Original Article

The Impact of Endometriosis on Reproductive Outcomes in ART Cycles

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Abstract

Background: Endometriosis is defined as the existence of endometrial glands and stroma outside the uterine cavity. This disease is responsible for about 15% of the indications for assisted reproductive technologies (ART).

Materials and Methods: This study is a retrospective cross-sectional study on 1382 women aged 18-42 who underwent ART in Yazd Reproductive Sciences Institute during 2018-2022. Women were divided into two groups: women with endometriosis (N = 173) and women with a tubal factor or unexplained infertility as the control group *(N = 1209)*. Chemical and clinical pregnancy rates and live birth rates were compared.

Results: Women with endometriosis had significantly ($P < 0.001$) lower retrieved oocytes (7.73 ± 5.52 vs 11.53 ± 7.46), metaphase II oocytes (6.27 ± 4.72 vs 9.37 ± 6.62), and the total number of obtained embryos (3.95 ± 3.52 vs 6.13 ± 5.02). Chemical ($P = 0.001$) and clinical ($P = 0.028$) pregnancy rates were lower in women with endometriosis, while live birth rates showed no difference between the two groups ($P = 0.069$).

Conclusion: The findings of this study showed that endometriosis can disturb reproductive outcomes after ART.

Keywords: Assisted reproductive technique, embryo implantation, endometriosis, fertilization, live birth, pregnancy

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Introduction

Endometriosis is a chronic benign disease that is defined as the existence of endometrial tissue outside the uterine cavity. This disease is one of the most common chronic diseases in female reproductive age that is estimated to be about 5%–15% of the general population and 30%–50% of infertile women, which shows the relationship between endometriosis and infertility.[1-4] The pathogenesis is still widely debated. Endometriosis is related to dyspareunia, dysmenorrhea, chronic pelvic pain, and infertility, which can affect the quality of life. Endometriosis has become one of the most common indications for assisted reproductive technique.[5,6]

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Endometriosis can affect fertility in different mechanisms, including adhesion with altered tubo-ovarian function, pelvic inflammation, and diminished ovarian reserve. This disease is responsible for about 15% of the cases of assisted reproduction. Endometriosis affects fertility by creating a harmful environment for the oocyte and embryo. Surgical management of endometriosis can create a more suitable situation for successful conception.[7] Findings showed that the pregnancy rate after surgery in endometriosis is nearly similar to assisted reproductive technologies (ART). However, surgical intervention may be associated with the risk of diminished ovarian reserve.[8-10] Therefore,

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ART can be considered a preferable technique for these infertile women.[2,11] The impact of endometriosis on *in vitro* fertilization (IVF) outcomes has been investigated in many studies, but results remain ambiguous. Fewer retrieved oocytes and lower implantation and pregnancy rates compared to the control group have been reported. On the other hand, it was reported that in women with endometriosis, the stage or severity of the disease and the presence of endometrioma did not worsen ART results.[12] On the other hand, some evidence reported that adverse outcomes in endometriosis are mostly induced by diminished antral follicle count and ovarian response.[13-15]

Considering that the effect of endometriosis on IVF is still debated, we decided to investigate the pregnancy outcomes after ART in women with endometriosis.

