

## Original Article

# The impact of endometriosis on IVF/ICSI outcomes

Xiyuan Dong, Xiuhua Liao, Rui Wang, Hanwang Zhang

*Reproductive Medicine Center, Tongji Hospital, Tongji Medicine College, Huazhong University of Science and Technology, Wuhan, 430030, The People's Republic of China*

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**Abstract:** This retrospective cohort study was aimed to investigate the impact of endometriosis on the IVF/ICSI outcomes. A total of 1027 cycles of patients undergoing IVF/ICSI treatment in a reproductive medicine unit of academic hospital were enrolled. In the present study, 431 cycles of patients with endometriosis constituted the study group, including 152 cycles of patients with stage I-II endometriosis and 279 cycles of patients with stage III-IV endometriosis, while 596 cycles of patients with tubal factors infertility were considered as the control group. Ovarian stimulation parameters and IVF/ICSI outcomes were compared. Patients with stage I-II and stage III-IV endometriosis required higher dosage and longer duration of gonadotropins, but had lower day 3 high-quality embryos rate, when compared to patients with tubal infertility. In addition, the number of oocytes retrieved, the number of obtained embryos, the number of day 3 high-quality embryos, serum E2 level on the day of hCG, fertilization rate were lower in patients with stage III-IV endometriosis than those in tubal factors group. Except reduced implantation rate in stage III-IV endometriosis group, no differences were found in other pregnancy parameters. This study suggests that IVF/ICSI yielded similar pregnancy outcomes in patients with different stages of endometriosis and patients with tubal infertility. Therefore, IVF/ICSI can be considered as an effective approach for managing endometriosis-associated infertility.

**Keywords:** Endometriosis, IVF, fertilization rate, implantation rate, clinical pregnancy rate

## Introduction

Endometriosis is a condition in which endometrial tissue is present outside the uterine cavity. The prevalence rate of endometriosis has been estimated to reach around 10-15% in reproductive-age women [1]. Women with endometriosis typically present dysmenorrhea, chronic pelvic pain, dyspareunia, infertility, an adnexal mass or completely asymptomatic disease [2, 3]. Approximately, 25-50% of infertile women may be affected by endometriosis and 30-50% patients with endometriosis may suffer from infertility [1]. It is widely accepted that endometriosis exerts negative effects on the fecundity of women. However, the mechanism of endometriosis associated infertility remains incompletely understood. Several mechanisms have been proposed for the association of endometriosis and infertility, including distorted pelvic anatomy [4], impaired ovary function [4-6], altered microenvironment [7-9], affected endometrial receptivity [10-12], and reduced oocyte/embryo quality [13-15].

Although Assisted Reproductive Technology is believed as the most effective therapy of endometriosis associated infertility [16-19], there is no consensus concerning the impact of endometriosis on the IVF/ICSI outcomes. Several previous studies suggested that the IVF/ICSI results of patients with endometriosis were significantly worse than the results of patients with tubal factors [7, 20]. A meta-analysis by Barnhart et al. [21] proposed that the chance of achieving pregnancy was lower for endometriosis patients compared to those with tubal factor infertility (OR 0.56; 95% CI, 0.44 to 0.70). The inferior IVF/ICSI outcomes of endometriosis women may result from decreasing number of retrieved oocytes [21, 22], affected quality of oocytes/embryos [15, 23], impaired uterine receptivity [7, 11, 20] and inhibited sperm motility [24]. In contrast, several studies presented that the endometriosis patients who underwent IVF/ICSI achieved comparable outcomes to infertile patients with tubal factors [17, 25-27]. The improvement of Controlled Ovarian

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Hyperstimulation (COH) with GnRH-a down-regulation and the application of ICSI technology may suppress some negative influence of endometriosis on pregnancy [17, 20]. The present study was undertaken to compare IVF/ICSI outcomes of women with endometriosis to those with tubal factors who underwent IVF/ICSI during the same period of time, to supply further evidence of impact of endometriosis on pregnancy, and to investigate whether endometriosis affects pregnancy results in contemporary IVF/ICSI treatment.

