

Improved Fertility Following Enucleation of Intramural Myomas in Infertile Women

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Abstract

Background: The relationship between intramural myomas and fertility remains unclear. The main debate rests on whether cavity-distorting intramural myomas (CDMs) adversely affect fertility more than non-CDMs. We aimed to compare the effects of enucleating non-CDMs and CDMs on fertility improvement in females with unexplained infertility.

Methods: We prospectively recruited 83 women undergoing myomectomy for unexplained infertility with intramural myomas between June 2008 and November 2012 and classified them into non-CDMs group ($n = 45$) and CDMs group ($n = 38$). We then compared postoperative infertility rates, spontaneous pregnancy rates, pregnancy outcomes, live birth rates, and obstetric complications. For continuous variables, we calculated the mean \pm standard deviation, median and interquartile range, and analyzed the data using Student's t -test and the Mann-Whitney U -test. For categorical variables, the Pearson's Chi-square test, the continuity correction test, and Fisher's exact test were used.

Results: Patients' demographics and myoma characteristics were comparable between the two groups. The overall spontaneous pregnancy rate increased from 0% to 68.42% following myomectomy. The postoperative infertility rate was significantly higher in the non-CDMs group than that in the CDMs group (50.00% vs. 23.53%, $t = 5.579$, $P = 0.018$), whereas the postoperative spontaneous pregnancy rate was significantly lower in the non-CDMs group than that in the CDMs group (47.62% vs. 70.59%, $t = 4.067$, $P = 0.044$). Compared with the enucleation of non-CDM, the enucleation of CDM patients was a protective factor for the fertility restoration (risk ratio [RR] = 3.717, 95% confidence interval [CI]: 1.284–10.753, $P = 0.015$), although postoperative fertility restoration declined with age ($RR = 1.141$, 95% CI: 1.005–1.295, $P = 0.041$).

Conclusions: Intramural myomas are associated with impaired fertility. Women experiencing unexplained infertility, and possessing intramural myomas, have a better chance of conception following myomectomy, and these benefits are more obvious for younger patients and patients with CDM.

Key words: Infertility; Myoma; Pregnancy Outcome; Uterine Myomectomy

INTRODUCTION

Myomas are the most common benign tumor in women of reproductive age. The prevalence of myomas within this specific population of women is 20–50%.^[1] Within the infertile population, the incidence of myomas has been reported to be 5–10%; indeed, it has been reported that myomas serve as the sole factor underlying infertility in 1–2.4% of cases.^[2-4]

Previous studies have focused on the relationship between myomas and infertility. The consistent viewpoint arising from the earlier work is that submucous myomas, intramural

myomas, and subserous myomas all adversely affect fertility.^[5,6] Submucous myomas are associated with inferior fertility, an increased incidence of miscarriages, and obstetric complications; hysteroscopic myomectomy improves

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implantation rates and is associated with improved pregnancy outcomes for infertile women.^[7-9] Subserous myomas cause little adverse effect on fertility, and the enucleation of such myomas does not result in any obvious benefit for subsequent pregnancy.^[5,6] The relationship between intramural myomas and infertility, and the improvement of spontaneous implantation rate and pregnancy outcomes following the enucleation of intramural myomas remain a matter of debate, particularly in terms of whether cavity-distorting intramural myoma (CDM) adversely affects fertility to a greater degree than non-CDM. To the best of our knowledge, there have been no published prospective cohort studies comparing the effect of enucleation on different types of intramural myomas and associated improvements in fertility. The aim of this prospective cohort study was to compare fertility improvement following the enucleation of non-CDM and CDM in women with unexplained fertility.

METHODS

Ethical approval

The study was conducted in accordance with the *Declaration of Helsinki* and was approved by the local ethics committee (No. 2011-KY-0516, No. IEC-C-03-V03). Informed written consent was obtained from all patients before their enrollment in this study.

