JMIG The Journal of Minimally Invasive Gynecology

Original Article

The Effect of Intramural Myomas Without an Intracavity Component on In Vitro Fertilization Outcomes in Single Fresh Blastocyst Transfer Cycles

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ABSTRACT **Study Objective:** To assess clinical pregnancy rate (CPR) and live birth rate (LBR) in the presence of non–cavity-deforming intramural myomas in single fresh blastocyst transfer cycles.

Design: Retrospective cohort study (Canadian Task Force classification II-2).

Setting: Academic fertility center.

Patients: A total of 929 fresh single blastocyst transfer cycles were included, 94 with only non–cavity-distorting intramural myomas and 764 without myomas. Cleavage embryo transfers were excluded to reduce bias based on embryo quality.

Interventions: None.

Measurements and Main Results: CPR and LBR were assessed. There were no differences noted in gravidity, parity, or body mass index between patients with myomas and those without myomas. Women with myomas required higher doses of gonadotropins (mean, 2653 ± 404 IU vs 2350 ± 1368 IU; p = .04) than women without myomas. However, the total number of mature oocytes collected and the total number of blastocysts created were similar. CPR (47% vs 32%; p = .005) and LBR (37.8% vs 25.5%; p = .02) were lower in patients who had intramural myomas compared with those without myomas. CPR and LBR were significantly reduced in the presence of even 1 myoma (odds ratio [OR], 0.53; 95% confidence interval [CI], 0.33–0.83 and OR, 0.56; 95% CI, 0.35–0.92, respectively). In patients with myomas >1.5 cm, LBR was also significantly reduced, even after adjusting for age, smoking, quality of embryo transferred, antral follicle count, and dose of gonadotropins (OR, 0.53; 95% CI, 0.29–0.97). This LBR finding was not significant if all myomas were included (including those <1.5 cm in diameter), but CPR was still significantly reduced.

Conclusion: Relatively small (>1.5 cm) non–cavity-distorting intramural myomas negatively affect CPR and LBR in in vitro fertilization cycles, even in the presence of only 1 myoma. Journal of Minimally Invasive Gynecology (2018) 25, 1241–1248
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Keywords: Blastocyst transfer; Fibroids; Live birth rate; Clinical pregnancy rate; In-vitro fertilization

Myomas are the most common benign tumors of the female genital tract, occurring in up to 40% of women of reproductive age [1,2]. Myomas are often classified based on their location as intramural, submucosal, and subserosal. Subseroral myomas have consistently been shown to have no effect on fertility [3–6]; however, submucosal myomas apparently reduce clinical pregnancy rates (CPRs) and live birth rates (LBRs), and the general consensus is that they should be removed before any fertility treatment [3–6]. Although non-submucosal intramural myomas are known to cause menstrual irregularities, their effect on fertility remains unclear. Myomas have been hypothesized to cause infertility through several mechanisms, including anatomic distortion, functional changes in the endometrium and myometrium, and endocrine and paracrine changes that may alter the uterine environment and affect implantation [7]. Those same mechanisms also have been proposed as possible factors associated with reduced pregnancy rates with infertility treatment in women with uterine leiomyomas. A possible association between myomas and an increased risk of miscarriage has been noted as well

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Submitted October 24, 2017. Accepted for publication March 3, 2018.
Available at www.sciencedirect.com and www.jmig.org

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https://doi.org/10.1016/j.jmig.2018.03.005

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[8,9]. The mechanism for this may involve cavity distortion, with areas overlying myomas being poorly vascularized and thus poor locations for implantation [8].

Whether intramural myomas have a detrimental effect on fertility is controversial [10–14]. Myoma size, as well as the exact location of the myomas in relation to the endometrial cavity, have been suggested as possible variables for identifying patients who may benefit from surgical intervention [5–7,15],. However, those previous studies are limited by possible biases, including previous myomectomies, in a subset of patients.

Physicians are commonly faced with the decision as to whether to remove intramural myomas before in vitro fertilization (IVF) treatment. There are many barriers to adequately assessing the effect of myomas on IVF, with many centers performing multiple embryo transfers or removing myomas before IVF. At the time of data collection for this study, a unique situation existed in Quebec. There was a long wait list for myomectomy of at least 1 year. The government funded 3 cycles of IVF and all resulting frozen embryo transfers. The government of Quebec mandated single embryo transfer; therefore, all subjects with myomas attempted at least 1 IVF cycle before surgery.

