ORIGINAL ARTICLE

Effect of the Distance of Interstitial Fibroid of Less Than 4 cm from the Outer Surface of the Endometrium on Outcome of Intra Cytoplasmic Sperm Injection

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Abstract

Background: ***Uterine fibroids, the most prevalent benign tumors of the female reproductive system, affect about 25% of women undergoing in vitro fertilization-embryo transfer (IVF-ET). In the general population, they are 20–50% prevalent and usually afflict women between the ages of 30 and 50. It is well recognized that uterine distorting intramural or submucous fibroids reduce the efficiency of reproductive therapies; yet, their removal appears to boost fertility.***

Aim of the Work: ***To assess the effect of the distance of interstitial fibroid from the outer surface of the endometrium on outcomes of Intra Cytoplasmic Sperm Injection cycles.***

Patients and Methods: ***This prospective clinical trial was conducted on 300 infertile women underwent ICSI and were recruited from the ART-unit of the International Islamic Center for Population trial and Research from September 2021 to September 2023.***

Results: ***Our study results revealed that Live birth rate was significantly highest in control group (44%), followed by fibroid >3 mm group (27%) and lowest in fibroid 1-3 mm group (23%), with no statistically significant difference between the two fibroid groups (p value= 0.003).***

Conclusion: ***Non-cavity-distorting intramural fibroids have a detrimental effect on the clinical pregnancy, rates of implantation and live birth in patients undergoing IVF-ICSI, based on the smallest distance among intramural uterine fibroids and the endometrium in type 3 fibroids. However, they do not significantly raise the clinical miscarriage risk in either of the two kinds of uterine fibroids (1–3 mm and >3 mm).***

Keywords: Endometrium; Interstitial Fibroid; Intra Cytoplasmic Sperm

1. Introduction

On the other hand, subserous fibroids do not appear to affect fertility, and asymptomatic women do not gain reproductively from their treatment. However, there is conflicting evidence in the literature about the effects of intramural fibroids, the most common kind of leiomyoma, without altering the uterine cavity, on IVF-ET results and fertility .[1] Other investigations were unable to verify the idea that the non-cavity-distorting intramural fibroids had a detrimental effect on the result of reproduction .[2]

Furthermore, the quantity and size of intramural fibroids that might impair fertility have no known threshold. Some studies found no significant relation between the size or amount of intramural fibroids and reproductive outcomes; however, others claimed that intramural fibroids larger than 2.85 cm or 3 cm were adversely related to IVF-ET success.[3] Non-cavity-distorting intramural fibroids would significantly decrease the clinical pregnancy, chance of implantation and live delivery after IVF treatment while greatly increasing the risk of miscarriages.[4]

Accepted 20 January 2025.
Available online 31 January 2025

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https://doi.org/10.21608/aimj.2025.446472

Preterm delivery, pelvic discomfort, infertility, impingement, spontaneous abortion, pelvic outlet blockage, menorrhagia and other associated problems are among the clinical consequences of uterine fibroids, which vary in number, size, and location .[5] It was agreed that uterine fibroids, particularly submucosal fibroids, may negatively affect a woman's ability to conceive by changing the intracavitary environment and structurally distorting the endometrial cavity. According to several studies, cavity-involved fibroids may make IVF-ET less successful .[6]

Since many intramural fibroids do not show endometrial cavity distortion, it is unclear how they affect IVF-ET outcomes. The treatment of these fibroids is debatable .[7] The fact that 12.6% of infertile women undergoing IVF had uterine fibroids is very astounding .[8]

The percentage of infertility problems caused by uterine fibroids may continue to expand at a comparatively high pace, given the lengthening of women's reproductive timelines brought about by advancements in medical treatment and the present trend of delaying childbirth.[8]

It is critical to determine if non-cavity-distorting intramural fibroids would impact the success of IVF-ET treatment, as well as the most effective technique for managing these fibroids in infertile women. This will provide suggestions on how to treat non-cavity-distorting intramural fibroids once the results are evident .[3]

So, the current study aim to assess the effect of the distance of interstitial fibroid from the outer surface of the endometrium on outcomes of Intra Cytoplasmic Sperm Injection cycles.

2. Patients and methods

This prospective clinical study, conducted at the ART-unit of the International Islamic Center for Population Study and Research, included 300 infertile women who had ICSI and were willing to participate in the study after getting ethical committee approval and patients' written informed consent.