Materials and Methods

This retrospective cross-sectional study was conducted to compare pregnancy outcomes in women with endometriosis and a control group aged 18-44 years who had undergone IVF or intra-cytoplasmic sperm injection (ICSI) between April 2018 and March 2022 at Yazd Reproductive Sciences Institute in Yazd, Iran. This study was approved by the Ethics Committee of Yazd Reproductive Sciences Institute, Shahid Sadoughi University of Medical Sciences, Yazd, Iran (IR.SSU.MEDICINE>REC.1401.052). Endometriosis was diagnosed with ultrasound imaging or surgical diagnosis by a gynecologist and confirmed by a radiologist if necessary. Women with tubal factors or unexplained infertility are considered the control group. Women with uterine anomalies, missing data, or cases of oocyte donation, uterine surrogacy, and severe male factor infertility were excluded. The data were collected from electronic medical records. Patients were stimulated with antagonist protocol, and one or two embryos were transferred to the cleavage stage.[16] Live birth rate per transfer is considered the primary outcome, defined as live birth at ≥24 weeks of gestation. Secondary outcomes were implantation rate (number of intrauterine gestational sacs observed by ultrasonography divided by the total number of transferred embryos), chemical pregnancy rate (serum β human chorionic gonadotropin (HCG) >50 IU/L, 14 days after embryo transfer (ET)), and clinical pregnancy rate (detection of fetal heart activity by ultrasound 2-3 weeks after positive β-HCG test).

Statistical analysis

The data were analyzed by SPSS software version 25 (IBM Corp. Released 2017, IBM SPSS Statistics for Windows, Version 25.0, Armonk, NY: IBM Corp.). Categorical variables were compared using the Chi-square test, while continuous variables were compared using the Student's *t*-test and Mann–Whitney *U*-test. A logistic regression analysis was used to identify the variables influencing outcomes. Differences were considered significant at $P < 0.05$.

Results

Of a total of 1382 women who underwent IVF/ICSI cycle with fresh transfer, 173 women were diagnosed with endometriosis and 1209 had tubal factor or unexplained infertility. The baseline characteristics of the two groups are presented in Table 1. There was no significant difference in terms of age ($P = 0.132$). The duration of infertility in women with endometriosis was 5.29 ± 3.27 years and in women without endometriosis was 6.53 ± 6.02 years, which was statistically significant ($P < 0.001$) and women with endometriosis had a shorter duration of infertility. As expected, anti-Müllerian hormone levels as a marker of ovarian reserve were lower in women with endometriosis. The ovarian reserve in women with endometriosis was 2.09 ± 1.89 and in women without endometriosis was 2.86 ± 2.16, which was statistically significant ($P \leq 0.001$). Women with endometriosis received statistically significant higher doses of gonadotropin ($P = 0.033$) [Table 1].

The number of retrieved oocytes, metaphase II oocytes, and the total number of embryos obtained from women with endometriosis were less than those without endometriosis [Table 2].

IVF outcomes were reported in Table 3. Chemical and clinical pregnancy rates were significantly lower in women

Table 1: Baseline characteristics in women with and without endometriosis

Variable	Endometriosis group (*n*=173)	Control group (*n*=1209)	*P*
Age (years)	34.15±5.04	34.64±5.28	0.132*
Duration of infertility (years)	5.29±3.27	6.53±4.01	<0.001**
AMH (ng/mL)	2.09±1.89	2.86±2.16	<0.001**
Gonadotropin dose (IU)	2449.19±914.71	2336.69±1012.24	0.033**

Data presented by mean±SD. *Student's *t*-test and **Mann–Whitney *U* test were used for comparison. AMH=Anti-Müllerian hormone

Table 2: Lab information in women with and without endometriosis

Variable	Endometriosis group (*n*=173)	Control group (*n*=1209)	*P**
Retrieved oocytes (*n*)	7.73±5.52 MD=7 IQR=7.50	11.53±7.46 MD=10 IQR=9	<0.001
Metaphase II oocytes (*n*)	6.27±4.72 MD=5 IQR=6	9.37±6.62 MD=8 IQR=7	<0.001
Total obtained embryos (*n*)	3.95±3.52 MD=3 IQR=3.50	6.13±5.02 MD=5 IQR=5	<0.001

Data presented by mean±SD, and median (MD) IQR. *Mann–Whitney *U*-test were used for comparison

with endometriosis. The live birth rate per embryo transfer and implantation rate tend to be lower in the endometriosis group; however, the difference was not statistically significant [Table 3].