In this study, we investigated the relationship between non–cavity-distorting intramural myomas and pregnancy outcomes in patients undergoing IVF with single blastocyst transfers. Owing to the long wait lists for surgery and the extremely generous infertility funding at that time, we were presented with a unique situation involving an unselected patient population that had not undergone myomectomy, and thus bias was minimized.

Materials and Methods

We conducted a retrospective cohort study performed at a single academic reproductive center (McGill University Health Center) between January 2012 and June 2015. The study was approved by McGill University's Institutional Review Board (15-249-MUHC). All single fresh blastocyst transfer cycles in women age <43 years performed during the study period of January 2012 to July 2015 were included. Doctors were required to transfer a single embryo in most patients, unless multiple failed embryo transfers had occurred. Cycles with donor oocytes, previous myomectomies, hydrosalpinges, multiple embryo transfers, cleavage-stage embryo transfers, and genetic screening of embryos were excluded. Cleavage-stage embryo transfers were excluded to reduce bias based on embryo stage, quality, and pregnancy potential. All included subjects underwent a fresh embryo transfer.

After the foregoing exclusions, there were 929 fresh single-blastocyst transfer cycles, including 165 in patients with myomas and 764 in patients without myomas. Patients with only intramural myomas were included in the analysis (n = 94). Patients with an intramural myoma and any other type of myoma (submucosal or subserosal) or a submucosal or subserosal component of the intramural myoma were excluded. These exclusions were done to limit heterogeneity in the cases. Patients who had a myoma approaching the uterine cavity on transvaginal ultrasound performed on cycle days 2 to 5 of a spontaneous or progesterone-induced menses underwent hysteroscopy or hysterosalpingography to rule out cavity involvement. All patients underwent this baseline ultrasound screening by physicians at our center. Cavity distortion was assessed by hysterosalpingography or hysteroscopy, and patients with detected cavity distortion were excluded.

During the treatment cycle, patients were stimulated with the following IVF protocols: microdose flare protocol, fixed antagonist protocol, or midluteal long agonist protocol, as prescribed by the treating physician. More detailed information on the stimulation protocols used has been published previously [16]. Final oocyte maturation was induced with urinary or recombinant human chorionic gonadotropin when at least 2 follicles were ≥18 mm in diameter. Oocyte collection was performed 35 to 38 hours after human chorionic gonadotropin triggering using a 17-gauge single-lumen collection needle (Cook Medical, Sydney, Australia). Aspiration pressure was maintained at 145 mmHg with a vacuum pump (K-Mar 8200; Cook Medical). Insemination of retrieved oocytes was done by conventional IVF or intracytoplasmic sperm injection (ICSI). Fertilization was assessed at 16 to 18 hours after insemination for the appearance of 2 distinct pronuclei and 2 polar bodies. Culture to the blastocyst stage was performed using sequential media (Cook Medical). All embryos were cultured in cleavage medium (Cook Medical) until day 3 and subsequently transferred to blastocyst medium (Cook Medical) for culture to the blastocyst stage.

Embryos were scored according to Gardner's criteria, with good-quality embryos defined as Gardner score ≥3BB (grade 1 or 2) [17] and poor-quality embryos defined as Gardner score <3BB on day 5 (grade 3 or 4) [18].

All embryos were transferred day 5 after oocyte retrieval at the blastocyst stage. The pregnancy test was performed 11 days after the transfer, and if positive, patients continued luteal support until 12 weeks of pregnancy. Luteal support has been described in detail previously [17]. All patients received both progesterone and estrogen luteal support. A viability scan was scheduled 2 weeks after a positive pregnancy test. A clinical pregnancy was defined as an intrauterine pregnancy with visible fetal cardiac activity at gestational age 6 to -7 weeks. A live birth was defined as any fetus with a birth weight >500 g or gestational age >20 weeks with active signs of life.

