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Uterine myomata and outcome of assisted reproduction

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The aim of this work was to study the effect of uterine myomata on the implantation rate and outcome in in-vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI). Among 406 patients, 51 (12.6%) were found to have uterine corporeal myomata. Twelve patients were excluded from the study as they had large myomata, submucous myomata or intramural myomata encroaching on the cavity. These patients were advised to have myomectomy before being enrolled in the IVF/ICSI programme. The remaining patients (n = 39) were sorted according to the number, site and size of the myomata as assessed by transvaginal sonography. Three patients had more than one myoma. Most of the myomata were subserous (72.7%) and the mean diameter of the myomata was 3.5 ± 0.9 cm. A control group (n = 367) was chosen with normal uteri and no history of uterine reconstruction surgery. The mean age of myoma patients was 34.7 ± 3.6 years as compared to 34.0 ± 4.4 years in the control group. The age, period of infertility, body mass index, duration and number of human menopausal gonadotrophin ampoules needed for stimulation, oestradiol levels, number of oocytes retrieved and the fertilization rate were not significantly different in the myoma patients compared to the control group. Fifteen myoma patients (38.5%) subsequently showed one or more pregnancy sacs on ultrasonography of which three (20%) spontaneously aborted during the first trimester and two (13.3%) had preterm labour, as compared to 123 (33.5%), 19 (15.5%) and nine (7.3%) respectively, among the control group (P = 0.27, 0.33 and 0.21). In conclusion, uterine corporeal myomata, not encroaching on the cavity and <7 cm in mean diameter, do not affect the implantation or miscarriage rates in IVF or ICSI.

Key words: ICSI/implantation/IVF/leiomyoma/reproduction/uterus

Introduction

Uterine leiomyomata are essentially asymptomatic. However, in some cases they have been assigned as a probable cause of infertility (Buttram and Reiter, 1981). Myomectomy has become popular as a line of treatment of infertile patients having myomata (Rosenfeld, 1986). Several studies have investigated the conception rate among infertility patients following myomectomy, suggesting promising results (DeCherney, 1990; Verkauf, 1992; Dubuisson *et al*., 1996).

A higher incidence of spontaneous abortion, premature labour, fetal growth retardation, abnormal fetal presentation was noted among pregnant women having uterine myomata (Lanouette and Diamond, 1996). This was in addition to haemorrhage, red (carneous) degeneration and increased incidence of postpartum sepsis (Excoustòs and Rosati, 1993). Most of these complications, however, occurred in cases of large, multiple, mostly submucous myomata (Bronson and Wallach, 1977; Pritchard and McDonald; 1980; Buttram and Reiter, 1981; Lanouette and Diamond, 1996).

The interference of uterine myomata with gamete transport, normal uterine contractility (Hunt and Wallach, 1974; Vollenhoven *et al*., 1990) and in particular completion of the process of implantation has been a point of concern (Deligdish and Lowenthal, 1970; Buttram and Reiter, 1981).

With the evolution of assisted reproduction there has been revival of interest in the potential effect of uterine myomata on the uterine vasculature and the associated endometrial changes that may interfere with nidation and ultimately the success of the treated cycles. The purpose of this work was to study the effect of uterine fibromyomata on the outcome of in-vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI) cycles.

Material and methods

This retrospective controlled study included the analysis of 406 embryo transfer cycles, among primary infertility patients undergoing IVF/ICSI programmes in the Egyptian IVF–ET Centre from December 1995 to May 1996. The study group included 39 patients (group I) undergoing IVF or ICSI cycles and having uterine fibromyomata. This group did not include patients found to have large myomata (⩾7 cm), or myomata encroaching on the cavity. An age-matched control group (group II, n = 367) was established having normal uteri and with no history of uterine reconstruction surgery.

Trial 'dummy' embryo transfer is performed routinely for all our patients before starting the IVF/ICSI programme (Mansour *et al*., 1990).

