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The effect on IVF outcome of small intramural fibroids not compressing the uterine cavity as determined by a prospective matched control study

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BACKGROUND: Several studies have reported that the presence of intramural fibroids affects conception following IVF. We attempted to corroborate or refute the conclusions relating to IVF and leiomyomas of the aforementioned studies. METHODS: Women with small intramural leiomyomata (≤5 cm) discovered on initial pelvic sonographic studies performed in preparation for IVF were prospectively matched by age, with the next patient of the same age undergoing IVF who did not demonstrate fibroids (controls). RESULTS: Though no significant differences were found in outcome when comparing these two groups, there was a distinct trend for lower live delivery rates and higher miscarriage rates. CONCLUSIONS: These data support the conclusions of the only other prospective matched control study evaluating similar factors, i.e. that small intramural fibroids can negatively affect IVF outcome. Nevertheless, we think that a multicentre study should be conducted first before evaluating whether myomectomy improves outcome or not.

Key words: IVF/leiomyoma/matched controls/pregnancy rates/pre-term delivery

Introduction

There have been several unmatched studies claiming that abdominal myomectomy improved pregnancy rates (Babaknia *et al*., 1978; Berkely *et al*., 1983; Rosenfeld, 1986; Gehlbach *et al*., 1993). A review of seven published studies of patients with unexplained infertility following abdominal myomectomy found a 53.9% pregnancy rate (Dubuisson and Chapron, 1996). Another study found a 44.4% pregnancy rate following laparoscopic myomectomy (Dubuisson *et al*., 1996). Other studies support improvement of pregnancy outcome following laparoscopic or hysteroscopic removal of submucous fibroids (Starks, 1988; Katz *et al*., 1989; Rosati *et al*., 1989; Narayan *et al*., 1994; Goldenberg *et al*., 1995; Ubaldi *et al*., 1995; Sudik *et al*., 1996; Darai *et al*., 1997; Seinera *et al*., 2000). The precise mode of how intramural fibroids would cause infertility is not known. Some theories include cornual occlusion that could be caused if the intramural fibroid is adjacent to the intramural tubal segment (Ingersoll, 1963). Other theories are that fibroids could cause dysfunctional uterine contractility which could interfere with ovum transport, nidation, sperm migration, impairment of blood supply to the endometrium, atrophy and ulceration of the endometrium (Jacobson and Enzer, 1956; Deligdish and Lowenthal, 1970; Hunt and Wallach, 1974; Buttram and Reiter, 1981; Iosif and Akerland, 1983; Vollenhoven *et al*., 1990).

However, myomectomy is not without its risks. Uterine fistulae (Nezhat, 1992) and uterine rupture (Harris, 1992; Dubuisson *et al*., 1995) have been reported after laparoscopic myomectomy. Subsequent abdominal and pelvic adhesions have complicated myomectomy whether performed with laparotomy (Starks, 1988; Tulandi *et al*., 1993; Bulletti *et al*., 1996) or laparoscopy (Nezhat *et al*., 1994). In many of the published series, myomectomy was performed by the most experienced surgeons (Babaknia *et al*., 1978; Berkely *et al*., 1983; Rosenfeld, 1986; Verkauf, 1992; Gehlbach *et al*., 1993; Dubuisson and Chapron, 1996; Dubuisson *et al*., 1996). Thus before physicians suggest myomectomy, it is important to determine if the benefits of myomectomy outweigh the risks.

IVF is an expensive invasive procedure. One question facing a physician is whether myomectomy should be performed prior to embryo transfer. Unfortunately there have been several conflicting studies in the literature as to whether smaller intramural fibroids adversely affect IVF pregnancy outcome. One study (Stovall *et al*., 1998) concluded that leiomyomata decreased implantation rates, but no distinction was made between intramural or subserosal fibroids. Another group (Eldar-Geva *et al*., 1998) concluded that intramural and

submucosal fibroids but not subserosal fibroids decrease implantation rates even if no uterine cavity distortion is present.

However, Ramzy *et al*. concluded that uterine corporal myomata <7 cm that do not encroach the uterine cavity had no adverse affect on implantation or spontaneous abortion rates (Ramzy *et al*., 1998). Another study (Farhi *et al*., 1995) found that decreased implantation is associated with uterine fibroids only when uterine cavity abnormalities coexist.

A priori, smaller intramural or subserosal fibroids which do not compress the uterine cavity would seem to be less likely to impair implantation or increase the risk of spontaneous abortion than larger (>5 cm) fibroids, fibroids of any size which compress the uterine cavity, or submucosal fibroids. Before any randomized study comparing conservative treatment versus myomectomy to improve IVF success rates in women with smaller fibroids with no uterine cavity involvement should be performed, it is necessary to establish first whether these fibroids reduce fecundity with IVF. Since one study concluded that smaller, intramural (but not subserosal) fibroids lead to decreased implantation rates (Eldar-Geva *et al*., 1998) we decided to limit our study to women who have at least one intramural fibroid.