Statistical Analysis

The main pregnancy outcome variables were clinical pregnancy and live birth in the binary form (yes/no). Patient demographic characteristics, ovarian stimulation variables, and pregnancy outcomes (including clinical pregnancy and live birth) with and without myomas were compared using

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Table 1

Baseline characteristics of women with and without intramural myomas

Variable	Without myomas (n = 764)	With myomas (n = 94)	p value
Age, yr, mean (SD)	34.17 (3.96)	36.26 (3.24)	<.0001*
BMI, kg/m^2, mean (SD)	25.07 (6.12)	25.32 (5.90)	.7626*
Previous pregnancies, mean (SD)	0.8 (1.2)	1.0 (1.3)	.1004*
Previous term deliveries, mean (SD)	0.3 (0.6)	0.3 (0.5)	.4998*
Infertility duration, yr, mean (SD)	3.4 (2.4)	4.0 (3.2)	.083*
Basal serum FSH, IU/L, mean (SD)	7.33 (2.94)	7.10 (2.39)	.463*
Basal serum LH, IU/L, mean (SD)	6.56 (16.23)	4.31 (1.86)	.1927*
Baseline estradiol, pmol/L, mean (SD)	206.13 (754.06)	169.03 (79.63)	.6432*
AFC, mean (SD)	18.9 (12.3)	15.3 (9.2)	.007*
TSH, IU/L, mean (SD)	1.73 (0.97)	1.75 (1.05)	.8113*
AMH, ng/mL, mean (SD)	8.30 (13.83)	8.02 (11.36)	.9686*
Infertility diagnosis, n (%)			
Male factor	261 (34.6%)	31 (33.0%)	.4834†
Anovulation	70 (9.3%)	6 (6.4%)	
Tubal factor	66 (8.8%)	12 (12.8%)	
Unexplained	165 (21.9%)	20 (21.3%)	
Single/same sex	30 (4.0%)	2 (2.1%)	
Endometriosis	41 (5.4%)	9 (9.6%)	
Combined	60 (8.0%)	5 (5.3%)	
Diminished ovarian reserve	61 (8.1%)	9 (9.6%)	
Sperm, n (%)			
Fresh	660 (86.7%)	84 (89.4%)	.5411†
Frozen	16 (2%)	3 (3.2%)	
Surgical sperm extraction	34 (4.5%)	4 (4.3%)	
Donor sperm	51 (6.7%)	3 (3.2%)	
Smoking, n (%)			
Yes	58 (8%)	13 (14%)	.0383†
No	706 (92%)	81 (86%)	

BMI = body mass index; FSH = follicle-stimulating hormone; LH = luteinizing hormone; AFC = antral follicle count; TSH = thyroid-stimulating hormone; AMH =
* *t* test.
† χ^2 test.

Student's *t* test for continuous variables and the χ^2 test for categorical variables. The results are presented in Tables 1, 2, and 3, respectively.

As the main analysis, the differences between the 2 study groups (with and without myomas) for the pregnancy outcome variables (clinical pregnancy and live birth) were assessed using logistical regression models. Univariate and multivariable models were performed. Adjustments were made by including variables with imbalance in the multivariable logistic regression. Only the variables that were significantly associated with study group were included in the adjustment list (i.e., age, smoking, quality of embryo transferred, antral follicle count [AFC], and gonadotropin dose).

An additional analysis of the association between the myoma size and the main pregnancy outcome variables (clinical pregnancy and live birth) was performed using simple (unadjusted) and multivariable (adjusted) logistic regressions with the imbalanced variables defined in the main analysis. Myoma size was calculated as a continuous variable, largest myoma diameter. The logistic regression model was also used to test the nonlinearity of the continuous largest myoma diameter variable, with the quadratic term added to the model.

The subgroup sensitivity analysis was carried out only for women without myomas or those with the largest myoma diameter >1.5 cm, to verify whether exclusion of patients with a relatively small myoma size would affect the main results. The same models as in the main analysis were applied. To choose a cutoff for small myomas, patients with myomas were divided into quartiles based on myoma size. Patients with myomas in the smallest 25th percentile (<1.5 cm) were excluded to allow for analysis of only larger myomas. The results of all modeling are presented in Table 4. Descriptive statistics of myoma characteristics are presented in Table 5.

All tests were 2-sided, with $p < .05$ considered to indicate significance. Odds ratios and 95% confidence intervals of estimate were computed from the models. All calculations were performed by a PhD-level medical statistician using SAS version 9.4 (SAS Institute, Cary, NC).