Stimulation protocol

All patients received buserelin acetate (Suprefact nasal spray; Hoechst AG, Frankfurt am Main, Germany), 200 μg in each nostril, at 8 hourly intervals 1 week before the expected day of menstruation. This was continued through the treatment cycle until the time of

human chorionic gonadotrophin (HCG) injection. Human menopausal gonadotrophin (HMG) (Pergonal; I.F. Serono, S.P.A. Rome, Italy), two ampoules every 12 h, was administered after the concentration of serum oestradiol reached its basal value, and was continued for 5 days. The dose was tailored thereafter according to the number and sizes of follicles as monitored daily using a vaginal transducer (7 MHz Model 8538, of Bruel & Kjaer Ultrasound Scanner Model 1849, DK-2850 Naerum, Denmark). Serum oestradiol was measured daily starting on day 8 of HMG treatment. HCG (Pregnyl; El Nile Company, Egypt) 10 000 IU i.m., was administered when the mean diameter of two or more lead follicles reached 18 mm. Transvaginal ovum retrieval was planned 36 h later. Embryo transfer was performed 48–72 h following fertilization. Luteal phase support was supplied for all patients in the form of HCG (Pregnyl) injections, 2500 IU i.m., every fourth day starting the day of embryo transfer and continued for 2 weeks. In cases of positive serum β-HCG, support was continued until the twelfth week of gestation. Cases that were considered at high risk of developing ovarian hyperstimulation syndrome (OHSS), progesterone injections (Steris Laboratories, Inc., Phoenix, AZ 85043, USA) (50 mg/ml), 2 ml daily i.m., were given as an alternative luteal phase support starting the day of embryo transfer and following the same schedule thereafter as for HCG.

Ovarian response

Response to the given ovarian stimulation protocol used in this study was considered sufficient if more than four follicles developed during the cycle and continued to show linear growth until the day of HCG. Women failing to show sufficient response were excluded from this study.

Patients were enrolled in either IVF or ICSI programmes. The IVF ($n = 162$) and ICSI ($n = 244$) cycles were included together for the sake of this study. Age, period of infertility, body mass index (BMI), duration and number of HMG ampoules needed for stimulation, oestradiol level, the fertilization rate, the number of embryos transferred per cycle, the total and clinical pregnancy rates per embryo transfer, the implantation, abortion and preterm labour rates were determined for all patients in both groups.

Myoma assessment

Transvaginal ultrasound was carried out routinely for all our patients before the treatment cycle. Findings were reported in the patients records and hard copies were retained in their files. Those with uterine myomata had detailed sonographic evaluation starting with a transabdominal scan with full bladder to be followed by transvaginal ultrasound after voiding. Scanning of the uterus was carried out in two planes (sagittal and coronal) at the level of maximum width. Three dimensions were measured for each myoma. If more than one myoma was identified, the mean diameter and location of the largest was used as a reference. Multiplicity of the myomata was also noted.

A myoma with >50% of its diameter bulging out of the uterine contour line was defined as subserous. Intramural myomata were those strictly located within the uterine contour. Patients with submucous myomata or intramural myomata encroaching on the cavity line were usually submitted for hystersalpingography (HSG), if that had not been performed recently. Patients having myomata that distorted the cavity, or myomata ⩾7 cm were usually advised to have myomectomy before being re-scheduled for an assisted reproduction cycle. The latter group of patients were not included in our present study.

During ovum retrieval, ultrasonographic re-evaluation of the myomata were re-recorded and included in the patients' files.

Statistical analysis

Comparisons between means among the study groups were performed using Student's *t*-test. Results are presented as mean values ± SD.

Table I. Cycle profiles

	Group I	Group II	
n	39	367	
No. of HMG ampoules	49.1 ± 20.46	39.3 ± 17.7	NS
Days of stimulation	11.18 ± 2.3	11.5 ± 2.0	NS
Mean oestradiol (pg/ml)	2007 ± 1192.6	1968 ± 1294.3	NS
Mean no. of oocytes	12.4 ± 9.6	12.5 ± 6.9	NS
Fertilization rate per retrieved oocyte	57.8%	58.3%	NS
Mean no. of embryos transferred	3.3 ± 1.5	3.2 ± 1.2	NS

HMG = human menopausal gonadotrophin, NS = not significant.

