The Effect of Adenomyosis on the Outcome of Fresh Embryo Transfer in ICSI Cycles: a Retrospective Case-control Study

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Abstract

Background: Adenomyosis is known to cause reduced clinical pregnancies and increased miscarriage rates in ART (Assisted Reproductive Technology) cycles. The detrimental effect was found to be enhanced if these women would undergo fresh embryo transfer without optimal suppression by GnRH agonist treatment. Several mechanisms were proposed as causative factors such as increased myometrial contractions, decreased implantation and altered endometrial receptivity. But the conclusions from previous studies were mutually conflicting. To ensure adequate regression of the disease prior to embryo transfer, these women would commonly undergo freeze-all and subsequent frozen embryo transfer. On contrary to this, fresh embryo transfer may be necessary in certain justifiable clinical situations. The present study was designed as a retrospective case-control study to compare the ICSI-fresh embryo transfer outcomes of women with adenomyosis to those with tubal factor infertility. This study is aimed to find the extent to which adenomyosis compromises the outcomes of fresh embryo transfer in ICSI cycles.

Methods: The data of the eligible patients as per the study criteria, was obtained from the hospital medical records of a tertiary care University teaching hospital, in Chennai, South India. The study groups (Group A: women with adenomyosis, GroupB; women with tubal factor infertility) were compared for the fresh embryo transfer outcomes such as pregnancy rate, clinical pregnancy rate, miscarriage and live birth rates. SPSS version 17 software was used and and $P<0.05$ was considered statistically significant.

Results: The data of 89 women included in the study (Group A: 47, and Group B: 42) were analysed. The data analysis showed significantly reduced pregnancy, clinical pregnancy, implantation and live birth rates in Group A compared to Group B (25.7 vs. 52.4%; 23.4 vs. 52.4%; 7.6% vs. 26.2%; 17.0 vs. 47.6%, respectively).

Conclusions: We found that adenomyosis is associated with a less favourable outcome in ICSI -fresh embryo transfer. Though these results are justifiable if performed with appropriate indications, the cost-effectiveness and indications of such an approach needs to be evaluated on a larger prospective data.

Background:

Adenomyosis is defined as the presence of endometrial glands and stroma deep in the myometrium, associated with smooth muscle hyperplasia. This condition is increasingly seen in women in third and fourth decade of life and hypothesised to be predisposed by parity and previous gynaecological surgery[1,2]. Adenomyosis occurs in 8–27% of women in reproductive age, and about 28% of women with infertility[3]. These women commonly present with chronic pelvic pain, menorrhagia, dysmenorrhea, metrorrhagia and dyspareunia[1]. It is diagnosed by imaging: transvaginal sonography (TVS), and MRI in doubtful cases[3]. Though histopathology remains to be the gold standard for diagnosis, it is impractical and useful only for retrospective confirmation of diagnosis in hysterectomy specimens[3]. Grimbizis et al classified adenomyosis into the following categories depending on the distribution of lesions and

myometrial invasion: Diffuse adenomyosis, focal adenomyosis, polyploid adenomyomas, other rare forms (endocervical type and retroperitoneal)[4]. Though its effect on fertility and pregnancy remains controversial, it is usually treated by medical methods such as GnRH agonist, or surgery in case of focal lesions, prior to infertility treatment. Adenomyosis can have an adverse effect on the outcome of ART due to altered myometrial contractility, decreased implantation, altered endometrial receptivity due to dysfunctional hyperperistalsis of junctional zone, and alteration in sex steroid pathway[5]. These alterations probably result from increased expression of estrogen receptor and down regulation of progesterone receptor, increased inflammatory markers and oxidative stress[5,6]. Reduced expression of implantation markers, lack of expression of adhesion molecules, and altered function of HOXA 10 gene have been noted[5–8]. Also, the window of implantation is found to be displaced in 47% of women with adenomyosis[9].