Patients

Between June 2008 and November 2012, we prospectively recruited 83 women with unexplained infertility and intramural myomas. Intramural myomas were defined as myomas within the myometrium. Infertility was defined as when a woman could not achieve pregnancy after regular sexual intercourse without contraception for more than one year. Unexplained infertility was defined as an infertile couple without any identified problems associated with ovulation, fallopian tubes, male fertility, or immune factors. Before recruitment, all women underwent a transvaginal ultrasound, or transabdominal ultrasound, to confirm the type of myoma and the shape of the uterine cavity. All women were recruited from the gynecology clinic following the investigation of ovulation, hysterosalpingography, the partner's sperm, antisperm antibody, antiendometrium antibody, anti ovary antibody, and anticardiolipin antibody; all these tests were negative. During hysterosalpingography, a gynecologist reconfirmed the shape of the uterine cavity. The inclusion criteria were as follows: (1) unexplained infertile female with intramural myomas; (2) age from 20 to 42 years; (3) histopathology diagnosed as benign uterine smooth muscle tumor; (4) desired fertility following myomectomy. The exclusion criteria were as follows: (1) abnormal sperm, endocrine disease, congenital uterine anomalies; (2) intrauterine adhesion; (3) ectopic pregnancy; (4) presence of submucous myomas; (5) histopathology diagnosed as uterine adenomyosis; (6) histopathology diagnosed as malignant uterine tumor; (7) underwent hysterectomy after myomectomy for other disease. Women were also excluded if their clinical condition was complicated by

pelvic adhesions, adnexal disease (e.g., ovarian tumor or tubal adhesions), or by pelvic endometriosis during surgery.

To exclude potentially confounding factors, we recruited only women with unexplained infertility and intramural myomas which were >3 cm but <14 cm and less than four in number. All ultrasounds were conducted by the same two experienced ultrasound doctors. According to ultrasound and hysterosalpingography results, we divided the women into a non-CDMs group and a CDMs group. Non-CDM was defined as an intramural myoma with a normal uterine cavity shape. CDM was defined as an intramural myoma with a twisted uterine cavity shape. As to the choice of surgical approaches, all women were fully informed of the advantages and disadvantages of laparoscopic myomectomy (LM) and transabdominal myomectomy (TAM), and chose the surgical approach at their own will. Patients underwent myomectomy on a gynecology ward. All surgeries were conducted by the same two experienced gynecologists.

Laparoscopic myomectomy procedure

LM procedure was conducted as follows. First, using a monopolar hook electrode at 50 W, an incision was made in the uterine serosa up to the myometrium to expose the myoma surface. Then, the myoma was hooked by forceps to perform the traction necessary for its gentle enucleation; this procedure was assisted using another set of forceps inserted in the space underneath the myometrium and myoma. Hemostasis of the small vessels was selectively achieved by bipolar or monopolar scissors (always at 50 W). The myometrium and serosa were closed in a double-layer with coated Vicryl™ 1 (4.0 metric/Ph. Eur., VCP359.P30, Johnson & Johnson Company, Somerville, New Jersey 08876-0151, USA). If the uterine cavity was accidentally penetrated, one more layer was sutured after sterilization with povidone-iodine. Patients were then advised to use contraception for 1–2 years depending on the extent of the myometrium incisions.

Data collection

We prospectively collected the following data age, weight, height, body mass index (BMI), type of infertility (primary or secondary), period of infertility, myoma characteristics, uterine cavity shape, and perioperative characteristics. Using hospital records during follow-up, we also collected data regarding the last menstrual period, pregnancy method (spontaneous pregnancy, *in vitro* fertilization [IVF]), pregnancy numbers, pregnancy results (miscarriages, ectopic pregnancy, live birth, preterm delivery <37 gestation weeks), obstetric complications, gestation age at delivery, and delivery mode (vaginal delivery, cesarean section). Follow-up work was completed in October 2015.

Statistical analysis

All data were entered and analyzed in SPSS (version 19.0, IBM, Armonk, NY, USA). Continuous study variables, which were normally distributed, were expressed as means ± standard deviation (SD). Continuous study variables,

which were not normally distributed, were expressed as medians (interquartile range [IQR]). Categorical variables were expressed as relative frequencies. Continuous study variables from the two groups were compared using the Student's *t*-test or the Mann-Whitney *U*-test. Categorical variables from the two groups were compared using the Pearson's Chi-square test, continuity correction test, or Fisher's exact test. To identify dangerous factors for postoperative fertility restoration, we used Cox regression. Statistical significance was determined at $P < 0.05$.

RESULTS

We prospectively recruited a total of 83 women (non-CDMs group, 45 women; CDMs group, 38 women). Forty-eight of these patients underwent TAM, whereas 35 underwent LM. Seven women were lost during follow-up (three in the non-CDMs group and four in the CDMs group); the lost to follow-up rate was 8.43% (7/83). Follow-up details for women with unexplained infertility and intramural myomas, and who underwent myomectomy, are shown in Figure 1. There was no significant difference in follow-up duration when compared between the two groups. Similarly, the mean age, BMI, type of infertility, duration of infertility, myoma characteristics (e.g., number and size), and follow-up period were not significantly different between the two groups, as shown in Table 1.

