Effects of leiomyomas less than 5 cm in diameter on the outcomes of assisted reproductive technology

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Abstract

Objectives. *To evaluate the effects of intramural and subserosal uterine leiomyomas with a diameter less than 5 cm, on the outcome of assisted reproductive technology (ART).* ***Methods.*** *A retrospective, cohort study conducted in a referral center. Patients with subserosal and /or intramural myomas less than 5 cm constituted the myoma group (n=152), while patients with tubal factor infertility without uterine myomas formed the control group (n=160). Only the patients undergoing their first cycle of ART were included in the study.* ***Results.*** *After adjusting for age, the difference in implantation, the clinical pregnancy and live birth rates between the groups were no longer significant. Preterm delivery rate was comparable between the groups.* ***Conclusion.*** *As intramural and subserosal myomas less than 5 cm in diameter appeared to have no effect on the rates of clinical pregnancy and implantation following ART, myomectomy should not be offered routinely to patients with myomas less than 5 cm in size.*
Keywords: *assisted reproductive technology, infertility, leiomyoma, myomectomy*

Introduction

Leiomyomas are the most common solid tumors of the uterus and estimated to occur in 20% to 50% of women, with increased frequency during the late reproductive years[1]. Leiomyomas are among the factors that cause infertility. The incidence of myomas as the cause of infertility has been estimated to range from 1% to 2.4%[2]. Primarily two mechanisms have been propounded concerning the relation between leiomyomas and infertility, obstruction of gamete transport and impaired implantation. The size, number and localization of myomas may play an important role in infertility. Submucosal fibroids disrupt the continuity of the inner myometrium and compromise the physiology of early reproductive process. Submucosal myomas are proposed to be removed surgically before assisted reproductive technology (ART) applications[3]. However, there is no consensus on intramural and subserosal myomas, yet. Especially myomas which are bigger than 5 cm are recommended to be operated prior to the infertility treatment. The influence of small, non-cavity-distorting myomas on infertility is controversial; and yet, no consensus has been made on this issue.

The aim of this study was to evaluate the effects of intramural and subserosal uterine leimyomas with a diameter less than 5 cm not distorting the uterine cavity on the outcome of IVF/ICSI treatment.

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Methods

A retrospective, cohort study was conducted in a referral center for assisted reproduction.

One hundred and fifty-two patients, with subserosal and/or intramural myomas that were less than 5 cm in size and did not distort the uterine cavity, constituted the myoma group and patients admitted to the clinic in the same period with tubal factor infertility without uterine myomas formed the control group (n=160). The ethics committee approved the study protocol. An informed consent was obtained routinely from all participants before beginning ART cycle, which allows using patients' information for scientific purposes. Women older than 40 years of age, and those with any kind of ovarian cysts were excluded from the study. All women included had day 3 (D3) follicle stimulating hormone (FSH) levels of <15 mIU/mL. In the myoma group, no other cause of infertility other than myomas was identified. Only the patients undergoing their first cycle of IVF were included in the study.

A standard long gonadotropin-releasing hormone (GnRH) agonist protocol was used for the treatment. Pituitary desensitization was achieved by daily subcutaneous administration of a GnRH analog (Lucrin, Abbott, USA) which was started at 21st day of menstrual cycle. Thereafter ovarian stimulation was initiated with recombinant FSH (Puregon, MSD, USA or Gonal F, Merck-Serono, Switzerland). Transvaginal ultrasound (US) was performed for monitoring oocyte development. In order to trigger the final stage of ovulation 10.000 IU human chorionic gonadotropin (hCG) (Pregnyl, MSD, USA) was administered. Transvaginal US-guided oocyte retrieval was performed 36 hours after hCG administration. All mature oocytes were subjected to ICSI. Ultrasound-guided embryo transfer was performed at 48 or 72 hours of oocyte retrieval.

Statistical analysis of the data was performed using Statistical Package for the Social Sciences (SPSS) for Windows (version

13.0; SPSS Inc., Chicago, IL, USA). Demographic characteristics between two groups were compared by student t test and a p value less than 0.05 was considered as statistically significant.