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Table 2

Ovarian stimulation and IVF parameters in women with and without intramural myomas

Variable	Without myomas (n = 764)	With myomas (n = 94)	p value
Gonadotropin days, mean (SD)	9.14 (1.93)	9.26 (1.86)	.5757*
Gonadotropin dose, IU, mean (SD)	23450 (1368)	2653 (1404)	.0444*
Estradiol level, pmol/L, mean (SD)	6083 (3228)	6401 (3309)	.3738*
Endometrial thickness, mm, mean (SD)	10.3 (2.3)	10.2 (2.1)	.6176*
Number of metaphase II oocytes, mean (SD)	9.27 (4.71)	8.48 (3.93)	.1176*
Total number of blastocysts, mean (SD)	2.85 (1.89)	2.62 (1.78)	.4135*
Number of frozen blastocysts, mean (SD)	2.03 (2.07)	1.60 (1.69)	.0499*
Stimulation protocol, n (%)			
Fixed antagonist	480 (63.2)	46 (48.9)	<.0001†
Midluteal long agonist	164 (21.6)	18 (19.1)	
Microdose flare	114 (15.0)	29 (30.9)	
Natural cycle	0 (0.0)	1 (1.1)	
IVF/ICSI, n (%)			
IVF	170 (22.3)	19 (20.2)	.8169†
ICSI	557 (73.0)	72 (76.6)	
50% IVF/50% ICSI	33 (4.3)	3 (3.2)	
Rescue ICSI	3 (0.4)	0 (0.0)	
Embryo freezing, n (%)			
Yes	556 (72.8)	63 (67.0)	.2403†
No	208 (27.2)	31 (33.0)	
Quality of embryo transferred, n (%)			
Good	657 (86.0)	83 (88.3)	.0813†
Average	42 (5.5)	2 (2.1)	
Poor	59 (7.7)	6 (6.4)	
Unknown	6 (0.8)	3 (3.2)	

IVF = in vitro fertilization; ICSI = intracytoplasmic sperm injection.
* *t* test.
† χ^2 test.

With an actual sample size of 858 patients, the study had 80% and 72% power to detect a significant difference between the 2 groups in a CPR of 32% and 47% and an LBR of 25% and 38%, respectively, using the χ^2 test for 2 independent proportions at a confidence level of $\alpha = 0.05$ and group proportions of 0.11 and 0.89.

Results

There were a total of 764 transfer cycles in the women without myomas and 94 cycles in the women with intramural myomas included in our analysis. Among the 165 patients with myomas were 4 patients with only submucosal myomas, 37 with only subserosal myomas, and 30 with both intramural and subserosal myomas, all of whom were excluded from our analysis. The patients with myomas were slightly older than those without myomas (mean age, 36.3 ± 3.2 years vs 34.2 ± 3.9 years; p < .001). There were no differences in gravidity, parity, or body mass index between patients with and without myomas. However, women with intramural myomas had a lower AFC, although the difference apparently was not clinically significant (15.3 ± 9.2 vs 18.9 ± 12.3; p = .007), and were more likely to be smokers (p = .04) (Table 1).

Table 2 summarizes the response to ovarian stimulation and IVF parameters in the 2 groups. Women with myomas required higher doses of gonadotropins (2653 ± 404 IU vs 2350 ± 1368 IU; p = .04); however, the total number of mature oocytes collected and the total number of blastocysts created were similar in the 2 groups. In terms of causes of infertility, the majority of patients in both groups had male factor infertility. There were slightly more cases of endometriosis and diminished ovarian reserve in the patients with intramural myomas; however, the differences were not statistically significant. The most common protocol used in both groups was antagonist therapy (Table 1). The microdose flare protocol was more common in the women with myomas (30.9% vs 15%; p < .0001). In both groups, >85% of the patients had a good-quality embryo transferred, and a similar proportion in each group had surplus blastocysts to freeze (Table 1).

Table 3 presents cycle outcomes in the 2 study groups. CPR (47% vs 32%; p = .005) and LBR (37.8% vs 25.5%; p = .02) were lower in the patients with intramural myomas. The miscarriage rate was not statistically significantly different between the 2 groups, however (15.8% vs 19.4%; p = .83). Patients with intramural myomas appeared more likely to undergo cesarean section delivery (53% vs 33%), but the difference