### Materials and methods

#### *Patients*

This was a retrospective, non-interventional, single-center cohort study of patients undergoing IVF/ICSI treatment at reproductive medicine center, Tongji hospital between January 2011 and July 2012. A total of 1027 cycles were enrolled. The study groups included 152 cycles of patients with stage I-II endometriosis and 279 cycles of patients with stage III-IV endometriosis, while 596 cycles of patients with tubal factors infertility were considered as the control group. All patients in endometriosis groups underwent complete removal of endometriosis lesion by laparoscopy before IVF/ICSI treatment. Endometriosis was staged according to the American Society for Reproductive Medicine (ASRM) 1996 classification [3]. All patients in the control group were diagnosed as tubal infertility by laparoscopy, and patients with other factors for infertility besides tubal pathology, such as polycystic ovarian syndrome, uterine malformation, underlying immune conditions, and paternal abnormalities were excluded. Institutional Review Board approval was not necessary, since all patients in the cohort underwent the routine IVF/ICSI treatment in our center and no additional intervention was applied.

#### *Protocol for COH and IVF/ICSI*

Patients with endometriosis underwent COH with GnRH-a long protocol or GnRH-a prolonged protocol. Briefly, the patients who underwent prolonged down-regulation received 3.75 mg intramuscularly GnRH-a (Leuprorelin Acetate, Takeda, Japan) every 28 days for 3 months before COH. As for patients taking long protocols, subcutaneous injection of 0.1 mg GnRH-a

(Decapeptyl (Ferring, Switzerland) or Dipheline (Ipsen, Australia)) was administered daily from midluteal phase of the preceding cycle, which was reduced to 0.05 mg once adequate down-regulation was achieved. The complete pituitary suppression was confirmed by serum E2 level <30 pg/mL and serum LH level <2 mIU/mL. All patients with tubal factors received GnRH-a long protocol.

Ovarian stimulation with recombinant FSH (Gonal-F (Serono, Switzerland) or Puregon (Organon, Netherlands)) was started with administration of 150 IU/d intramuscularly. The dosage of FSH was adjusted according to ovarian response which was assessed by ultrasound and serum E2 level. Recombinant hCG (Serono, Switzerland) was given to trigger follicle maturation when at least two follicles reached a mean diameter of 18 mm. Oocytes retrieval was performed transvaginally 34-36 hours after hCG injection. ICSI was performed when sperm quality was unexpectedly low on the day of oocytes retrieval.

Main variables in assessment of embryos included the cleavage rate, equality of blastomeres, the degree of fragmentation, and mononuclearity in blastomeres. Embryos were classified as Class 1 to Class 4: Class 1 embryos were defined as 4-6 cells on day 2, 8-10 cells on day 3, equal, fragmentation <10%, and no multinucleated blastomeres. Class 2 embryos were defined as 3 or >6 cells on day 2, 6-7 or >10 cells on day 3, equal or less equal, fragmentation 10-20%, and no multinucleated blastomeres. Class 3-4 embryos were those 0-2 cells on day 2, 1-5 cells on day 3, unequal, fragmentation >25%, with or without multinucleated blastomeres. Class 1 and Class 2 embryos were considered as high-quality embryos. Fewer than three embryos were transferred on the day 3 after oocyte retrieval, and excessive high-quality embryos were cryopreserved for subsequent FET cycles. Injections with 60 mg progesterone intramuscularly were administered as luteal phase support from the day of oocyte retrieval.

#### *Outcomes measures*

In the present study, primary outcomes included implantation rate, clinical pregnancy rate (CPR) per initiated cycle, CPR per embryo transfer cycle, and live birth rate. Secondary out-

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**Table 1.** Demographics and clinical characteristics