During the follow-up period, 52 women achieved 53 pregnancies (25 pregnancies in the non-CDMs group and 28 pregnancies in the CDMs group; one woman from the CDMs group achieved two pregnancies). Eight of these pregnancies arose following IVF. The overall pregnancy rate was 68.42% (52/76), the overall spontaneous pregnancy rate was 57.89% (44/76), and the postoperative infertility rate was 38.16% (29/76). Of these women, two had twin pregnancies following IVF. Moreover, 38.16% (29/76) of women still suffered from infertility after myomectomy.

The postoperative infertility rate (50.00% vs. 23.53%, $t = 5.579$, $P = 0.018$) was significantly higher in the non-CDMs group than that in the CDMs group [Table 2]. Furthermore, the spontaneous pregnancy rate was significantly lower in the non-CDMs group than that in the CDMs group [Table 2]. Among the pregnant women, the live birth rate

(88.00% vs. 64.29%, $t = 4.012$, $P = 0.045$) was significantly higher in the non-CDMs group than that in the CDMs group [Table 2]. Regardless of whether women underwent induced abortion after myomectomy due to social factors (two in the non-CDMs group and one in the CDMs group), the postoperative adverse pregnancy outcome rate in the non-CDMs group was significantly lower than that in the CDMs group [Table 2].

The mode of delivery (vaginal delivery or cesarean delivery) was not significantly different between the two groups [Table 2]. However, the rate of cesarean section indication as a result of a previous history of myomectomy was significantly lower in the non-CDMs group than that in the CDMs group [Table 2]. During selective cesarean sections, two women in the non-CDMs group were identified as possessing previous myomectomy uterine scars with defective impairment, as evidenced by thinning of the membrane. However, due to timely cesarean section, both mothers and their babies were safe.

The premature labor rates (9.09% vs. 11.11%, $P = 1.000$), placenta accrete rates (0% vs. 11.10%, $P = 0.382$), postpartum hemorrhage rates (4.50% vs. 5.60%, $P = 1.000$), premature rupture of membranes rates (13.64% vs. 16.67%, $P = 1.000$), fetal distress rates (9.09% vs. 0%, $P = 0.560$), and uterine dehiscence rates (9.09% vs. 0%, $P = 0.560$), were not significantly different between the non-CDMs and CDMs groups.

Postoperative pregnancy outcomes did not differ significantly according to myomas of different sizes [Table 3]. When patients were classified according to the surgical approach undertaken, we observed that postoperative pregnancy outcomes were not significantly different between the two groups of women; although, pregnancy rate was significantly higher in the TAM group than that in the LM group [Table 3]. Additional analysis showed that the rate of CDM (25 [52.1] vs. 13 [37.1], $P = 0.177$), myoma number (2 [1–2], 1 [1–2], $P = 0.148$), largest myoma diameter (7 [5.3–8.0] cm, 6 [5.0–7.0] cm, $P = 0.050$), and age (32.48 ± 4.15 years vs. 32.66 ± 4.12 years, $P = 0.847$) were not significantly different when compared between the TAM group and the LM group.

Table 1: Patient demographic characteristics

Characteristic	Non-CDM ($n = 45$)	CDM ($n = 38$)	Statistical value	<i>P</i>
Age (years)	32.87 \pm 4.10	32.18 \pm 4.15	0.751*	0.455
BMI (kg/m ²)	22.83 \pm 2.97	23.65 \pm 3.28	-1.195*	0.235
Infertility type				
Primary infertility	19 (42.22)	22 (57.89)	2.025 [†]	0.155
Secondary infertility	26 (57.78)	16 (42.11)		
Infertility period (years)	3 (2.0–4.0)	3 (1.8–4.0)	836 [‡]	0.859
Myoma number	1 (1.0–3.0)	1 (1.0–2.3)	850 [‡]	0.964
Diameter of largest myoma (cm)	6 (5.0–7.5)	6.5 (5.0–8.0)	832 [‡]	0.831
Follow-up period (months)	34.09 \pm 13.79	31.15 \pm 13.33	0.981*	0.330

Data are presented as *n* (%) or mean \pm SD or median (interquartile range). **t* value; [†] χ^2 value; [‡]Mann-Whitney *U*-test. BMI: Body mass index; CDM: Cavity-distorting intramural myoma; SD: Standard deviation.