All infertile women who attended ART-unit were divided into three groups: Group A (Uterine Fibroid group) included 100 infertile women with intramural uterine fibroids ≤ 4 cm in diameter, which were 1-3 mm from the outer surface of the endometrium. Group B: (Uterine Fibroid group) includes 100 infertile women with intramural uterine fibroids ≤ 4 cm in diameter, which are more than 3 mm from the outer surface of the endometrium. Group C: (Control group), the other 100 infertile women without uterine fibroids.

The study included women between the ages of 20 and 35 who had undergone an IVF cycle and a fresh embryo transfer, had a BMI between 20 and 25, were normal responders, had one or more intramural fibroid(s) with a diameter of ≤ 4 cm that did not distort the uterine cavity, as determined by a 2D transvaginal ultrasound scan (TVS), and had a normal male factor. The research excluded smokers with diabetes mellitus, poor responders, those with a single or multiple intramural fibroid(s) larger than 4 cm in diameter, submucous or uterine abnormalities, those with a history of endometriosis or myomectomy, those with endometrial lesions, and those with sonographic signs of adenomyosis.

All women were subjected to a full detailed history, complete examination, normal and hormonal investigation, and a transvaginal two-dimensional (2D) ultrasound was performed by the same physician (Medison ultrasound).

Intramural Uterine Fibroids Measurement: The patients were put in the lithotomy posture after their bladders had been emptied. The probe was covered with smeared coupling material. The uterine fornix and cervix were touched with the probe.

In vitro Fertilization-Embryo Transfer: Antagonist Protocol was described for all the patients, and the dose of HMG was adjusted according to ovarian reserve, age of the patient and history of the previous protocol.

Following incubation of the oocytes and semen, fertilization was seen 24 hours later, and cleavage was shown 48 hours later. Five days following oocyte retrieval, ET was carried out. The patient's age determined how many embryos were transplanted.

The outcome measures of the study were implantation rate (IR), abortion rate and live birth rate (LBR).

Statistical Analysis: Microsoft Office Excel 2007 and IBM SPSS Statistics software version 22.0 were used to code, tabulate, and statistically analyze the collected data. Descriptive statistics were utilized for both qualitative and quantitative data. Qualitative data were represented by numbers and percentages, while quantitative data were represented by mean±SD and range. Following that, proper statistical analyses were conducted. P values less than 0.050 are deemed significant; otherwise, they are considered non-significant.

3. Results

Table (1) showed that: No statistical significant differences between the study groups regarding demographic characteristics; age, BMI, parity, type of infertility and duration of infertility.

Table (2) showed that: No statistical significant differences between the studied groups regarding quality and number of transferred embryos.

Table (3) showed that: Clinical pregnancy was

significantly most frequent in control group, followed by fibroid >3 mm group and least frequent in fibroid 1-3 mm group, with no statistical significant difference between fibroid groups.

Table (4) showed that: Multiple pregnancy was most frequent in control group, followed by fibroid >3 mm group and least frequent in fibroid 1-3 mm group, the differences were statistically non-significant.

Table (5) showed that: Implantation rate was significantly highest in control group, followed by fibroid >3 mm group and lowest in fibroid 1-3 mm group, with no statistical significant difference between fibroid groups.

Table (6) showed that: Abortion was least frequent in control group, followed by fibroid >3 mm group and most frequent in fibroid 1-3 mm group, the differences were statistically non-significant.

Table (7) showed that: Live birth rate was significantly highest in control group, followed by fibroid >3 mm group and lowest in fibroid 1-3 mm group, with no statistical significant difference between fibroid groups.