Logistic regression analysis showed women without endometriosis had a 2.04 times higher chance of chemical pregnancy, and a 1.59 times higher chance of clinical pregnancy compared to women with endometriosis [Table 4]. Endometriosis reduces the chance of chemical and clinical pregnancy in women undergoing ART.

Discussion

This study showed women with endometriosis experience poorer ART outcomes. The present study revealed that women with endometriosis have lower retrieved and metaphase II oocytes, and total number of embryos obtained despite receiving more gonadotropin. These findings are in line with previous studies that compared women with endometriosis to women with unexplained infertility and showed endometriosis is associated with fewer oocytes retrieved and embryos.[2,17]

Our analysis demonstrates that endometriosis is associated with lower chemical and clinical pregnancy rates compared to the control group and that this result is in agreement with a previous study that showed a lower pregnancy rate in women with endometriosis.[18]

Our findings showed live birth rate per cycle was comparable between groups that confirmed in a large retrospective study on 27,294 cycles of IVF/ICSI from Latin America that showed that endometriosis does not reduce live birth rate compared to tubal and unexplained infertility despite fewer obtained oocytes and embryos. They suggested that ART is a preferable treatment in infertile women suffering from endometriosis.[2] On the other hand, another retrospective study claimed that endometriosis decreases the likelihood of live birth rate compared to women with unexplained infertility.[17] Inconsistency between results could be due to different diagnostic methods for endometriosis in different centers and various study designs in the control group. Senapati *et al*.[18] reported that when endometriosis was accompanied by other pathologies in the reproductive system, it led to the lowest chance of live birth but women with isolated endometriosis experienced similar live birth rates. They concluded that endometriosis disturbs ART outcomes in terms of lower oocyte count, implantation, and pregnancy rates.

We also found that patients with endometriosis have lower anti-Müllerian hormone levels as a marker of ovarian reserve. This is in accordance with most evidence that showed endometriosis had adverse effects on ovarian function by increased radical oxidative stress and imbalance in the levels of cytokines, interleukins, and various growth factors.[7,19-21] Romanski *et al*.[22] found that women with endometriosis had lower ovarian reserve regardless of whether or not they had a history of ovarian surgery. It was hypothesized that endometriosis causes chronic inflammation and disturbs the immune system in the ovary, which can inherently distract follicular reserve.

A limitation of our study is that it was not possible to do a laparoscopy on all participants to confirm the absence of endometriosis in the control group and also determine the stage of endometriosis.

Conclusion

Our findings show that endometriosis probably has adverse effects on pregnancy outcomes in ART. Endometriosis is associated with lower retrieved and mature oocytes and can lead to a lower pregnancy rate.

Table 3: ART outcomes in women with and without endometriosis

	Endometriosis group ($n=139$)	Control group ($n=889$)	P*
Chemical pregnancy rate (%)	30/139 (21/6%)	320/889 (36%)	0.001
Clinical pregnancy rate (%)	32/139 (23%)	287/889 (32/3%)	0.028
Implantation rate (%)	35/241 (14.5%)	319/1613 (19.8%)	0.05
Miscarriage rate (%)	7/139 (5%)	73/889 (8/2%)	0.194
Live birth rate (%)	26/139 (18/7%)	230/889 (25/9%)	0.069

Data presented by frequency (%). *Chi-square test used for comparison

Table 4: Logistic regression analysis of pregnancy outcomes in women without endometriosis in comparison with endometriosis

Variables	Chemical pregnancy rate	Clinical pregnancy rate	Implantation rate	Miscarriage rate	Live birth rate
With endometriosis	ref	ref	Ref	Ref	ref
Without endometriosis	2.04 (1.33-3.13) P=0.001	1.59 (1.05-2.42 P=0.029	1.45 (0.99-2.2) P=0.05	1.69 (0.76-3.74) P=0.19	1.51 (.096-2.38) P=0.07

Results presented by OR (95% CI)

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Conflicts of interest
There are no conflicts of interest.

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