The available data on the outcome of ART in women with adenomyosis is mutually conflicting. Many studies show a negative influence of adenomyosis on implantation and clinical pregnancy after ART, whereas a few studies show no effect of this condition on ART outcome[7,10–25]. A study that performed endometrial gene expression in women with adenomyosis showed only mild dysregulation which does not affect implantation[13]. The existing data is also affected by non-homogenous comparisons (adenomyosis group being much smaller to no adenomyosis group) and presence of potential confounders such as advanced age of these women, co-existing endometriosis and decreased ovarian reserve. Freeze all and cryoembryo transfer after adequate treatment with GnRH agonists, is the recommended approach in the management of these patients. But there are a few situations in the clinical practice that may provoke physicians to resort to fresh embryo transfer. These include low number of embryos, poor embryo quality, which would probably occur due to the presence of co-existing factors such as advanced age, and endometriosis. Social and financial reasons such as increased cost of embryo freezing may also render freezing less preferrable by some patients. The studies performed on the effect of adenomyosis in Indian population were very few and do not specifically address the outcome of fresh embryo transfer in this subgroup of patients with adenomyosis. The present study is aimed to find the effect of adenomyosis on pregnancy, implantation, clinical pregnancy and miscarriage in fresh embryo transferred ICSI cycles.

Methods:

The present study is a retrospective case-control study performed in the department of Reproductive Medicine and Surgery, at a tertiary care University teaching hospital. Of 1516 ICSI cycles performed between Jan 2002 to March 2019, only those women with adenomyosis and underwent fresh embryo transfer were included in the cases (Group A), and those women who had tubal factor infertility alone were included as controls (Group B). Adenomyosis was diagnosed by 2D transvaginal sonography (TVS) performed by a probe with a frequency of 9 MHz. The presence of two or more features on transvaginal sonography such as heterogeneous myometrial echoes, globular asymmetric uterus, irregular myometrial cystic spaces, myometrial linear striations, poor definition of endomyometrial junction, myometrial

anterior posterior asymmetry, thickening of anterior and posterior myometrial wall and increased or decreased echogenicity, was used to diagnose adenomyosis in this study[3]. A total of 89 cases were recruited, of which 47 cases were grouped as Group A and 42 controls as Group B. The data was obtained from the hospital medical records. The cases with incomplete data, women of advanced age (≥ 38 years), poor quality embryos (grade 3 &4 by Veeck's grading) available for transfer, donor oocyte cycles, surrogacy cycles, freeze-all cycles, and severe uterine factor such as Asherman syndrome, were excluded from the analysis[26]. All women in our study underwent controlled ovarian stimulation (COS), by either agonist (long agonist, short, ultrashort) or antagonist protocols. Ovulation trigger was administered by uhCG 10,000 IU when two or more follicles reached a mean diameter of 20 mm. All the study participants underwent ICSI, as it was our department protocol. Embryo quality was assessed by Veeck's grading system[26]. As per our department protocol, fresh embryo transfer was performed in patients with adenomyosis only if the number of cleavage stage embryos (day 2/3) were ≤ 4 and/or the number of good quality cleavage stage embryos (grade – 1 and 2) were ≤ 4 and/or patient's were not willing for freezing due to social and financial reasons. Fresh embryo transfer was performed on day 2 or day 3 post- oocyte retrieval. Pregnancy was diagnosed by positive b-hCG > 5 mIU/ml, on day 14 post-embryo transfer. The statistical analysis was performed by SPSS version 17 software. Chi square test, Mann-Whitney test, T test and logistic regression analysis were applied to analyse the data.

Results:

The study groups were comparable with respect to demographic parameters such as age, body mass index (BMI), duration of infertility (Table-1). The ovarian reserve tests were comparable between the study groups (Table-2). The various indications of ART in the study groups are shown in table-3. There was no significant difference in the COH (controlled ovarian hyper stimulation) protocols used between the two groups (Table-4).

Table 1
Comparison of demographic characteristics between the study groups

Parameter	Group A (n = 47) [Mean ± SD]	Group B (N = 42) [Mean ± SD]	Significance
Age (yrs)	31.6 ± 5.2	29.1 ± 4.1	P = 0.018, S*
BMI (KG/M^2)	27.0 ± 3.3	24.9 ± 6.5	P = 0.059
Duration of infertility (yrs)	8.2 ± 6.1	6.0 ± 3.8	P = 0.056

Table 2
Comparison of the ovarian reserve tests between the study groups

Parameter	Group A (n = 47) [Mean ± SD]	Group B (N = 42) [Mean ± SD]	Significance
FSH (mIU/ml)	7.2 ± 2.5	7.0 ± 2.5	P = 0.645
LH (mIU/ml)	5.2 ± 3.2	5.6 ± 3.1	P = 0.542
E2 (pg/ml)	44.8 ± 16.9	54.0 ± 28.9	P = 0.088
AMH (ng/ml)	3.3 ± 3.1	4.6 ± 10.0	P = 0.481
AFC	12.7 ± 5.9	13.8 ± 4.6	P = 0.360