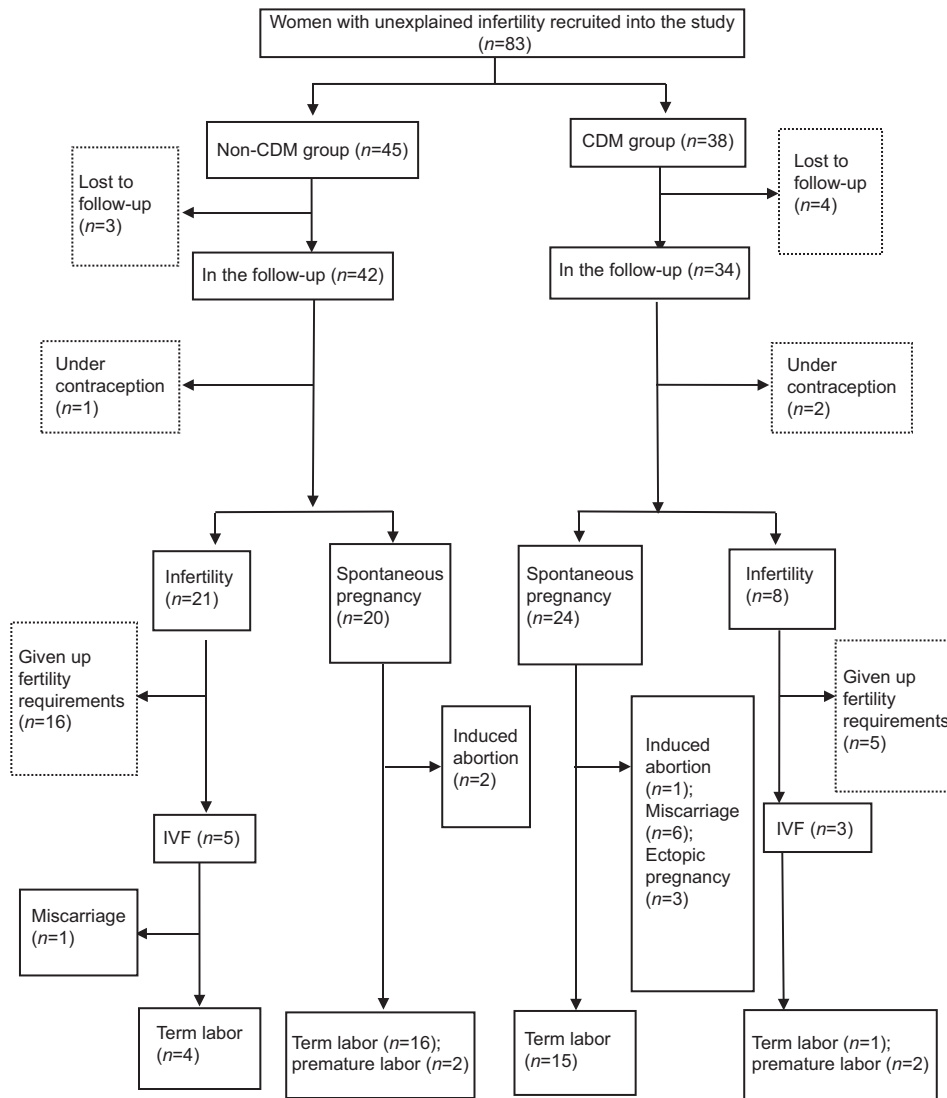


Figure 1: Flow chart of patients included in the study. CDM: Cavity-distorting intramural myomas; IVF: *In vitro* fertilization.

Table 2: Pregnancy outcomes following myomectomy

Pregnancy outcome	Non-CDM (n = 42)	CDM (n = 34)	Statistical value	P
Infertility rates	21 (50.00)	8 (23.53)	5.579*	0.018
Pregnancy rates	25 (59.52)	27 (79.41)	3.440*	0.064
SP rates	20 (47.62)	24 (70.59)	4.067*	0.044
Live birth rates	22 (88.00)	18 (64.29)	4.012*	0.045
Delivery mode				
Vaginal delivery	5 (22.70)	2 (11.10)	0.296*	0.587
Cesarean section	17 (77.30)	16 (88.90)		
Myomectomy as sole reason for CS	3 (17.60)	14 (82.40)		0.032†
Adverse pregnancy outcome	1 (4.35)	9 (33.33)	4.836*	0.028

Data are presented as n (%). *t value; †Fisher's exact test. CDM: Cavity-distorting intramural myoma; SP: Spontaneous pregnancy; CS: Cesarean section.