Table II. Myoma characteristics

Anatomic location ($n = 44$)	
Intramural	12
Subserous	32
Mean diameter of intramural myomata	3.2 ± 1.1 cm
Mean diameter of subserous myomata	3.8 ± 0.9 cm

All reported *P* values are tested by the χ^2-test. $P < 0.05$ was considered statistically significant.

Results

The mean age among group I patients was 34.7 ± 3.6 years as compared to 34.0 ± 4.4 years among those of group II ($P > 0.05$). The period of infertility in group II patients was 9.2 ± 5.1 years as compared to 8.7 ± 4.9 years in group I.

Intracytoplasmic sperm injection cycles were indicated for patients with poor semen characteristics. IVF cycles were indicated for cases of tubal disease (48 patients, including 12 cases of hydrosalpinx), partial or total tubal obstruction together with pelvic adhesions (32 patients), or endometriosis as documented by laparoscopy (28 patients). Twenty four patients had documented ovarian endometriomata. The remaining patients ($n = 30$) had unexplained infertility.

The duration and number of HMG ampoules required for stimulation, oestradiol levels, number of oocytes retrieved and the fertilization rate were not statistically significantly different between group I and group II patients (Table I).

From a total of 58 patients having uterine myomata, seven were found to have a history of myomectomy and 51 were found to have uterine myomata as documented by hysterosalpingography or laparoscopy in addition to transvaginal sonography. Five patients had submucous myomata or intramural myomata encroaching on the cavity line and seven had myomata >7 cm in mean diameter. These were excluded from the study. The remaining 39 patients were included in our study (group I).

The majority of myomata, according to our definition, were subserous (72.7%). The mean diameter of all the myomata (subserous and intramural) was 3.5 ± 0.92 cm. Three patients had multiple myomata. One patient had two myomata and two patients had three (Table II)

The incidence of uterine myomata increased with advancing age (Table III). More patients aged ⩾36 years (17/39 patients,

Table III. Patients distribution among age group

	Age (years)				
	20–25	26–30	31–35	36–40	>40
Group I (39 patients)	0	6 (15.4%)	16 (41.03%)	13 (33.3%)*	4 (10.3%)*
Group II (367 patients)	12 (3.3%)	105 (28.6%)	166 (45.2%)	71 (19.4%)*	13 (3.5%)*

*$P < 0.05$.

Table IV. Pregnancy outcome among cases

	Total pregnancies	Clinical pregnancies	Implantation per embryo	Abortions	Pre-term labour	Deliveries (% total cases)
Group I (39 cycles)	18 (45.0%)	15 (38.5%)	16/128 (12.5%)	3 (20.0%)	2 (13.3%)	9 (23.1%)
Group II (367 cycles)	154 (42.0%)	123 (33.5%)	165/1192 (13.8%)	19 (15.5%)	9 (7.3%)	95 (25.9%)
Total (406 cycles)	172 (42.4%)	138 (34.0%)	181/1320 (13.7%)	22 (15.9%)	11 (8.0%)	105 (25.9%)

43.6%) were present in the population with uterine myomata than in the control group (84/367, 22.9%). The difference was statistically highly significant ($P < 0.005$).

Patients with uterine myomata showed no tendency towards excess body fat. The body mass index for the myoma group was 26.8 ± 3.95 (21.3–38.1) as compared to 26.99 ± 3.90 (18.7–40.8) kg/m^2 in the control group (not significant).

No noticeable changes in the size or echogenicity of the myomata were reported during re-evaluation on the day of ovum retrieval. Before starting the HMG treatment the mean diameter of intramural myomata was 3.2 ± 1.1 cm, and that of the subserous myomata was 3.8 ± 0.9 cm. On re-evaluation, the mean diameters were 3.26 ± 1.2 and 3.72 ± 0.9 cm respectively.

Embryo transfer was difficult in three patients in group I (7.7%) and 13 in group II (3.5%). Difficult embryo transfer essentially entails the use of tenaculum, or uterine sound before passage of the embryo transfer catheter. The cause of difficulty mainly is attributed to a distorted, excessively curved or elongated cervical canal.