Table 1. Demographic characteristics among the studied groups

VARIABLES	MEASURES	FIBROID 1-3 MM GROUP (TOTAL=100)	FIBROID >3 MM GROUP (TOTAL=100)	CONTROL GROUP (TOTAL=100)	P-VALUE
AGE (YEARS)	Mean±SD	28.6±3.3	27.9±3.3	28.1±3.3	^0.376
	Range	21.0–35.0	21.0–35.0	21.0–35.0	
BMI (KG/M²)	Mean±SD	22.7±1.0	22.5±1.1	22.8±1.1	^0.242
	Range	20.3–24.9	20.2–24.8	20.0–25.0	
PARITY (N, %)	Nulli	70 (70.0%)	69 (69.0%)	64 (64.0%)	#0.642
	Multi	30 (30.0%)	31 (31.0%)	36 (36.0%)	
TYPE OF INFERTILITY (N, %)	Primary	70 (70.0%)	69 (69.0%)	Not applicable	#0.878
	Secondary	30 (30.0%)	31 (31.0%)		
DURATION OF INFERTILITY (YEARS)	Mean±SD	2.4±1.1	2.6±1.1	Not applicable	¤0.437
	Range	1.0–5.0	1.0–5.0		

BMI: Body mass index. ^ANOVA test. ¤Independent t-test. #Chi square test.

Table 2. Number and quality of transferred embryos among the studied groups

MEASURES	FIBROID 1-3 MM GROUP	FIBROID >3 MM GROUP	CONTROL GROUP	P-VALUE
NUMBER OF TRANSFERRED EMBRYOS				
TOTAL	100	100	100	^0.473
MEAN±SD	2.9±0.6	2.9±0.7	2.8±0.7	
RANGE	2.0–4.0	2.0–4.0	2.0–4.0	
SUM	293	285	282	
QUALITY OF TRANSFERRED EMBRYOS				
TOTAL	293	285	282	#0.682
GOOD	211 (72.0%)	214 (75.1%)	205 (72.7%)	
POOR	82 (28.0%)	71 (24.9%)	77 (27.3%)	

^ANOVA test. #Chi square test.

Table 3. Clinical pregnancy among the studied groups

FINDINGS	FIBROID 1-3 MM GROUP (TOTAL=100)	FIBROID >3 MM GROUP (TOTAL=100)	CONTROL GROUP (TOTAL=100)	P-VALUE
POSITIVE	27 (27.0%)a	31 (31.0%)a	48 (48.0%)b	#0.004*
NEGATIVE	73 (73.0%)	69 (69.0%)	52 (52.0%)	

#Chi square test. *Significant. Homogenous groups had the same symbol “a,b” based on post hoc Bonferroni test.

Table 4. Multiple pregnancy among the studied groups

FINDINGS	FIBROID 1-3 MM GROUP (TOTAL=100)	FIBROID >3 MM GROUP (TOTAL=100)	CONTROL GROUP (TOTAL=100)	P-VALUE
TWIN	1 (3.7%)	2 (6.5%)	6 (12.5%)	§0.452
SINGLE	26 (96.3%)	29 (93.5%)	42 (87.5%)	

§Fisher’s Exact test.

Table 5. Implantation rate among the studied groups

FINDINGS	FIBROID 1-3 MM GROUP (TOTAL=293)	FIBROID >3 MM GROUP (TOTAL=285)	CONTROL GROUP (TOTAL=282)	P-VALUE
POSITIVE	28 (9.6%)	33 (11.6%)	54 (19.1%)	#0.002*
NEGATIVE	265 (90.4%)	252 (88.4%)	228 (80.9%)	

#Chi square test. *Significant. Homogenous groups had the same symbol “a,b” based on post hoc Bonferroni test.

Table 6. Abortion among the studied groups

FINDINGS	FIBROID 1-3 MM GROUP (TOTAL=)	FIBROID >3 MM GROUP (TOTAL=)	CONTROL GROUP (TOTAL=)	P-VALUE
POSITIVE	4 (14.8%)	4 (12.9%)	4 (8.3%)	§0.679
NEGATIVE	23 (85.2%)	27 (87.1%)	44 (91.7%)	

§Fisher's Exact test.

Table 7. Live birth rate among the studied groups

FINDINGS	FIBROID 1-3 MM GROUP (TOTAL=100)	FIBROID >3 MM GROUP (TOTAL=100)	CONTROL GROUP (TOTAL=100)	P-VALUE
POSITIVE	23 (23.0%)a	27 (27.0%)a	44 (44.0%)b	#0.003*
NEGATIVE	77 (77.0%)	73 (73.0%)	56 (56.0%)	

#Chi square test. *Significant. Homogenous groups had the same symbol "a,b" based on post hoc Bonferroni test.

4. Discussion

Finding out how the distance between the interstitial fibroid and the outer surface of the endometrium impacted intracytoplasmic sperm injection cycle outcomes was the aim of this study.