	Stage I-II endometriosis	Stage III-IV endometriosis	Tubal factors
No. of initiated cycles	152	279	596
No. of embryo transfer cycles	124	228	505
Age (years)	31.0±3.2	30.7±3.8	30.8±4.7
BMI (kg/m <sup>2</sup> )	20.6±2.1 <sup>a</sup>	20.9±2.4 <sup>a</sup>	21.5±2.6
Infertility type			
Primary infertility (%)	53.9 (82/152)	54.1 (151/279)	52.0 (310/596)
Secondary infertility (%)	46.1 (70/152)	45.9 (128/279)	48.0 (286/596)
Duration of infertility (years)	5 (5-16)	5 (5-20)	5 (2-20)
Basal serum FSH level (mIU/mL)	6.81 (2.00-25.33) <sup>b</sup>	6.78 (1.79-37.23) <sup>b</sup>	7.13 (1.02-36.78)
Basal serum LH level (mIU/mL)	4.41 (1.74-12.70)	3.93 (0.29-25.01)	3.72 (2.10-11.30)
Basal serum E <sub>2</sub> level (pg/mL)	54.9 (0.50-170.66)	61.61 (0.19-190.41)	52.92 (25.44-122.20)
Antral follicle count	13.1±5.8	10.6±5.6 <sup>a</sup>	13.4±5.5
Day 3 endometrial thickness (mm)	5.1±1.6	5.4±2.0	4.6±1.7

Note: <sup>a</sup><0.01. <sup>b</sup>=0.02.

**Table 2.** COH performances and embryo parameters

	Stage I-II endometriosis	Stage III-IV endometriosis	Tubal factors
No. of initiated cycles	152	279	596
No. of embryo transfer cycles	124	228	505
IVF (%)	81.6 (124/152)	82.8 (231/279)	80.9 (482/596)
ICSI (%)	18.4 (28/152)	17.2 (48/279)	19.1 (114/596)
Duration of Gonadotropins (days)	11 (6-23) <sup>c</sup>	11 (2-23) <sup>c</sup>	10 (3-17)
Dosage of Gonadotropins (ampules)	38.8±14.7 <sup>a</sup>	39.0±15.3 <sup>a</sup>	34.1±12.8
No. of oocytes retrieved	12.9±7.2	9.2±6.3 <sup>a</sup>	12.4±6.3
Serum E <sub>2</sub> level on the day of hCG (pg/mL)	4378.89±3000.25	3955.73±2674.91 <sup>b</sup>	4479.39±2595.50
Postwash sperm concentration (X10 <sup>6</sup> )	68.1±29.7	64.4±26.8	68.2±28.5
Postwash sperm motility (%)	55.8±15.2	53.7±17.0	58.0±15.6
Fertilization rate (%)	62.5 (1223/1958)	61.6 (1568/2545) <sup>b</sup>	64.0 (4753/7428)
No. of obtained embryos	8.1±5.5	5.6±4.6 <sup>a</sup>	8.0±4.8
No. of day 3 high-quality embryos	5.7±4.6	4.0±3.9 <sup>a</sup>	6.3±4.5
Day 3 high-quality embryos rate (%)	70.6 (864/1223) <sup>a</sup>	70.1 (1099/1568) <sup>a</sup>	78.4 (3728/4753)

Note: <sup>a</sup><0.01. <sup>b</sup>=0.03. <sup>c</sup>=0.04.

comes were COH and embryo parameters, such as dosage and duration of gonadotropins, the number of oocytes retrieved, E<sub>2</sub> level on the day of hCG, fertilization rate, the number of obtained embryos, the number and rate of day 3 high-quality embryos. Clinical pregnancy was defined as a serum hCG level >20 IU/L and confirmed by observation of gestational sac on transvaginal ultrasound scan 5-7 weeks after transfer. Implantation rate was defined as the number of gestational sacs present on ultrasound scan 5-7 weeks after transfer divided by the number of embryos transferred [28].

### Statistical analysis

Shapiro-Wilks test was used to evaluate the distribution of the data. The Continuous data with normal distribution were given as mean±SD. Data with non-normal distribution were presented as median (range). Groups were compared with one-way analysis of variance (ANOVA) with Bonferroni adjustment or Kruskal-Wallis test as appropriate. Categorical variables were presented as percentage and number. Differences between proportions or rates were evaluated with chi-square test and

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**Table 3.** IVF/ICSI outcomes

