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Adenomyosis is Associated with Sub-Optimal Outcomes in Fresh Embryo

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ABSTRACT

Context: Adenomyosis is known to affect the outcome of ART by reduced clinical pregnancies and increased miscarriage rates. 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.

Aims: to study the effect of adenomyosis on the outcome of ICSI cycles.

Objectives: Primary: To study the effect of adenomyosis on pregnancy rate in ICSI fresh embryo transfer cycles.

Secondary: To study the effect of adenomyosis on implantation, clinical pregnancy and miscarriage rates in ICSI fresh embryo transfer cycles.

Settings and Design: Retrospective case control study. Performed at a tertiary care university teaching hospital.

Methods and Material: The data of 89 women, who underwent ICSI and fresh transfer from Jan 2002 to March 2019 and satisfied the study criteria, was obtained from the hospital medical records department. Of them 47 women who were diagnosed to have adenomyosis by transvaginal sonography were included in the study.

Statistical analysis used: SPSS version 17 software was used and P<0.05 was considered statistically significant.

Results: The pregnancy, clinical pregnancy, implantation rates and live birth rates were 25.7, 23.4, 7.6% and 17%, respectively.

Conclusions: Adenomyosis is associated with decreased pregnancy, implantation and live births in ICSI cycles.

Key words: Human mandibles, Mandible, Mandibular condyle, Mandibular foramen, Linguala

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INTRODUCTION

Adenomyosis is defined as the presence of endometrial glands and stroma deep in the myometrium, associated with smooth muscle hyperplasia. This condition commonly occurs in women in third and fourth decade of life [1,2]. Adenomyosis occurs in 8-27% of women and about 28% of women with infertility [3]. These women usually present with chronic pelvic pain, menorrhagia, dysmenorrhea, metrorrhagia and dyspareunia. This condition is usually diagnosed by transvaginal ultrasonography (TVUS), and MRI is performed in doubtful cases. Though histopathology remains to be the gold standard for diagnosis, it is impractical and useful only for retrospective confirmation of diagnosis in hysterectomy specimens. Grimbizis et al. classified adenomyosis into the following categories depending on the distribution of lesions and myometrial invasion: Diffuse adenomyosis, focal adenomyosis, polyploid adenomyomas, and other rare forms (endocervical type and retroperitoneal) [4]. The effect of adenomyosis on fertility and pregnancy remains controversial. A significant proportion of these women would undergo ART due to presence of other associated factors such as endometriosis, decreased ovarian reserve, tubal and male factor. Adenomyosis is known to have an adverse effect on the outcome of ART. The possible reasons to this effect include altered myometrial contractility, decreased implantation and altered endometrial

receptivity. Adenomyosis is also associated with reduced expression of implantation markers, lack of expression of adhesion molecules, and altered function of HOXA 10 gene [5–8]. The window of implantation is affected in adenomyosis and was found to be displaced in 47% of women with adenomyosis [9].

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]. Therefore available data on adenomyosis is mutually conflicting. Though freeze all and cryoembryo transfer after adequate treatment with GnRH agonists to ensure optimal regression of adenomyosis is the ideal management in those patients with adenomyosis, there are a few situations which would require fresh embryo transfer in women with adenomyosis. These include low number of embryos and poor embryo quality in these patients due to other factors that affect ovarian response in these women such as advanced age, and co-existing endometriosis. Moreover, the studies performed on Indian population were very few. The present study is aimed to find the effect of adenomyosis on pregnancy, implantation, clinical pregnancy, miscarriage and live birth rates in fresh embryo transferred ICSI cycles.

SUBJECTS AND METHODS

The present study is a retrospective cohort 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, and those women who had tubal factor infertility alone were included as controls. Adenomyosis was diagnosed by 2D transvaginal sonography (TVS) was 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 endometrial myometrial 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 47 cases satisfying the study criteria were included. 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. 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. GnRH agonist trigger (0.2 mg Triptorelin) was administered in cases at risk of OHSS, as per the department protocol. Embryo quality was assessed by Veeck's grading system [26,27]. Fresh embryo transfer was performed on day 2 or day 3 post- oocyte retrieval. Pregnancy is diagnosed by positive b-hCG >5 mIU/ml, on day 14 post-embryo transfer. The statistical analysis was performed by SPSS version 17 software.

RESULTS

The demographic characteristics of the study participants are summarized (Table 1). The ovarian reserve tests of the study participants such as FSH, AMH and AFC are summarized (Table 2). The various indications of ART in the study participants is shown in Table 3. The COH (controlled ovarian hyper stimulation) protocols followed in the study participants include both agonist and antagonist protocols (Table 4).

The ovarian stimulation characteristics such as duration of stimulation, total gonadotropin dosage, estradiol and progesterone on the day of ovulation trigger are summarized (Table 5).

Table 1: Demographic characteristics of the study participants.

Parameter	Group A (n=47) (Mean ± SD)
Age (yrs.)	31.6 ± 5.2
BMI (KG/M2)	27.0 ± 3.3
Duration of infertility (yrs.)	8.2 ± 6.1

Table 2: Ovarian reserve tests of the study participants.