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Table 3

Pregnancy outcomes in the women with and without intramural myomas

Variable	Without myomas (n = 764)	With myomas (n = 94)	p value
Gestational age at birth, wk, mean (SD)	38.3 (2.6)	38.5 (1.7)	.6372*
Birth weight, g, mean (SD)	3308 (617)	3274 (547)	.794*
Clinical pregnancy, n (%)			
No	404 (52.9)	64 (68.1)	.0052†
Yes	360 (47.1)	30 (31.9)	
Live birth, n (%)			
No	475 (62.2)	70 (74.5)	.0194†
Yes	289 (37.8)	24 (25.5)	
Pregnancy outcome, n (%)			
Live birth	289 (80.3)	24 (77.4)	.834†
Miscarriage	57 (15.8)	6 (19.4)	
Ectopic	4 (1.1)	1 (3.2)	
Unknown	4 (1.1)	0 (0.0)	
Intrauterine fetal death	3 (0.8)	0 (0.0)	
Termination	3 (0.8)	0 (0.0)	
Delivery mode, n (%)			
Vaginal delivery	182 (64.3)	10 (45.5)	.1669†
Planned cesarean section	49 (17.3)	5 (22.7)	
Emergency cesarean section	45 (15.9)	7 (31.8)	
Instrument delivery	7 (2.5)	0 (0.0)	

* *t* test.
† χ^2 test.

between the 2 groups was not statistically significant. The results of the statistical modeling for main pregnancy outcomes are presented in Table 4.

Based on the significant association with study group, the following variables were selected for adjustment: age, smoking, AFC, gonadotropin dosage, and the quality of embryo transferred. In the adjusted analysis, the CPR was significantly lower in patients with any intramural myomas compared to those without (odds ratio [OR], 0.58; 95% confidence interval [CI], 0.36–0.93).

The effect of largest myoma diameter on main pregnancy outcomes was significant for CPR (OR, 0.80; 95% CI, 0.68–0.93) and LBR (OR, 0.85; 95% CI, 0.72–0.99) in the unadjusted model but only for CPR after patient imbalance

Table 4

Associations between myoma group or myoma size and main pregnancy outcomes

		Clinical pregnancy (yes/no)		Live birth (yes/no)	
Model	Predictor	OR (95% CI)	p value	OR (95% CI)	p value
Main analysis (n = 858)					
Unadjusted model*	Myoma group (with vs without)	0.53 (0.33–0.83)	.0059	0.56 (0.35–0.92)	.021
Adjusted model†	Myoma group (with vs without)	0.58 (0.36–0.93)	.0246	0.65 (0.39–1.08)	.0979
Additional analysis (n = 858)					
Unadjusted model*	Largest intramural myoma diameter	0.80 (0.68–0.93)	.0053	0.85 (0.72–1.00)	.0442
Adjusted model†	Largest intramural myoma diameter	0.81 (0.69–0.96)	.0123	0.87 (0.74–1.03)	.1006
Subgroup analysis (n = 831)‡					
Unadjusted model*	Myoma group (with vs without)	0.35 (0.20–0.63)	0.0004	0.47 (0.26–0.86)	.0138
Adjusted model†	Myoma group (with vs without)	0.37 (0.20–0.67)	0.0011	0.52 (0.28–0.96)	.0365

OR = odds ratio; CI = confidence interval; NA = not applicable.
* Simple logistic regression.
† Multivariable logistic regression, adjusted by patient imbalance variables (female age, smoking, quality of embryo transferred, AFC, and gonadotropin dose).
‡ Including women without myomas or with myomas >1.5 cm.

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Table 5

Characteristics of myomas (n = 94)

Variable	Mean	SD	Minimum	First quartile	Median	Third quartile	Maximum
Largest intramural myoma diameter, cm	2.7	1.7	0.7	1.5	2.1	3.4	9.1
Largest intramural myoma volume, cm^3	19.0	43.8	0.1	1.3	3.0	13.0	275.8
Total intramural myoma volume, cm^3	20.5	44.4	0.1	1.4	4.1	13.7	275.8
Number of myomas	1.5	0.7	1	1	1	2	4

adjustment (OR, 0.82; 95% CI, 0.70–0.97). The quadratic terms of largest myoma diameter were not significant (p = .2081 for CPR and p = .1638 for LBR; data not shown).

In patients with myomas >1.5 cm, the LBR also was significantly reduced, even after adjustment (OR, 0.52; 95% CI, 0.28–0.96). However, this finding was not statistically significant if all myomas were included, including those <1.5 cm in diameter (OR, 0.65; 95% CI, 0.39–1.08). The same trend was seen when assessing myomas based on volume. The reduction in CPR was seen mostly in women with a myoma with a volume >1.3 cm^3 or total myoma volume >1.4 cm^3 (data not shown).