As mentioned, some theories suggest that obstruction to gamete transport may be responsible for the impairment of fertility (Farhi *et al*., 1995). Another theory is that fibroids may impair implantation (Farhi *et al*., 1995). This is the reason for choosing the IVF group to study since at least obstruction to gamete transport would be eliminated. Thus, the study would also evaluate whether fibroids in this category impair implantation and possibly whether they affect subsequent fetal survival.

Materials and methods

Sixty-one women with intramural leiomyomata discovered on initial pelvic sonographic studies performed in preparation for their first IVF cycle (study group) were prospectively matched by age with women without leiomyomata (control group) having their first IVF cycle. When a patient with a fibroid was selected, she was matched with the next IVF case where the woman was of the same age who did not demonstrate a fibroid. Further requirements for the study group were that the leiomyoma did not have a submucosal component, the patient never had previous surgery for leiomyomata or other uterine surgery (from medical history), all fibroids were ≤5 cm, and no other uterine cavity abnormalities existed, e.g. uterine septum or large polyps. All patients were required to have a hysterosalpingogram within 1 year of the IVF procedure. A patient could be included if other leiomyomata were present, e.g. subserosal or pedunculated (subserosal type) as long as they had at least one intramural fibroid and no submucosal fibroids.

All patients were treated between January 1, 1997 and March 31, 1998. Staffing, laboratory conditions and IVF protocols were not changed during this period.

Diagnosis of uterine fibroids was made using transvaginal sonography performed with a multi-frequency endovaginal transducer on a GE Logic 400 (General Electric Medical Systems, Milwaukee, WI, USA). Recorded was the type of fibroid (intramural, subserosal, submucosal, or pedunculated) based on the location in the uterus. The measurements of the dimensions of the fibroids, i.e. length, width and depth, and the mean diameter was then calculated. Also recorded was the position of the fibroid in the uterus based on height (fundus, corpus, lower uterine segment or cervical). If more than 3 months elapsed between the initial sonogram and the start of an IVF cycle, the fibroid was re-measured every 3 months to determine any increase or decrease in size.

Table I. Comparison of IVF variables

	Control group (n = 61)	Fibroid group (n = 61)
Baseline FSH[a]	5.34 ± 2.7	6.7 ± 4.5
Stimulation protocol		
Luteal phase	30 (49.2)	28 (45.9)
Follicular phase	31 (50.8)	33 (54.1)
Aetiology for IVF	14 (22.9)	18 (29.5)
Tubal factor		
Male factor	9 (14.8)	4 (6.5)
Male and female factors	13 (21.3)	12 (19.7)
Other female factors	25 (41.0)	27 (44.3)
Use of ICSI	21 (34.4)	24 (39.3)
No. of embryos transferred[a]	3.3 ± 1.2	3.2 ± 1.2
No. blastomeres per embryo transfer[a]	6.4 ± 2.1	6.5 ± 2.3

Values in parentheses are percentages.
[a]Mean ± SD.

The first embryo transfer occurring following ovarian stimulation and oocyte retrieval was included in the evaluation. If embryo transfer was deferred after the retrieval, because of inadequate endometrial thickness or risk of hyperstimulation, the outcome of the first frozen transfer was used. This occurred for six patients in the study group and 11 in the control group. Ovarian stimulation regimens used leuprolide acetate started either in early follicular phase or in mid-luteal phase in dosages ranging from 0.1 mg daily to 2 mg daily. The gonadotrophins were either all FSH (either urinary or recombinant) or mixtures of HMG and FSH. Exclusive use of FSH for stimulation was used by 29 women in the fibroid group and 32 of the controls. Embryo transfer occurred 3 days after oocyte retrieval. If available, up to twice as many embryos as intended to transfer were allowed to cleave and the rest were cryopreserved at the two-pronuclear stage. The best embryos (based on blastomere number and fragmentation) were transferred and any leftover embryos were then cryopreserved at the multi-cell stage (Baker *et al*., 1997). Assisted hatching was performed on all embryos transferred. A small hole was drilled in the zona pellucida of each embryo using acidic Tyrode's solution gently expelled from a small glass needle (Cohen *et al*., 1990; Check *et al*., 1996).

A serum β-HCG value >100 mIU/ml was considered as a chemical pregnancy. Demonstration of a sac by ultrasound at 8 weeks was a clinical pregnancy. A live delivery is self-explanatory.

χ^2-Analysis was used to compare the pregnancy rates by presence of fibroids. $P \leq 0.05$ was considered significant.