	Stage I-II endometriosis	Stage III-IV endometriosis	Tubal factors
No. of initiated cycles	152	279	596
No. of embryo transfer cycles	124	228	505
Cycle cancellation rate (%)	18.4 (28/152)	18.3 (51/279)	15.3 (91/596)
Biochemical pregnancy rate (%)	3.2 (4/124)	3.9 (9/228)	1.8 (9/505)
Implantation rate (%)	35.0 (85/243)	29.1 (126/433) <sup>b</sup>	34.5 (345/999)
Pregnancy with single gestational sac (%)	60.7 (37/61)	76.2 (77/101) <sup>a</sup>	63.1 (159/252)
Pregnancy with two gestational sacs (%)	39.3 (24/61)	23.8 (24/101) <sup>a</sup>	36.9 (93/252)
CPR per initiated cycle (%)	40.1 (61/152)	36.2 (101/279)	42.3 (252/596)
CPR per embryo transfer cycle (%)	49.2 (61/124)	44.3 (101/228)	49.9 (252/505)
Live birth rate (%)	78.8 (67/85)	81.7 (103/126)	82.0 (283/345)
Miscarriage rate (%)	16.5 (14/85)	15.1 (19/126)	13.6 (47/345)
Ectopic pregnancy rate (%)	4.7 (4/85)	3.2 (4/126)	4.4 (15/345)

Note: <sup>a</sup>=0.02. <sup>b</sup>=0.04.

**Table 4.** Multiple logistic regression analysis of clinical features

	OR (95% CI)	P value
BMI	0.99 (0.90-1.09)	0.85
Basal serum FSH level	1.00 (0.92-1.09)	1.00
Antral follicle count	1.01 (0.96-1.05)	0.76

the Fisher exact test. Multiple logistic regression analysis was performed for adjustment of clinical features. A *P* value <.05 was considered statistically significant. SPSS version 13.0 (SPSS Inc.) was used for statistical analysis.

### Results

Demographic data and clinical characteristics are shown in **Table 1**. The BMI and basal serum FSH level were lower in endometriosis groups than those in tubal factors group. Moreover, patients with stage III-IV endometriosis had fewer antral follicles as compared to patients with tubal factors. No differences were found in age, infertility type, duration of infertility, basal serum LH, E2 level, and day 3 endometrial thickness.

COH performances are presented in **Table 2**. Women with endometriosis required more days and higher dosage of ovarian stimulation, but had lower day 3 high-quality embryos rate when compared to patients with tubal infertility patients, irrespective of stage of endometriosis. Additionally, the number of oocytes retrieved, the number of obtained embryos, the number of day 3 high-quality embryos, serum

E2 level on the day of hCG, fertilization rate were lower in patients with stage III-IV endometriosis than those in patients with tubal factors.

IVF/ICSI outcomes were illustrated in **Table 3**. The cycle cancellation rate, biochemical pregnancy rate were similar among the three groups. Patients with stage III-IV endometriosis obtained lower implantation rate and lower proportion of pregnancy with two gestational sacs than patients with tubal infertility. No differences were found in other pregnancy parameters among the three groups, in terms of CPRs, live birth rate, miscarriage rate and ectopic pregnancy rate.

To adjust the endometriosis and tubal infertility groups for clinical features in BMI, basal serum FSH level and antral follicle count, multiple logistic regression analysis was undertaken. In the present study, BMI, FSH, as well as antral follicle count was not associated with chance of achieving pregnancy (**Table 4**).

### Discussion

In the present study, we found that patients with endometriosis responded worse to ovarian stimulation than patients with tubal factors, as indicated by longer duration and higher dosage of gonadotropins required in endometriosis groups. In addition, patients with moderate/severe endometriosis obtained lower E2 level on the day of hCG and fewer retrieved oocytes, suggesting that besides the decreased ovarian

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response, the follicle-genesis may also be affected. Our results were in general agreement with previous studies [22, 26, 27].

There was evidence suggesting that impaired oocyte/embryo quality may be one of the causes of endometriosis-associated infertility [13-15]. Indeed, decreased day 3 high-quality embryos rate was found in patients with minimal/mild endometriosis, which suggests that minimal/mild endometriosis lesion can affect embryo-development, but the fertilization rate, the number of obtained embryos and the number of day 3 high-quality embryos were not significantly affected. As for moderate/severe endometriosis cases, fertilization rate, the number of obtained embryos, the number of day 3 high-quality embryos and the day 3 high-quality embryos rate were all decreased. Moderate/severe endometriosis lesion can impair the follicle/oocytes quality, embryogenesis and subsequent embryo viability.