The clinical pregnancy rate, implantation per embryo, abortion and preterm labor rates were not statistically significantly different between the two groups (Table IV).

In this study 16 sets of twins, eight of triplets and four of quadruplets were reported. The only multiple pregnancy among the myoma group of patients was one set of triplets. Three sets of quadruplets and six sets of triplets had successful selective embryo reduction. There were no procedure-related abortions or serious complications. One set of triplets was to a patient with a single uterine myoma. This patient refused selective embryo reduction and unfortunately aborted spontaneously at 18 weeks. There were no ectopic pregnancies.

No group I patients suffered from symptoms suggesting degenerative changes within the myomata during pregnancy.

Discussion

Uterine myomata are found in ~25% of women of childbearing age (DeCherney, 1990). Most of these women are non-symptomatic and fertile. In the fourth and fifth decades of life, uterine myomata occur in increasing frequency, unfortunately at a time when some women may seek pregnancy either willingly or following periods of infertility (Verkauf, 1995). In this respect, uterine myomata may act as a deterrent to conception and successful culmination of pregnancy. It has been stated that 40% of women undergoing myomectomy are infertile (Rubin, 1954) and that 5% of infertile women have uterine myomata (Hunt and Wallach, 1974).

In the present series, 13.7% of the studied group had uterine myomata or a history of myomectomy. This higher percentage may be due to the fact that every patient attending an assisted reproduction programme, is scrutinized by transvaginal sonography for genital tract abnormalities, in addition to hysterosalpingography, hysteroscopy or laparoscopy. This provided better diagnostic modalities for uterine myomata.

The mean age of patients in the present study was 34.5 years. Most of our patients (44.8%) belonged to the 31–35 year age group. Similar findings were found in related studies (Seoud *et al*., 1992; Farhi *et al*., 1995). There were various explanations for this, including the possibility that women may choose to delay marriage and childbearing in favour of advanced education or established careers (Mosher and Pratt, 1991). This may not be applicable to patients from our part of the world (Middle East), where in our study, as an example, about one-third of patients (30.3%) were <30 years old and one-quarter (25.0%) were >35 years. However, other explanations may be related to our patients such as economics, tradition, delay in seeking medical consultation or a preference to exhaust means of spontaneous pregnancy, whether medical or surgical, before resorting to assisted reproduction. The consideration of age has also highlighted the higher proportion of uterine myomata among older infertile females. In our series there were significantly more older patients with uterine myomata, even after excluding large myomata and those encroaching on the uterine cavity.

The cause–effect relationship of myomata with infertility has not been clearly established. An intramural fibroid adjacent to the intramural tubal segment may cause cornual occlusion and a large posterior fibroid may interfere with the relationship between the tube and the ovary and disturbs ovum retrieval

(Ingersoll, 1963). A submucous or an intramural myoma may cause dysfunctional uterine contractility, interfering with sperm migration, ovum transport or nidation (Hunt and Wallach, 1974; Buttram and Reiter, 1981; Vollenhoven *et al*., 1990). In addition, uterine myomata may be associated with preconception (implantation) failure or gestation discontinuation (abortion) due to focal endometrial vascular disturbance as well as endometrial inflammation, secretion of vasoactive substances, or enhanced endometrial androgen environment (Deligdish and Lowenthal, 1970; Buttram and Reiter, 1981; Mattingly and Thompson, 1985).

Myomectomy is most commonly performed for women who are interested in preserving or enhancing their reproductive potential (Verkauf, 1992). Some cases with primary infertility, who had myomectomy for submucous and intramural myomata distorting the cavity, were found during surgery to have other factors that may explain their infertility including tubal disease, pelvic adhesions, or endometriosis (Berkeley *et al*., 1983; Seoud *et al*., 1992; Verkauf, 1992).