A total of 29 patients still suffered from infertility following myomectomy. Cox regression showed that preoperative duration of infertility, type of infertility, BMI, myoma number, myoma size, myomectomy approach, and whether the myoma penetrated into the uterine cavity or not during myomectomy, were not identified

as risk factors for subsequent fertility. Compared with non-CDM, CDM was identified as a risk factor for fertility. Following the enucleation of CDM, the postoperative risk of infertility was 0.269 times lower than enucleation of non-CDM (risk ratio [RR] = 0.269, 95% confidence interval [CI]: 0.930–0.779, P = 0.015). For every 1 year increase

Table 3: Comparison of pregnancy outcomes according to myoma number and surgical approach

Pregnancy outcome	Largest myoma diameter (cm)		Statistical value	P	Surgery approaches		Statistical value	P
	<5	≥5			TAM (n = 48)	LM (n = 35)		
Infertility rates	5 (55.6)	24 (35.8)	0.607*	0.436	13 (29.5)	16 (50.0)	3.285*	0.070
Pregnancy rates	6 (66.7)	46 (68.7)	<0.001*	1.000	35 (79.5)	17 (53.1)	5.985*	0.014
SP rates	4 (44.4)	40 (59.7)	0.261*	0.609	29 (65.9)	15 (46.9)	2.753*	0.097
Live birth rates	3 (50.0)	37 (80.4)	1.320*	0.251	26 (74.3)	14 (82.4)	0.088*	0.767
Delivery mode								
Vaginal delivery	1 (33.3)	6 (16.2)		0.448†	5 (19.2)	2 (14.3)	<0.001*	1.000
Cesarean section	2 (66.7)	31 (83.8)			21 (80.8)	12 (85.7)		
Myomectomy as sole reason for CS	0	12 (38.7)		0.523†	9 (42.9)	3 (25.0)	0.422*	0.516
Adverse pregnancy outcome	3 (50.0)	7 (15.9)	2.000*	0.157	7 (21.2)	3 (17.6)	<0.001*	1.000

Data are presented as n (%). * χ^2 value; †Fisher's exact test. TAM: Transabdominal myomectomy; LM: Laparoscopic myomectomy; SP: Spontaneous pregnancy; CS: Cesarean section.

in age, the postoperative risk of infertility increased by 1.141 times ($RR = 1.141$, 95% CI : 1.005–1.295, $P = 0.041$).

Until the end of the follow-up period, three patients were using contraception (two women had given up their desire for fertility due to social factors, whereas the third underwent the second myomectomy due to relapse, and planned to try to conceive after an appropriate interval on contraception from the time of the second surgery

DISCUSSION

For over a decade, there has been great debate on the link between intramural myoma and fertility, and few studies have attempted to address this association. The main debate rests on whether CDM adversely affects fertility to a greater degree than non-CDM.^[10,11]

In this study, the clearly higher pregnancy rate, spontaneous pregnancy rate, and reduced rate of infertility provided strong evidence that the enucleation of intramural myomas plays an important role in fertility improvement in women with unexplained infertility and intramural myomas. However, we had no specific control group featuring women with unexplained infertility and intramural myomas, who did not undergo myomectomy; consequently, it is not clear how important the role of myomectomy is in terms of improving infertility. However, the significantly higher postoperative pregnancy rate and lower postoperative infertility rate observed in this study demonstrated that intramural myomas do adversely affect fertility.

Compared with the non-CDMs group, the lower postoperative infertility rate, and higher postoperative spontaneous pregnancy rate in the CDMs group clearly show that CDM adversely affects fertility to a greater extent and that more benefit can be gained after the enucleation of CDM in women with unexplained infertility. Among the postoperative pregnant women, the greater incidence of adverse pregnancy outcomes in the CDMs group showed that even though enucleation of CDM might improve fertility to a greater extent, this type of surgery might damage the myometrium or endometrial receptivity such that more pregnancies result in adverse outcomes.