Table 3
Comparison of the indications of ICSI between the study groups

Parameter	Group A (%) (n = 47)	Group B (%) (N = 42)
Male factor	14 (29.8)	Nil
Tubal factor	08 (17.0)	42
Endometriosis	06 (12.8)	Nil
Decreased ovarian reserve	12 (25.5)	Nil
Unexplained	07 (14.9)	Nil

Table 4
Comparison of the stimulation protocols used between the study groups

PROTOCOL	Group A (%) (n = 47)	Group B (%) (N = 42)	Significance
Long agonist	15 (31.9)	15 (35.7)	P = 0.567
Short	05 (10.6)	03 (7.1)	
Ultrashort	04 (8.5)	01 (2.4)	
Antagonist	23 (48.9)	23 (54.8)	

There were no significant differences in the COH characteristics such as duration of stimulation, total gonadotropin dosage, estradiol and progesterone on the day of ovulation trigger, between the study groups (Table-5). There were no significant differences in the oocyte number and maturity between the study groups (Table-6).

Table 5
Comparison of the various characteristics of ovarian stimulation between the study groups

Parameter	Group A (n = 47) [Mean ± SD]	Group B (N = 42) [Mean ± SD]	Significance
Duration of stimulation (days)	12.0 ± 2.3	12.0 ± 2.6	P = 0.800
Total gonadotropin dose (IU)	4435.7 ± 1856.2	3638.9 ± 1600.9	P = 0.034, S*
E2 on the day of trigger (pg/ml)	3172.0 ± 3639.5	2923.7 ± 1680.3	P = 0.723
P4 on the day of trigger (ng/ml)	1.3 ± 0.9	1.2 ± 0.6	P = 0.915
Endometrial thickness on trigger day (mm)	10.8 ± 1.8	10.5 ± 1.8	P = 0.403

*- P < 0.05 = statistically significant

Table 6
Comparison of ICSI outcome between the study groups

Parameter	Group A (n = 47) [Mean ± SD]	Group B (N = 42) [Mean ± SD]	Significance
No. Of oocytes	13.7 ± 6.9	14.4 ± 7.7	P = 0.664
M-II oocytes	10.7 ± 6.0	11.2 ± 6.4	P = 0.720
Fertilisation rate (%)	77.4 ± 17.4	85.1 ± 16.2	P = 0.036, S*
No. Of embryos transferred	2.8 ± 0.6	2.6 ± 0.6	P = 0.198
Pregnancy rate (%)	12 (25.7)	22 (52.4)	P = 0.009, S*
Implantation rate (%)	7.6 ± 14.6	26.2 ± 31.0	P = 0.001, S*
Clinical pregnancy rate (%)	11 (23.4)	22 (52.4)	
Miscarriage rate (%)	04/12 (33.3%)	02/22 (9.1)	P = 0.076
Live birth rate (%)	08 (17.0)	20 (47.6)	P = 0.003, S*

*- P < 0.05 = statistically significant

The fertilisation, implantation and pregnancy (OR = 0.32, CI = 0.13–0.78) rates were significantly lower in Group A compared to Group B (TABLE-6). The clinical pregnancies and live births were significantly reduced in Group A compared to Group B (OR = 0.26, CI = 0.10–0.65; OR = 0.24, CI = 0.09–0.63; respectively). The miscarriage rate was higher in the Group A compared to Group B, but not statistically

significant (OR = 4.44, CI = 0.68–28.86). The probable effect modifiers between the pregnant and non-pregnant women were analysed (Table- 7) There was no significant effect of any of these factors on the pregnancy. The logistic regression of the potential confounding factors such as age, duration of infertility and PCOS on pregnancy was performed, and was found to have no effect (Table – 8).