Parameter	Group A (n=47) (Mean ± SD)
FSH (mIU/ml)	7.2 ± 2.5
LH (mIU/ml)	5.2 ± 3.2
E2 (pg/ml)	44.8 ± 16.9
AMH (ng/ml)	3.3 ± 3.1
AFC	12.7 ± 5.9

Table 3: The indications of ICSI in the study participants.

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

Table 4: Stimulation protocols used in the study participants.

Protocol	Group A (%) (n=47)
Long agonist	15 (31.9)
Short	05 (10.6)
Ultrashort	04 (8.5)
Antagonist	23 (48.9)
Unexplained	07 (14.9)

Table 5: Ovarian stimulation characteristics of the study participants.

Parameter	Group A (n=47) [Mean ± SD]
Duration of stimulation (days)	12.0 ± 2.3
Total gonadotropin dose (IU)	4435.7 ± 1856.2
E2 on the day of trigger (pg/ml)	3172.0 ± 3639.5
P4 on the day of trigger (ng/ml)	1.3 ± 0.9
Endometrial thickness on trigger day (mm)	10.8 ± 1.8

Table 6: ICSI outcome of the study participants.

Parameter	Group A (n=47) [Mean ± SD]
No. Of oocytes	13.7 ± 6.9
M-II oocytes	10.7 ± 6.0
Fertilisation rate (%)	77.4 ± 17.4
No. Of embryos transferred	2.8 ± 0.6
Pregnancy rate (%)	12 (25.7)
Implantation rate (%)	7.6 ± 14.6
Clinical pregnancy rate (%)	11 (23.4)
Miscarriage rate (%)	04/12 (33.3%)
Live birth rate (%)	08 (17.0)

The ICSI and fresh embryo transfer outcomes such as fertilisation, implantation and pregnancy rate, clinical pregnancy rate, miscarriage and live birth rates are summarized (Table 6).

DISCUSSION

In a retrospective cohort study of 973 women Sharma ET al reported that the clinical pregnancy rate after fresh cleavage stage 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] [28]. In a retrospective cohort study of 213 patients who underwent IVF, 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 a study performed on the cumulative pregnancy rates after IVF-ICSI in women with colon rectal endometriosis, the subgroups of patients who had adenomyosis and who did not were compared by the pregnancy rates. The cumulative pregnancy rate in the adenomyosis patients were 19% vs.82% in women who did not have adenomyosis [29]. Similar observations of lower pregnancy, clinical pregnancy and live birth rates were noted in our study (Table 6). In a prospective observational study performed by Salim et al. 275 women who underwent IVF-ICSI were grouped into normal (n=256) and-adenomyosis (n=19) groups. The adenomyosis group had a significantly lower pregnancy rate (47.2% vs 22.2%, P<0.001), lower implantation rate (29.4 *vs.* 18.8% P<0.001), and significantly higher miscarriage rate (2.8 *vs.* 50%, P<0.001) [14]. These findings were similar to our study which showed lower pregnancy, implantation and clinical pregnancy rates and increased miscarriage rate. In a systemic review and meta-analysis performed by Younes et al. adenomyosis was associated with significantly lower cumulative clinical pregnancy rate(OR=0.73, CI=0.60-0.90), lower implantation rate (OR=0.66, CI=0.49-0.88) lower live birth rate (OR=0.59, CI=0.42-0.82) and significantly higher miscarriage rate (OR=2.2, CI=1.53-3.15) in women undergoing ART, 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 [19]. In our

study, due to its retrospective nature, selecting an appropriate control group was not possible. However, our observations were similar to this study.

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) [30]. Chiang et al. performed a case control study with 19 patients of adenomyosis diagnosed by USG with 144 age matched controls who had 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 we observed an increased number of miscarriages after fresh embryo transfer in women with adenomyosis, similar to the above two studies (Table 6).

Overall though our study is of retrospective in nature and lacks a comparison group. But this is justified by the fact that we have our department protocols that would render a freeze-all policy(without fresh embryo transfer) of about 80%, and majority of patients with adenomyosis would undergo freeze-all and subsequent frozen embryo transfer to achieve optimal outcomes. Hence these patients who underwent fresh embryo transfer with adenomyosis actually constitute a smaller proportion of our IVF patients. But the strengths of our study are adequate sample size, comprehensive and complete availability of the data of our study participants and presence of complete outcome of the ICSI cycles till live birth. It is obvious from our results that the fresh transfer live birth rate was significantly reduced in women with adenomyosis compared to controls (Table 6). But a live birth rate of 17% was clinically reassuring in women with adenomyosis in situations where frozen embryo transfer is not possible due to increased cost for embryo freezing, poor embryo quality or slow growing embryos, or low number of embryos which would not render the freezing cost-effective.

CONCLUSION

Adenomyosis is associated with a probability of reduced pregnancy, implantation and live birth rates and increased miscarriage rate in ICSI-fresh embryo transfer cycles. A prospective comparative study on a larger data is required to further confirm our findings.

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