This study was approved by the ethics committee for the Cooper Center for IVF. The matched control study was suggested by the Institutional Review Board (IRB) of Cooper Hospital as a prelude to any subsequent randomized study of myomectomy. All patients knew their results may be used for analysis and publication.

Results

A comparison of the study and control groups with regards to the possible confounding variables of stimulation protocol, baseline FSH, number of embryos transferred, use of ICSI and etiology for IVF showed no differences between the groups (Table I). Since the patients were matched for age, the

Table II. Description of the study group with intramural uterine fibroids

	No. of patients	Pregnancy rate
No. of fibroids		
1	29 (47.5)	14 (48.3)
2	15 (24.6)	7 (46.7)
3	9 (14.7)	3 (33.3)
4	4 (6.6)	1 (25.0)
5	2 (3.3)	1 (50.0)
6	0	
7	2 (3.3)	0 (0.0)
Location of fibroids		
Fundus	31 (50.8)	12 (38.7)
Lower uterine segment	30 (49.2)	14 (46.7)

Values in parentheses are percentages.
P = not significant, for all variables.

distribution of age in the two groups was practically the same. In the fibroid group, the ages ranged from 27 to 43 with a median of 37 years, mean and SD of 36.6 ± 4.5 years. In the control group, the ages ranged from 26 to 43 with a median of 37 years and a mean ± SD of 36.6 ± 4.5 years.

For the 61 women in the study group, the number of fibroids per patient ranged from 1 to 7 with an average ± SEM of 2.1 ± 0.18 (SD = 1.4) fibroids per patient. The average size of the fibroid per patient ranged from 0.5 to 3.8 cm with an average (± SEM) of 1.5 ± 0.09 cm (SD = 0.70). The largest fibroid per patient ranged from 0.5 to 5.1 cm with an average (± SEM) of 1.8 ± 0.1 cm (SD = 0.9). The distribution of the number of fibroids per patient is summarized in Table II. Most patients (47.5%) had only one fibroid. Forty-two patients (68.9%) had only intramural fibroids, 19 (31.1%) had intramural and subserosal. Six of the patients (9.8%) had pedunculated fibroids. The fibroids were located in the fundus in 31 patients (50.8%) and in the lower uterine segment in 30 patients (49.2%).

In the fibroid group, five of the six deferred transfers were because of elevated estradiol (E_2) levels and risk of ovarian hyperstimulation syndrome (OHSS), the other one was by patient request. In the control group, six of the 11 deferred transfers were due to elevated E_2 levels and risk of OHSS, three were deferred for elevated progesterone levels on day of retrieval, one was deferred for poor endometrial lining and one deferred due to patient illness.

A comparison of IVF outcome by presence of fibroids is presented in Table III. Positive pregnancy tests were observed in 52.4% of the controls and 42.6% of the study group (P = 0.277). Clinical pregnancy rates were 47.5 and 34.4% respectively (P = 0.141, not significant). The spontaneous abortion rates for clinical pregnancies was 20.7% (6/29) for the controls and 33.3% (7/21) for the study group (P = 0.314, not significant). The delivery rates were 37.7 and 22.9% respectively (P = 0.076, not significant). Ninety-five per cent confidence intervals (CI) for the delivery rates were 25.5 to 49.9 for the controls and 12.3 to 33.3 for the study group. A 95% CI for the difference in the delivery rates for the two groups is –0.01 to 0.31. Given the sample size available in each group, this study had 50% power to detect a difference

Table III. Comparison of IVF outcomes

	Control group (n = 61)	Fibroid group (n = 61)
Positive β-HCG (>100 mIU/ml) (P = 0.277)[a]	32 (52.4)	26 (42.6)
Chemical	2	3
Ectopic	1	2
Clinical pregnancy (P = 0.141)[a]	29 (47.5)	21 (34.4)
Spontaneous abortion (P = 0.314)[a]	6 (20.7)	7 (33.3)
Delivered (P = 0.076)[a]	23 (37.7)	14 (22.9)

Values in parentheses are percentages.
[a]Not significant.

of at least 15% in the rates assuming a baseline rate of 20% at the 5% level of significance. To detect the same effect with 80% power, one would need 163 patients per group. The average gestational age at delivery was 37.0 weeks in the study group and 36.9 weeks in the control group. There were two pre-term deliveries in the study group and three in the control group. The implantation rates were 20.2% (41 sacs/203 embryos transferred) in the control group versus 13.6% (27 sacs/208 embryos transferred) in the fibroid group (P = 0.08, not significant).

Further comparisons within the study group showed no difference in pregnancy rates by number of fibroids or site of fibroids (Table II). Patients with fibroids in the fundus had a pregnancy rate of 38.7% as compared with a pregnancy rate of 46.7% for patients with fibroids in the lower uterine segment.