Table 7
Comparison of the possible effect modifiers between the pregnant and non-pregnant women

Group	Effect modifiers (n)	Pregnancy (%)	No pregnancy (%)	Significance (P-value)
Cases	Male factor (14)	06 (42.8)	08 (57.2)	P = 0.448
	Tubal factor (8)	01 (12.5)	07 (87.5)	
	Endometriosis (6)	01 (16.6)	05 (87.4)	
	Decreased reserve (12)	02 (16.6)	10 (83.4)	
	Unexplained (7)	02 (28.5)	05 (71.5)	
Controls	Tubal factor (42)	22 (52.4)	20 (47.6)	

Table 8
logistic regression analysis of the potential confounding factors affecting pregnancy

Parameter	Beta Coefficient (B)	Significance	Odds ratio	CI (confidence intervals)
Age	-0.72	0.197	0.93	0.83–1.03
Duration of infertility	-0.052	0.348	0.94	0.85–1.05
Pregnancy	-1.027	0.03	0.35	0.14–0.90
PCOS	0.041	0.943	1.04	0.33–3.24

Discussion:

Sharma et al performed a retrospective cohort study of 973 women with adenomyosis, and reported that the clinical pregnancy rate after fresh cleavage stage embryo transfer (day 2/3) in IVF-ICSI cycles was significantly reduced when endometriosis was associated with adenomyosis than endometriosis alone (36.62% vs 22.72%; OR = 1.96, CI = 1.14–3.38). They also found that the groups having adenomyosis with endometriosis had significantly lower clinical pregnancies than those with tubal factor infertility [34.5% (161/466) vs.22.72% (20/88); OR = 1.79, CI = 1.05–3.06], where as those with adenomyosis without endometriosis had comparable pregnancy rate than cases with tubal factor[34.5(161/466 vs. 15/64(23.44%); OR = 1.72, CI = 0.93–3.17]. Though actually the pregnancy rate is lower in Adenomyosis group than tubal factor group, this did not reach statistical significance. This may be due to non-homogeneous distribution of cases where in tubal factor group, which was 6 times larger than Adenomyosis group (466 vs.64)[27]. Thalluri et al performed a retrospective cohort study of 213 patients

with adenomyosis who underwent IVF and fresh (day4/5) embryo transfer. The clinical pregnancy rate in adenomyosis and non-adenomyosis groups were 23.6% and 44.6% (P = 0.017), and miscarriage rates were 25% and 10% (P = 0.144), and biochemical pregnancy rates were 31.6% vs 49.7% (P = 0.042), respectively[11]. In our study, the pregnancy, clinical pregnancy and live birth rates were significantly reduced in group A compared to group B. Moreover, we had the cases and controls in comparable numbers (47 and 42) and have included women with only tubal factor infertility (without coexisting other infertility factors) as controls.

Ballester et al performed a prospective multicentric cohort study in women with colorectal endometriosis who underwent ICSI-IVF. In this study, 21(28%) of 75 women had adenomyosis. The cumulative pregnancy in three embryo transfers were 19% for those with associated adenomyosis compared to 82.4% for those without adenomyosis. Adenomyosis was found to independently affect pregnancy rates in ICSI, in that study[28].In our study, the number of cases with co-existing endometriosis were proportionately lower(14.2%) and hence such a comparison could not be made. Salim et al performed a prospective observational study in 275 women with adenomyosis who underwent IVF-ICSI. The study participants were grouped as normal (n = 256) and-adenomyosis (n = 19). The adenomyosis group had a significantly lower pregnancy rate (47.2% vs 22.2%, P < 0.001), lower implantation rate (29.4 vs 18 hi.8% P < 0.001), and significantly higher miscarriage rate (2.8 vs 50%, P < 0.001). But the groups were extremely heterogeneous in numbers (256 vs 19). Moreover, the normal group contained cases with other infertility factors such as male factor, endometriosis, anovulation, unexplained along with tubal factor rather than tubal factor alone. There is a probability that those results would have been modified by the presence of these factors (effect modifiers)[14]. But in our study, we included only those women with tubal factor infertility alone as controls, thereby increasing the validity of our results. Our study showed significantly lower pregnancy, implantation and clinical pregnancy rates in women with adenomyosis (Group A). The miscarriage rates in our study were higher in the cases (Group A) but did not reach statistical significance, probably due to lower numbers in the study groups. In a systemic review and meta-analysis performed by Younes et al, adenomyosis was found to significantly reduce the pregnancy rate per embryo transfer (OR = 0.753, CI = 0.610–0.930), in women undergoing IVF-ICSI compared to those without adenomyosis[23]. These findings were similar to our study.