All results were presented as estimates, with 95% confidence intervals (CI). A p value of <0.05 was considered significant when 'no effect' was not in the interval. Logistic regression analysis was performed to identify the possible predictors of pregnancy outcomes.

Results

The mean age of the patients in the myoma group was significantly higher than that of the control group (34.97±4.73 vs. 32.14±5.28 respectively; p<0.0001). Demographic characteristics of patients in terms of infertility duration (months), basal FSH and estradiol (E2) levels were similar in the groups (116.51±65.06 vs. 111.07±58.51; 7.58±2.68 vs. 7.90±2.62; 50.54±39.28 vs. 46.16±30.42, respectively) (Table 1).

The clinical pregnancy rates were statistically different between the two groups. Pregnancy rates were 11.8% for women with myoma and 26.9% in women without myoma (Odds ratio O.R.= 0.365, 95% CI = 0.2–0.668). Implantation rates were also different between the groups, 8.3% in the myoma group and 16.1% among controls (O.R.= 0.467, 95% CI= 0.291–0.751). Live birth rate was lower in women with myoma than in the no myoma group (9.2% vs. 21.3%, O.R.= 0.376, 95% CI= 0.192–0.733). Premature delivery (<37 weeks of gestation) is an undesired outcome that occurred in a higher proportion of patients with myoma than those without, 28.6% with myoma versus 23.5% in the no myoma group, but statistical significance was not reached (O.R. = 1.3, 95% CI = 0.319–5.295) (Table 2).

Logistic regression analysis was performed to understand the effect of myoma on the outcome of ART treatment. It showed that the two significant factors with regard to pregnancy outcome were presence of myoma and age. After adjusting for age in order to remove the effect of age as a confounding variable, the presence of myoma reduced the clinical pregnancy rate, although not reaching significance at the 95th CI. (O.R.= 0.48, p=0.023, 95%CI= 0.255-1.003).

After controlling for age there was a reduction both in implantation and live birth rates in myoma group, although this did not reach significance at the 95th CI. (O.R.= 0.58, p=0.027, 95%CI= 0.355-1.017 and O.R.= 0.42, p= 0.045, 95%CI= 0.238-1.011).

Discussion

The relationship between leiomyomas and infertility is not obvious. It is known that fibroids are more common in infertile women. Despite the many studies reporting this association, the mechanism by which the fibroids influence the reproductive functions remains unclear. However, there are a number of theories including altered contractility of the myometrium, uterine cavity distortion, endometrial inflammation, thinning and atrophy, and obstruction of gamete transport[2,4,5,6].

Donnez et al. performed a meta-analysis to evaluate the relation between leiomyomas and infertility, and reviewed

Table 1 Clinical characteristics of patients

	Myoma group (n=152)	Control group (n=160)	P
Age (years)	34.97±4.73	32.14±5.28	<0.0001
Infertility duration (months)	116.51±65.06	111.07±58.51	0.4376
Basal FSH (D3) (mIU/mL)	7.58±2.68	7.90±2.62	0.2871
Basal E2 (D3) (pg/mL)	50.54±39.28	46.16±30.42	0.2703

Results are given as mean±standard deviation

Table 2 *In vitro* fertilization outcomes of the groups

	Myoma group (n=152)	Control group (n=160)	O.R.	95% CI	p
Clinical pregnancy rate	18/152 (11.8%)	43/160 (26.9%)	0.365	0.2-0.668	0.0011
Implantation rate	27/327 (8.3%)	66/409 (16.1%)	0.467	0.291-0.751	0.0017
Live birth rate	14/152 (9.2%)	34/160 (21.3%)	0.376	0.192-0.733	0.0041
Preterm delivery (<37 weeks)	4/14 (28.6%)	8/34(23.5%)	1.3	0.319-5.295	0.366