Table 5 presents data on myoma size and volume. The largest myoma diameter ranged from 0.7 cm to 9.1 cm (median, 2.1 cm) and the largest myoma volume ranged from 0.1 to 276 cm^2 (median, 3 cm^2).

Discussion

Our results show that women with intramural myomas that do not distort the endometrial cavity have compromised CPR and LBR after IVF in fresh single blastocyst transfer cycles. This finding was noted in women with myoma diameters of at least 1.5 cm. Much to our surprise, the presence of even 1 intramural myoma reduced the odds of clinical pregnancy by 58% (95% CI, 36%–93%) and the odds of live birth by 65% (95% CI, 39%–108%). Even after adjusting for the confounders of patient age, smoking, quality of embryo transferred, AFC, and gonadotropins dose, we still found that the presence of intramural myoma(s) has negative effects on CPR and LBR after IVF.

The LBR also was significantly reduced in patients with myomas >1.5 cm. After adjusting for patient characteristics, the odds of live birth were almost twice as high in controls compared with patients with myomas (OR, 0.52; 95% CI, 0.28–0.96).

The literature shows conflicting results on the association between the presence of myomas without cavity distortion and IVF success rates [10–12,19–21]. A large retrospective study conducted in China including 10,268 patients undergoing IVF/ICS (including 249 patients with myomas) showed that the presence of myomas that do not distort the cavity might not reduce pregnancy rates after IVF cycles [10]. However, that study included both subserosal and intramural myomas, even though there is significant evidence that subserosal myomas do not reduce CPR and LBR. Clearly, the inclusion of subserosal myomas in that analysis may have biased the results to show no difference [5,6]. In addition, approximately one-half of the patients with myomas initially identified in that study were excluded because they had had previous myomectomies. This highlights the fact that many published studies exclude patients with large or multiple myomas, because these patients are more likely to undergo surgery before IVF. This selection bias for patients with the most significant myomas undergoing surgery before fertility care likely affects the published results. This was not the case for our present study population, however. The medical climate in Quebec resulted in patients not being able to obtain surgery and instead undergoing IVF first. In fact, none of our patients were excluded from inclusion in the database because of a previous myomectomy. This is because myomectomies have incredibly long wait lists in Quebec, often longer that 1 year.

In another study, Somigilana et al [11] found that myomas smaller than 5 cm that did not distort the endometrial cavity did not affect IVF success rates. Even though this was a prospective study, the authors also included subserosal myomas in their analysis. Patients with both intramural and subserosal leiomyomas were included in the intramural myoma group. This again could have biased the results toward the null hypothesis, because subserosal myomas are known to not reduce pregnancy rates [5,6]. That study was also underpowered to detect a difference in CPR and LBR when only patients with intramural myomas were analyzed.

Similar results were reported by Klatsky et al [20], who found no significant difference in CPR in patients with non–cavity-distorting myomas who were recipients in egg donor cycles. Their preliminary analysis also grouped intramural and subserosal myomas together, with only 53% of patients having only intramural myomas. Moreover, 10% of their patients had undergone a previous myomectomy, which makes the study population heterogeneous, because undergoing myomectomy may have had an effect on implantation or may have removed the most significant myomas. In addition, the authors provided no information on the number and volume of myomas, variables that may be important in determining the effects of myomas on CPR and LBR.

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Khalaf et al [12] showed that the presence of intramural myomas <5 cm in diameter that did not distort the endometrial cavity still reduced pregnancy rates in IVF cycles. After adjusting for the confounding variables (age, number of oocytes collected, number of embryos available for transfer, and number of embryos replaced), the presence of myomas were found to significantly reduce the ongoing pregnancy rate at each cycle of IVF/intracytoplasmic sperm injection by 40%, and LBR at each cycle by 45% [12]. Similar results were reported by Surrey at al [13], who showed a trend toward lower CPR and LBR after IVF in women age <45 years with myomas and a normal uterine cavity on hysteroscopy.

A recent study by Christopoulos et al [21] found somewhat similar results as we report here. In patients with only intramural myomas that did not distort the endometrial cavity, they found a significantly reduced LBR in women with 2 or more myomas and in women with myomas ≥3 cm in diameter. However, unlike in our present study, the reduction in LBR was lost in patients with only 1 myoma and those with myomas <3 cm. It should be noted that in this study the 3-cm diameter cutoff was selected based on a previous study by a different group that suggested that only myomas >3 cm in diameter may have an effect. When examining the data of Christiopoulos et al, we could not determine the percentage of myomas in this group (<3 cm) with a diameter <1 cm. Had those authors used a cutoff of 1.5 cm diameter, they still may have detected a difference in outcomes; therefore, their results may be the same as ours on reanalysis.