This prospective clinical research was carried out on 300 infertile women who had ICSI at the ART-unit of the International Islamic Center for Population research and Research at Al Azhar University between September 2021 and September 2023. ET was carried out on the fifth day following oocyte retrieval.

Three hundred participants were enrolled in the research after 350 people had their eligibility evaluated. According to the inclusion criteria, 35 of the eligible patients were disqualified from the trial, while 15 patients declined to take part.

In the end, the analysis was predicated on the information of 300 infertile women who were further separated into three groups and scheduled to undergo ICSI: One hundred infertile women with intramural uterine fibroids < 4 cm in diameter, 1-3 mm from the endometrial surface, make up Group A (Uterine Fibroid group). One hundred infertile women with intramural uterine fibroids < 4 cm in diameter, which are more than 3 mm from the endometrial exterior surface, are included in Group B (Uterine Fibroid group). One hundred infertile women without uterine fibroids make up Group C, the control group.

Pregnancy outcomes are significantly influenced by the size of uterine fibroids, which also increases the risk of pregnancy problems. According to reports, uterine fibroids larger than 40 mm have a negative impact on pregnancy outcomes [9], and those larger than 50 mm should be avoided .[10]

Our study included an intramural uterine fibroid measuring less than 40 mm. Because they are 15-20 mm thick, intramural uterine fibroids cannot be contained within the uterine wall. Even if the intramural uterine fibroid did not penetrate the uterus, it may have reached the serous membrane.[11]

This is the first independent study that we are aware of that assessed the impact of interstitial fibroids on IVF-ICSI results based on the smallest distance between small intramural uterine fibroids and the endometrium in type 3 fibroids.

The demographic features of the groups under research, as age, BMI, parity, type of infertility, and length of infertility, did not differ statistically significantly (p values = 0.376, 0.242, 0.642, 0.878, 0.437), according to the current study.

The current study found no statistically significant differences in the number and quality of transplanted embryos between the groups under consideration (p value=0.473, 0.682).

The association between non-cavitary fibroids and the clinical pregnancy and LBR outcomes of IVF cycles has been the subject of several studies over the last ten years. However, their results have been inconsistent .[11]

These results are consistent with earlier research. In order to investigate the effects of FIGO type 3 fibroids on the results of IVF cycles, Bai et al.[6] conducted a retrospective case-control study in which they matched 194 women with normal uteri (controls) with 97 women with fibroids. The results showed that there was no significant difference between the two groups regarding age, duration, BMI, type and cause of infertility, or ovarian reserve tests, and the mean number of embryos transferred was similar (1.97 ± 0.51 vs. 2.02 ± 0.60, p = 0.513).

Our findings are consistent with past research. Yan et al.[12] conducted a retrospective cohort analysis of 151 women with type 3 intramural fibroids and 453 matched control women. Age, body mass index, day 3 serum FSH and E2 levels, indication for IVF-ICSI therapy, day 2, 3 and 5 embryo transfer, and ovarian reserve did not differ statistically significantly between the two groups, according to the research.

A prospective research on the effect of the distance between the endometrium and small intramural uterine fibroids (≤ 4 cm) on IVF-ET outcomes was carried out by Lu et al.[11], which included 117 infertile women with and without uterine fibroids. The study found that the group with tiny intramural uterine fibroids had a

significantly higher abortion rate than the group without ($p < 0.005$), despite lower endometrial volume on ET day, IR, and LBR.

Based on the lowest distance between the endometrium and small intramural uterine fibroids, the research population was split into three groups: those who were < 1 mm, those who were 1–3 mm, and those who were >3 mm. The findings showed that the ≤ 1-mm group had a bigger endometrial FI than the other two groups (1–3 and >3 mm), and the ≤ 1-mm group had a higher IR than the >3 mm group ($p < 0.05$).

By influencing the blood flow to the endometrium and uterine muscle, uterine fibroids may change the composition and course of blood vessels in the uterine wall. This results in annular or semi-annular blood flow surrounding the uterine fibroid. Because the endometrium next to the uterine fibroid may benefit from the creation of annular or semi-annular blood flow, the uterine fibroid with the smallest distance—less than 1 mm—had a bigger IR than the one with the shortest distance—more than 3 mm.[11]

No statistically significant difference was found between the fibroid groups, but the control group had a significantly higher rate of clinical pregnancy (48%), followed by the fibroid >3 mm group (31%), and the fibroid 1-3 mm group (27%). The percentage of multiple pregnancies was higher in the control group, the fibroid >3 mm group, and the fibroid 1-3 mm group. There was no statistical significance in these differences. Consequently, it appears that non-cavity distorting fibroids negatively impact clinical pregnancy.