CI - confidence interval

106 studies, seven of which have compared the results of IVF in women with untreated myomas and without myomas[2]. They showed a significant decrease in the pregnancy rates of patients with a distorted uterine cavity (9%) compared with patients without uterine distortion (29.1%) and those without myomas (25.1%). On the other hand, exposure of women with small intramural fibroids to the risks of myomectomy, with the sole aim of improving reproductive performance remains controversial[7]. It was reported that either naturally or with assisted techniques, pregnancy rates were increased after myomectomy in women with symptomatic deep intramural myoma[8]. Another study showed that patients who underwent precycle myomectomy for intramural myomas, which were considered clinically significant, had assisted reproductive technology cycle results similar to that of the controls with regard to ongoing pregnancy, implantation and miscarriage[9]. Considering the distinct results of the studies, it was reported that decision for surgical intervention should be made individually depending on the following factors: age of the woman, characteristics of the fibroids, concomitant presence of fibroid-related symptoms, and the presence of other causes of infertility[10].

Stovall et al. in their study stated that the presence of uterine leiomyoma (single or more, intramural or subserosal leiomyoma of <6 cm) significantly reduced the chance for a clinical pregnancy or delivery[11]. Eldar-Geva et al. concluded that pregnancy and implantation rates were not influenced if the patient had a subserosal myoma[12]. Ramzy et al. found that the presence of a myoma less than 7 cm in size which did not cause endometrial disruption, did not affect pregnancy rates in IVF cycles (38.5% in patients with myoma vs. 33.5% in patients without myoma)[13]. Jun et al. found no significant difference between the pregnancy outcome of women with untreated myomas measuring less than 7 cm not distorting the uterine cavity and women without myomas, after controlling for age and other risk factors (30.5% vs. 41.6%)[14]. Check et al. reported no difference between women with intramural leiomyoma of ≤5 cm and control subjects without myoma, in terms of IVF results[15]. Likewise, Oliveira et al. reported that patients with subserosal or intramural leiomyomas of <4 cm not encroaching on the uterine cavity had IVF/ICSI results comparable to those of the patients without such leiomyomas[16]. Contrarily, comparing the women that had small (≤5 cm) intramural fibroids with the control subjects without fibroids, Khalaf et al. found that the pregnancy, ongoing pregnancy and live birth rates were 23.6, 18.8 and 14.8% respectively in the study group and 32.9, 28.5 and 24% respectively in the control group ($p<0.05$)[17]. Furthermore, after adjusting for confounding variables, they found that the presence of fibroids significantly reduced the ongoing pregnancy rate by 40% and the live birth rate by 45% at each cycle of IVF/ICSI. In a recent meta-analysis, Sunkara et al. evaluated 19 observational studies comprising 6087 IVF cycles[18]. The results of the analysis revealed a significant decrease in live birth and clinical pregnancy rates following IVF treatment in the women that had non-cavity-distorting intramural fibroids compared with those without fibroids. They concluded that the presence of non-cavity-distorting intramural fibroids was associated with adverse pregnancy outcomes in women undergoing IVF treatment.

In our study, we found that clinical pregnancy rate, implantation rate and live birth rate were lower in the myoma group than that of the control group. The mean age of the patients with myomas was higher than that of the patients without myomas. Maternal age, independent from the presence of myomas, was an important factor. This might have created a bias for our study. However, after adjusting for age, the difference in the clinical pregnancy, implantation and live birth rates between the groups were no longer significant. The present study revealed no difference between the two groups in terms of preterm delivery rate; which was consonant with the results of the study conducted by Oliveira et al.[16].

Conclusions

It seems that intramural and subserosal myomas <5 cm in diameter have no effect on clinical pregnancy, implantation and live birth rates at ICSI cycles. Thus, myomectomy should not be performed routinely for myomas <5 cm in size before IVF cycles. As myomas is usually a problem of advanced ages, taking the postoperative healing period into consideration, deferral of the IVF therapy might be an unnecessary time loss in this group of patients, who are already in the advanced ages and may have a decreased ovarian reserve. Therefore, shifting to IVF therapy without myemectomy seems to be an appropriate approach for the patients with non-cavity-distorting intramural or subserous myoma smaller than 5 cm particularly at advanced ages. More prospective, large randomised controlled trials are needed for understanding the relationship between myomas and infertility. ■

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