical Bulletin*, **1**, 11–12. (Reprinted in Stat Technical Bulletin Reprints, volume 1, 62–64.)

Seoud, M.A., Patterson, R., Muasher, S.J. *et al.* (1992) Effects of myomas or prior myomectomy on *in vitro* fertilization (IVF) performance. *J. Assist. Reprod. Genet.*, **9**, 217–221.

Steer, C.V., Mills, C.L., Tan, S.L. *et al.* (1992) The cumulative embryo score: a predictive embryo scoring technique to select the optimal number of embryos to transfer in an in-vitro fertilization and embryo transfer programme. *Hum. Reprod.*, **7**, 117–119.

Stovall, D.W., Parrish, S.B., Van Voorhis, B.J. *et al.* (1998) Uterine leiomyomas reduce the efficacy of assisted reproduction cycles: results of a matched follow-up study. *Hum. Reprod.*, **13**, 192–197.

Templeton, A. (2000) Avoiding multiple pregnancies in ART. Replace as many embryos as you like – one at a time. *Hum. Reprod.*, **15**, 1662.

Templeton, A. and Morris, J.K. (1998) Reducing the risk of multiple births by transfer of two embryos after *in vitro* fertilization. *N. Engl. J. Med.*, **339**, 573–577.

Toner, J.P., Philput, C.B., Jones, G.S. *et al.* (1991) Basal follicle-stimulating hormone level is a better predictor of *in vitro* fertilization performance than age. *Fertil. Steril.*, **55**, 784–791.

Vellenhoven, B.J., Lawrence, A.S. and Healy, D.L. (1990) Uterine fibroids: a clinical review. *Br. J. Obstet. Gynaecol.*, **97**, 285–298.

Vercellini, P., Maddalena, S., De Giorgi, O. *et al.* (1998) Abdominal myomectomy for infertility: a comprehensive review. *Hum. Reprod.*, **13**, 873–879.

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

Vilos, G.A., Daly, L.J. and Tse, B.M. (1998) Pregnancy outcome after laparoscopic electromyolysis. *J. Am. Assoc. Gynecol. Laparosc.*, **5**, 289–292.

Wallach, E.E. (1992) Myomectomy. In Thompson, J.D. and Rock, J.A. (eds), *TeLinde's Operative Gynecology.* 7th edn. Lippincott, Philadelphia, pp. 647–662.

Received on April 11, 2001; accepted on August 7, 2001