A 2010 meta-analysis on the effect of intramural myomas without uterine cavity involvement on the outcome of IVF also supports our present results [19]. The authors found that CPR was reduced by 15% (relative risk [RR], 0.85; 95% CI, 0.77–0.94; p = .002) and LBR was reduced by 21% (RR, 0.79; 95% CI, 0.70–0.88; p < .0001) in women with non–cavity-distorting intramural myomas compared to women without myomas [19]. The meta-analysis also demonstrated that if only studies with women less than 37 years of age were included, there was still a statistically significant 18% reduction in CPR (RR, 0.82; 95% CI, 0.73–0.92; p = .0005), confirming that myomas are an issue even in younger women.

Whether myoma size plays a role in reducing pregnancy rates after IVF is also an issue, with conflicting data in the literature. In the present study, the presence of non–cavity-distorting intramural myomas was associated with reduced CPR (OR, 0.6; 95% CI, 0.37–0.96). However, when analyzing whether myoma size has an effect, myomas with a largest mean diameter of <1.5 cm apparently are not associated with reduced CPR. The same applies for myomas with a total volume of ≤1.4 cm^3. The reduction in CPR was seen more clearly with larger myomas. When looking at the number of myomas in relation to clinical pregnancies, our data demonstrate that the presence of only 1 myoma was sufficient to reduce CPR and LBR.

Our results also show similar miscarriage rates in women with non–cavity-distorting intramural myomas and women without myomas, a finding supported by previous studies [11,12,20,22]. Even though there is evidence to suggest that intramural myomas may reduce CPR and LBR, whether a myomectomy will help improve those rates remains unclear [23,24]. Surgery for myomas carries some risks, including increased risks of adhesions, tubal damage, and intrauterine synechiae postmyomectomy, and the recurrence rate of myomas is >25% [25]. Therefore, it is important to weigh the risks and benefits of myomectomy to appropriately counsel patients regarding the effects of small intramural myomas on CPR and LBR after IVF. Further studies are needed to evaluate the association of myomectomy with outcomes.

Our study has some inherent biases due to its retrospective cohort design,. Other limitations include the fact that we relied on transvaginal ultrasound for initial assessment of the myomas. Only women with suggested cavity involvement or a myoma within 5 mm of the cavity underwent hysteroscopy. This might not accurately reflect the extent of cavity involvement by the myomas. The use of hysteroscopy in combination with ultrasound in all cases might have provided more accurate results [26]. Unfortunately, at the time when the data were collected, there were not sufficient numbers of patients who had undergone myomectomy and subsequent embryo transfer to evaluate the effect of myomectomy on LBR and CPR. Moreover, with our sample size, the power for LBR was 72%, which might not have been sufficient to detect a significant difference for LBR.

Strengths of this study include the fact that we included only patients with intramural myomas, in contrast to previous studies that patients with intramural and subserosal myomas together, which might have altered their results. Moreover, all of our patients who presented with non–cavity-distorting intramural myomas underwent a cycle of IVF before considering myomectomy owing to the faster, government-covered access to multiple IVF cycles and all frozen embryo transfers compared with surgery. This would translate to a study with less selection bias in the myoma population. Because we only included fresh single blastocyst transfers, biases due to the number and stage of embryo development were eliminated. To the best of our knowledge, this study is the first to include only fresh single blastocyst transfers in patients with myomas undergoing IVF. Finally, we were able to evaluate LBR in addition to CPR, data that are not always easy to collect and are not consistently available in other studies.

In conclusion, our data show that relatively small (>1.5 cm) non–cavity-distorting intramural myomas negatively affect CPR and LBR in IVF cycles. Importantly, even a single myoma of this size may be sufficient to affect outcomes. This is important information to discuss with patients before the initiation of IVF treatments. Importantly, the LBR was 22% in women with myomas at least 1.5 cm in diameter. Further research should be directed to assessing whether or not removing or medically shrinking myomas increases pregnancy rates for patients who will undertake IVF.

We thank Alina Dyachenko, St Mary's Research Center for assisting with the statistical analysis.

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