Discussion

The first publication on small uterine fibroids not compressing the uterine cavity and IVF concluded that there was no effect on implantation rates (Farhi *et al*., 1995). However, three different studies in 1998 left this issue quite confusing. Two studies disagreed with the study by Farhi *et al*. (Farhi *et al*., 1995; Eldar-Geva *et al*., 1998; Stovall *et al*., 1998). Another study (Ramzy *et al*., 1998) supported the earlier conclusions that these fibroids do not reduce implantation rates. There has only been one previous matched control study (Stovall *et al*., 1998). The trend seen in our data of lower delivery rates in those with fibroids supports their conclusions even though the size of fibroids in the present study was smaller than patients in the Stovall *et al*. study. In the present study, about half of the fibroids were located in the lower uterine segment whereas 93% were in the fundus in the Stovall *et al*. study.

We had proposed to our IRB to randomly assign women with small intramural fibroids who failed to conceive after one embryo transfer to either having myomectomy before the next transfer or no surgery (controls). The committee concluded that the previous studies were equally divided as to whether or not these fibroids negatively affected implantation following IVF. They suggested that we should first evaluate a prospective matched study, as presented here, and if we found that in our own population fibroids appear to negatively affect fecundity, to resubmit the proposal to evaluate surgery.

These data presented here do not show a significant adverse affect of this type of fibroids on either the percentage of

positive β-HCG levels (>100 mIU/ml), clinical pregnancies or percentage delivered. However, there appeared to be a trend for lower delivery rates in this group, but there was insufficient power to demonstrate significance. The 42.6% rate of positive serum β-HCG level in the group with fibroids was respectable. It suggests that if smaller intramural fibroids have any negative affect on pregnancy outcome following IVF, it is probably not by preventing implantation but more so in losses occurring after conception. One would need 163 patients per group to detect a difference of 15% in the spontaneous abortion rates and delivery rates at the 0.05 level of significance with 80% power.

A study by Seoud *et al*. found only 11 of 1415 IVF patients without previous myomectomy having confirmed fibroids (Seoud *et al*., 1992). Possibly in another study we should eliminate women whose fibroids are below a certain size; the mean size for the study presented here was 1.5 cm but was 2.9 cm in Stovall's study (Stovall *et al*., 1998). If we kept the sizes the same, for the Cooper Center for IVF to have approximately the right number of patients to show significant differences it would take about 6 more years. Hopefully this study will encourage a multicentre cooperative study to evaluate sooner than this whether fibroids negatively affect IVF outcome.

There have been further publications since we began our prospective matched controlled study. One retrospective study concluded that the presence of untreated intramural fibroids significantly reduced the delivery rate following hysteroscopic resection of submucous myomas (Bernard *et al*., 2000). However, the most recent study, once again a retrospective analysis, did not show a significant difference in live birth rates in women <40 years with fibroids versus controls (though a mild trend for lower rates) (Surrey *et al*., 2001). However, they did find a lower implantation rate in those with fibroids (Surrey *et al*., 2001). Nevertheless because of the relatively high live birth rate in all groups, they stated that surgical intervention cannot be justified (Surrey *et al*., 2001).

Bajekal and Li recently reviewed the effect of fibroids on fertility and miscarriage (Bajekal and Li, 2000). They stated that different types of fibroids may affect reproductive outcome to a different extent. They suggested that submucous fibroids were most responsible for infertility and miscarriage, and subserosal the least responsible. Intramural fibroids have an intermediate role. They stated that proper assessment of the benefits and risks of surgery for individual patients should be carefully considered. If one combines the data from the only two prospective matched controlled studies (Stovall *et al*., 1998 and the present study) there seems to be a definite adverse effect of intramural fibroids ≤5 cm on the live birth rate. However, the live birth rates are sufficient so that myomectomy does not seem to be a reasonable procedure to suggest prior to attempting at least one IVF cycle. After a thorough review of the literature and evaluation of our own data, it is not likely that any one IVF centre would have a sufficient number of patients with small intramural fibroids not compressing the uterine cavity to be able to prospectively compare the effects of myomectomy for these type of fibroids. Thus we will not re-submit to our IRB. Instead we hope that this study encourages (rather than discourages as in the Surrey *et al*., 2001 study) a multicentre cooperative study to determine which patients to evaluate, and then randomly compare myomectomy or control to determine the risk/benefit ratio for this procedure.

Unless such data are provided, it is probably unethical as yet to subject women needing IVF to the risks of myomectomy for small intramural fibroids not encroaching the uterine cavity. However, based on these data, we think it more appropriate not to evaluate women failing to conceive after her first transfer, but rather women attaining a positive serum β-HCG level but failing to achieve a viable pregnancy.

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