Benaglia et al performed a prospective case-control study of 98 women (49 vs 49) who underwent IVF-ICSI and fresh embryo transfer (day 2 to day 5). In their study, the clinical pregnancy rate was 29% in adenomyosis group and 43% in controls, which was higher but did not reach statistical significance (OR = 1.88, CI = 0.81–4.34). The implantation rates were 32% and 21% (P = 0.14), and the live birth rates were 35% and 18% (OR = 2.36; CI = 0.93-6.00) that were not statistically significant. In this study though the controls were matched, they consisted of other factors of infertility such as male factor, endometriosis, decreased ovarian reserve and unexplained factor. Matching would reduce the confounding bias but may not eliminate it. In our study we did not include women with infertility factors other than tubal factor in the control group. This discrepancy in the results of our study with this study may be due to difference in characteristics of the control group[19].

In our study we had lower fertilisation rate in group A than group B. This may be due to higher number of women with advanced age in group A (Table-1). As adenomyosis is known to occur in older women, we could not avoid this mismatch. However, we clarified that this effect did not influence the pregnancy rate by logistic regression analysis (Table-8). Stanekova et al performed a retrospective cohort study of 171 women who conceived after single euploid blastocyst transfer. In that study, 34 women had adenomyosis by TVS and 137 had morphologically normal uterus. Adenomyosis group had significantly higher miscarriage rates than the non- adenomyosis group (53% vs.19.7%; P = < 0.0001)[29]. Chiang et al performed a case control study in which 19 women with adenomyosis diagnosed by USG and 144 age matched controls with sonographically normal uterus. There was no significant difference in the pregnancy rates in fresh cleavage stage (day2/3) embryo transfers, but spontaneous miscarriages were increased in adenomyosis group: 4 (66.7%) vs. 8 (21%)[18]. In our study, the miscarriage rates were higher in the Group A compared to Group B but did not reach statistical significance probably due to small numbers (Table-6).

Overall though our study is of retrospective in nature, it has the following observations that would merit concern: adequate sample size, the study groups were comparable in number and baseline characteristics, the control group included women with exclusively tubal factor infertility and did not include those with other factors that are likely to affect the implantation. Moreover it addresses a specific group of women with adenomyosis who underwent fresh embryo transfer contrary to the recommended practice but with justifiable reasons. It is obvious from our results that the fresh transfer live birth rate was significantly affected in women with adenomyosis (Table 6). But a live birth rate of 17% was clinically reassuring in women with adenomyosis in situations where freeze-all would not be acceptable by patients due to increased cost for embryo freezing, and/or low number of good quality embryos which would not render the freezing cost-effective. However the cost-effectiveness of this approach needs to be evaluated prospectively on a larger data.

Conclusion:

We found that adenomyosis is associated with sub-optimal outcomes in ART characterised by reduced pregnancy rates, clinical pregnancy, implantation and live birth rates compared to tubal factor infertility. However, the cost-effectiveness to perform fresh embryo transfer in clinically justifiable situtations needs to be evaluated on a large well designed prospective studies.

Abbreviations:

- ART: Assisted reproductive technology
- CI: Confidence interval
- COH: Controlled ovarian hyperstimulation
- hCG: human chorionic gonadotropin
- ICSI: intracytoplasmic sperm injection

- IVF: invitro fertilization
- MRI: Magnetic resonance imaging
- OR: Odds ratio
- SPSS: statistical package for social sciences
- TVS: transvaginal sonography
- Vs: Versus

Declarations:

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The datasets generated and/or analysed during the current study are not publicly available due to maintenance of confidentiality of patient information, but are available from the corresponding author on reasonable request.

Ethical approval and consent to participate:

As per our institutional guidelines, ethics approval is not mandatory for retrospective studies

Competing interests:

The authors declare that they have no financial or non-financial competing interests

Consent for publication:

as the identity of individual study participants is not disclosed, this may not be applicable for our manuscript

Author contributions:

NS collected the data and analysed with appropriate statistical methods. RNS helped with the idea and designing the research. He also proof read the manuscript. PM helped in review of literature, statistical analysis and critical evaluation and internal peer review of the manuscript. MT helped in data collection, data evaluation, validation and review of the manuscript. KK helped in data collection, collecting the missing data from additional medical records stored in electronic format, and preparation of the manuscript

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