Our study's results on the IR revealed that there was no statistically significant difference between the fibroid groups. The control group had the greatest rate, followed by the groups with fibroids greater than 3 mm and those with fibroids between 1 and 3 mm. Abortion rates were lowest in the control group, in the fibroid >3 mm group, and in the fibroid 1-3 mm group. With a p-value of 0.679, these differences were not statistically significant.

The control group had the greatest LBR (44%), followed by the fibroid >3 mm group (27%), and the fibroid 1-3 mm group (23%), according to the results of our study. The two fibroid groups did not, however, vary statistically significantly (p value=0.003).

Our work is supported by a number of research publications in the literature. In order to determine if FIGO type 3 myomas had an impact on IVF results, Favilli et al.[13] carried out a systematic review and meta-analysis with 1020 patients, 324 of whom had FIGO type 3 myomas and 696 controls (without myomas). They discovered that the LBR, CPR, and IR of women with untreated myomas were significantly lower than those of controls. Therefore, there is a significant association between FIGO type 3 myomas and lower rates of implantation, cumulative pregnancy, and live birth.

In line with our results, Bai et al.[6] reported that following fresh embryo transfer, there were 23 clinical pregnancies in the fibroids group and 74 in the controls. Successful live births were achieved by 16 women in the fibroid group and 59 women in the control group. A significantly reduced implantation rate (IPR), CPR, and LBR were associated with the fibroids group compared to the control group. Miscarriage rates were unchanged ($p > 0.05$).

Consistent with our findings, Wang et al.[8] conducted a meta-analysis of 28 studies with a combined total of 9189 IVF cycles. The study group's LBR was much lower than that of the control group. It also showed that the study group's CPR and IR were much lower than those of the control group, but their miscarriage rate (MR) was significantly greater.

Our findings align with previous studies. Christopoulos et al.[4] performed a retrospective, matched, single-center cohort study in which 163 women with fibroids were recruited and matched with 326 controls. The results showed a significant association between lower frequencies of live birth and clinical pregnancy and the presence of fibroids. The negative consequences of fibroids were also felt by women who had an embryo transfer on day five.

In earlier research assessing the impact of intramural fibroids on reproductive outcomes, the closeness to the uterus was unable to distinguish intramural fibroids that did not result in uterine distortion as a single group. These results were supported by several other recent studies that were not included in the meta-analysis. [11, 14] However, several investigations did not detect a significant negative correlation between infertile women's reproductive results and intramural fibroids that did not enter the endometrial cavity .[2,1].

The strength points of this study:

The prospective research design, the single tertiary care facility setting, and the fact that no patients were lost to follow-up during the study period are the study's strong aspects. Additionally, the trial was conducted at a single facility using the same anesthesia procedure and IVF team, which probably improved the validity of our findings. Since they can all impact endometrial receptivity and treatment results, intrauterine adhesions, adenomyosis, endometriosis, endometrial polyps, and uterine abnormalities are not included in the study. Instead, it focuses on fibroids of FIGO type 3.

The limitations of the study:

The study's limitations are noteworthy. The first is that, in comparison to earlier research, the sample size was lower, and the study was not multicentric, which has a high risk of publication bias. Second, the impact of having more than two fibroids as a risk factor for IVF failures was not assessed by us.

4. Conclusion

Based on the smallest distance between intramural uterine fibroids and the endometrium in type 3 fibroids, non-cavity-distorting intramural fibroids negatively impact the rates of implantation, clinical pregnancy, and live delivery in those undergoing IVF-ICSI. However, they do not significantly raise the clinical miscarriage risk in either of the two kinds of uterine fibroids (1–3 mm and >3 mm).

Disclosure

The authors have no financial interest to declare in relation to the content of this article.

Authorship

All authors have a substantial contribution to the article

Funding

No Funds : Yes

Conflicts of interest

There are no conflicts of interest.

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