Although it has been widely accepted that endometriosis can adversely influence fecundity and pregnancy, there are still controversies on the impact of endometriosis on pregnancy results in IVF/ICSI treatment cycles. Some studies described that although patients with endometriosis obtained inferior COH performance and/or inferior embryos when compared to patients with tubal factors, these differences did not transfer to pregnancy results [17, 29]. However, other studies reported adverse effects of endometriosis on pregnancy results in IVF/ICSI cycles, with respect to decreased implantation rate and/or CPRs [7, 20, 21]. Our data showed that IVF/ICSI treatment yielded comparable pregnancy results in patients with stage I-II endometriosis and those with tubal infertility. In patients with stage III-IV endometriosis, CPRs and live birth rate were similar to patients with tubal factors, whereas the implantation rate and the proportion of pregnancy with two sacs were lower. Comparable CPRs indicate that patients with moderate/severe endometriosis have similar probability to becoming pregnant as patients with tubal infertility, while reduced implantation rate and likelihood of two-embryo pregnancy suggest abnormalities in the course of embryo implantation, which might be due to impaired embryo-quality and/or alterations of endometrium. Further studies were needed to elucidate whether embryo factor or endometrial factor is the main

cause of impaired implantation in patients with moderate/severe endometriosis.

Despite the less well ovarian response, reduced oocyte/embryo quality, impaired implantation, patients with endometriosis obtained acceptable IVF/ICSI outcomes, as indicated by similar CPRs and live birth rate comparing to tubal infertile patients, irrespective of stage of endometriosis. Such results may attribute to the following facts. First, in order to yield more retrievable oocytes, higher doses of gonadotropins were used in our unit. Relatively aggressive COH might reduce some negative effects of endometriosis on ovaries and induce more available oocytes, which offers an elevated possibility to obtain high-quality embryos. Indeed, treatment with superovulation or ovulation was reported to yield superior outcomes in patients with endometriosis [30-32]. Second, appropriate GnRH-a down-regulation seemed to be essential to IVF/ICSI success. The mechanisms responsible for the beneficial effects of GnRH-a down-regulation remain elusive. GnRH-a may not exclusively prevent an endogenous LH surge but also suppress a number of inflammatory cytokines and soothe the toxic effects of peritoneal cytokines on oocytes and embryos [15]. Additionally, GnRH-a may also correct the endometrial alterations in endometriosis patients [33, 34]. Lastly, laparoscopy may also play an important role in increasing the pregnancy rate in endometriosis patients. The efficacy of laparoscopic procedures in managing endometriosis related infertility was reported by previous studies [35, 36].

Endometriosis has been associated with infertility. However, the mechanism has not been identified. Some studies suggested that the infertility in endometriosis patients mainly depend on the impaired ovarian reserve and reduced ovarian response, as indicated by lower anti-müllerian hormone, higher FSH and aberrant expression of some proteins [6, 23]. Besides, affected endometrial receptivity in endometriosis patients may also contribute to endometriosis-associated infertility. Some studies demonstrated that the expression pattern of various endometrial receptivity related factors were altered in endometriosis patients, such as Integrin, LIF, HOXA-10, IL-11 and P53 [10-12, 37-39]. Based on the data of our study, we proposed that endometriosis adversely impacts ovarian function, oocyte/embryo-

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development, which may be related to infertility. Furthermore, embryo implantation is affected in patients with advanced stage endometriosis, which also may constitute as a cause of endometriosis-associated infertility.

In conclusion, despite less well ovarian response, reduced embryo quality, and impaired implantation in moderate/severe cases, endometriosis patients obtained comparable IVF/ICSI success to patients with tubal factors infertility. Combination effect of aggressive COH, appropriate pituitary suppression, and efficient surgery before IVF seemed to be crucial in IVF/ICSI success of patients with endometriosis. Therefore, IVF/ICSI can be considered as an effective approach for managing endometriosis-associated infertility.

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### Disclosure of conflict of interest

There were no conflicts of interest.

**Address correspondence to:** Dr. Hanwang Zhang, Reproductive Medicine Center, Tongji Medicine College, Huazhong University of science and technology, Wuhan, People's Republic of China. Tel: +86-27-83662533; +86-13638610546; E-mail: hwzhang@tjh.tjmu.edu.cn

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