Moreover, uterine myomata may be present in patients who otherwise may be considered to have unexplained infertility. In their review of 18 reports, Buttram and Reiter (1981) found that 6% of 1193 infertile patients had myomata as the only finding in their infertility workout. An interesting report by Rosenfeld (1986) supports the role of uterine fibroids as a possible cause of infertility. He reported a pregnancy rate of 65.2% following myomectomy among 23 otherwise unexplained infertility patients with uterine fibroids, none of which were submucous in location. Dubuisson *et al*. (1996) reviewed the results from seven published studies of patients with uterine fibroids and unexplained infertility. He reported a mean intrauterine pregnancy rate following myomectomy via laparotomy of 53.9%. In their own series, the pregnancy rate following laparoscopic myomectomy reached 44.4% (Dubuisson *et al*., 1996).

In this respect, laparoscopic myomectomy, when performed by an experienced surgeon, may be a safe technique and may offer comparable results with those obtained by laparotomy (Dubuisson *et al*., 1996). However, in our view the debate is not about the technique for performing myomectomy but the justification for myomectomy itself as a treatment of infertility patients (Dubuisson and Chapron, 1996). There have been reports reflecting concerns about the sequel of laparoscopic myomectomy. Nezhat reported uterine indentation at all sites of laparoscopic removal of intramural or deep subserosal myomata at second look laparoscopy (Nezhat *et al*., 1991). Uterine fistulae have also been reported, in some cases, during follow-up of these patients (Nezhat *et al*., 1992). This has raised concerns about the potential compromise of the integrity of the uterine wall during subsequent pregnancies following laparoscopic myomectomy in infertile patients. Two reported cases of uterine rupture during the third trimester of pregnancy have been recorded following the procedure (Harris, 1992; Dubuisson *et al*., 1995). The development of abdominal and pelvic adhesions has also been reported following myomectomy whether performed via laparotomy (Starks, 1988; Tulandi *et al*., 1993) or laparoscopy (Nezhat *et al*., 1994).

Concerning the possible deterrent effect of uterine myomata on implantation and uterine contractility, the association must be considered between uterine myomata and an unfavourable outcome in IVF/ICSI cycles. In a study on the effect of uterine myomata on the outcome of IVF cycles, Seoud *et al*. (1992) reported comparable ongoing pregnancy rates in IVF patients having uterine myomata to those with prior myomectomy. Moreover, they found no significant difference in the total and ongoing pregnancy rates between patients with prior myomectomy and all IVF patients. Another study by Farhi *et al*. (1995) reported similar findings and that implantation rate and pregnancy outcome were impaired only in cases in which uterine myomata caused deformity of the cavity.

It is our policy not to allow patients with large myomata or those having myomata which are encroaching on the cavity line to be enrolled in an assisted reproduction programme. We usually counsel this group of patients very carefully, explaining clearly the aforementioned facts. We believe that until further studies have been carried out, this group of patients should be offered myomectomy as a wise option before including them in assisted reproduction cycles.

In our series, we did not include cases with a history of myomectomy. Our aim was to answer the question: Should all patients with uterine myoma be subjected to myomectomy before being referred for an assisted reproduction cycle, regardless of the size and site of the myomata? To answer this question, we compared the reproductive performance of normal unscarred uteri to those with uterine myomata. Multiple treatment cycles for the same patient were excluded from the study.

We did not include patients having large myomata and those having myomata that may cause deformity of the uterine cavity. With this exclusion the ongoing pregnancy rate was comparable in patients with uterine myomata and those with normal uteri. The implantation rates were comparable in both groups. Both the abortion and the preterm labour rates were higher among patients with uterine myomata (20 and 13.3% respectively) as compared to patients with normal uteri (15.5 and 7.3% respectively), but these differences were statistically non-significant. These rates in our study of cases with uterine myomata were similar to those reported in the literature (Lanouette and Diamond, 1996).

Caution should be exercised when making the decision to perform myomectomy in infertile patients even if they are to be enrolled in assisted reproduction cycles. We believe that uterine myomata should not necessarily be excised when diagnosed in infertile patients. Patients having myomata not encroaching on the cavity and of diameters <7 cm may not need myomectomy before being scheduled for assisted reproduction cycles. Further studies in a larger series of patients are required to confirm these views.

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