Myoma size, and the type of surgical approach were not identified as factors affecting fertility; this result concurred with our previous study.^[12] Furthermore, the pregnancy rate was significantly higher in the TAM group than that in the LM group, although there was no significant difference between these two types of surgical approach in terms of myoma number, myoma size, age, and whether the uterine cavity was distorted or not. The reason for why the TAM group resulted in a higher pregnancy rate remains unclear, although this might be attributable to the slightly larger myoma diameter in this group of women (7 [5.3–8.0] cm, 6 [5.0–7.0] cm, $P = 0.050$) in the TAM group.

Cox regression analysis showed that the postoperative rate of infertility in the CDMs group was 0.269 times lower than that in the non-CDMs group. Enucleation of CDM yields more benefits for women with unexplained infertility; this might be because CDM damages the uterine cavity volume in a more obvious manner compared with non-CDM, and that enucleation restores a normal uterine cavity. Enucleation of non-CDM patients might still be beneficial to fertility because intramural myomas might impair fertility by limiting embryo or semen transport, causing endometrial atrophy or inflammation, or by interfering with implantation. This study is supported by the work of Pritts *et al.*^[5] who performed a systematic literature review and meta-analysis and concluded that intramural myomas are associated with a lower pregnancy rate and live birth rate, as well as non-CDMs. Nevertheless, a recent publication showed that the enucleation of myomas causing distortion of the uterine cavity can significantly improve live birth rate from 23.3% to 52.0% in subsequent pregnancies, and that reservation myomas, which do not cause distortion of the uterine cavity can achieve a high live birth rate that is similar to women without myomas.^[13] This suggested that CDM adversely affects fertility in an obvious way, while non-CDM does not. Unfortunately, this previous study lacked a control group of women with CDM who did not undergo surgery. Similarly, Somigliana *et al.*^[11] conducted a prospective controlled study, which showed that non-CDM with a diameter less than 5 cm did not impact on the success of IVF procedures.

However, it is difficult to conclude that non-CDM has no adverse impact on fertility from the data presented in this previous publication because the study involved women with subserous myomas, which have a little adverse impact on fertility.

In this study, the overall pregnancy rate was 68.42% and the spontaneous pregnancy rate was 57.89%; these data concurred with a previous publication^[14] which showed that 74.00% of infertile women finally conceived after myomectomy. Thus, it is advisable to suggest to women with unexplained fertility and intramural myomas that they undergo myomectomy to improve their fertility, especially for women with CDM.

The data also show that the live birth rate was lower, and the adverse pregnancy outcome rate was higher, in the CDMs group than those in the non-CDMs group. This might be due to the fact that surgery involving enucleation of CDM is more difficult than non-CDM. During the operation, the fallopian tube and endometrium might be adversely influenced, thus resulting in a slightly higher ectopic pregnancy rate and miscarriage rate in the CDMs group.

As to the delivery mode, the higher rate of cesarean sections at the sole indication of a history of the previous myomectomy in the CDMs group was attribute to the over-concern of obstetricians and patients with regards to uterine rupture during vaginal delivery. The low uterine dehiscence rate, and obstetric complications rate, should serve as a reminder for obstetricians and patients that a history of myomectomy is not an absolute indication for caesarean section.

With regards to risk factors for postoperative infertility, the present results clearly show that the postoperative infertility rate increased with age. Sunkara *et al.*^[10] also showed that the adverse effects of intramural myomas on fertility was even greater when women were younger than 37 years. Furthermore, Borja de Mozota *et al.*^[15] conducted a study including 297 infertile women with myomas, and demonstrated that age (over 35 years, $RR = 2.450$) was a negative factor for fertility.

This study was limited by the fact that we had no control group of women with unexplained infertility and intramural myomas who did not undergo surgery. Consequently, we cannot state with absolute conviction that the enucleation of intramural myomas improves fertility. However, to include this type of control group in this study would have been ethically controversial because that the ability to restore postoperative fertility declined with age ($RR = 1.141$, 95% CI : 1.005–1.295, $P = 0.041$) and the infertile couples are desperate to undergo such surgery to achieve spontaneous pregnancy, or seek IVF.

In conclusion, irrespective of whether intramural myomas distort the uterine cavity or not, they can exert an adverse effect on fertility. Women with unexplained infertility and intramural myomas have a better chance of conception after myomectomy, particularly those with CDM. Since

postoperative improvement in fertility declines with age, conservative surgery should not be postponed for a long period.

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Conflicts of interest

There are no conflicts of interest.

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