Impact of Endometriosis on Pregnancy Outcome of Intracytoplasmic Sperm Injection

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ABSTRACT

Background: endometriosis is one of the most challenging diseases that constitute 20%-40% of women searching for their infertility diagnosis. The effects of endometriosis on assisted reproductive outcomes are the issues continuously debated. **Aim of the work**: This study was undertaken to compare the outcome of intracytoplasmic sperm injection (ICSI) in women with endometriosis and women with tubal factor infertility as controls. **Patients and Methods**: from 2016 to 2018 a retrospective study was carried out on patients with endometriosis (n=40) and tubal infertility (n=40) after treatment with ICSI. The main outcome measures were implantation rate, chemical and clinical pregnancy rates while secondary outcomes were COH, such as dosage and duration of gonadotropins, the number of oocytes retrieved, endometrial thickness and E2 level on the day of hCG, fertilization rate and the number of transferred embryos.
Results: no statistically significant difference between the two groups in percentage of metaphase II oocyte, number of embryo transferred, implantation rate and chemical and clinical pregnancy rates, suggesting that embryo quality and uterine receptivity remains unaffected despite the number of oocyte retrieved and fertilization rate were significantly lower in endometriosis group. **Conclusion**: our data suggest that the presence of endometriosis in patients undergoing ICSI does not affect pregnancy outcome, although significantly fewer oocytes retrieved from patients with endometriosis, and lower fertilization rate. .

Keywords: ICSI, COH, hCG, Endometriosis.

INTRODUCTION

Endometriosis is a known cause of subfertility characterized by the presence of ectopic endometrial glands and stroma. As a disease entity, it affects around 10-15% of all women of reproductive-age but as many as 20 to 40% of women who seek help with infertility. There are several theories in association with endometriosis, but the theory of retrograde remains dominant [(1)]. Many patients with endometriosis and infertility will require some assistance to conceive. The assisted reproductive technologies and, more specifically, in vitro fertilization (IVF/ICSI) represent the most successful means of achieving conception in endometriosis patients struggling with infertility. This approach bypasses anatomic distortion, potential compromise in tubal function, and aberrations in the peritoneal environment associated with this disease [(2)].

The effect of endometriosis on the success rates of IVF treatment remains an issue of some debate. One of the main problems has been a variety of conflicting studies either demonstrating a negative impact of endometriosis or no impact at all. There have been two primary theories for the proposed poor outcome after IVF in patients with endometriosis. First, the oocyte quality is poor, resulting in lower fertilization rates. Second, implantation is impaired either as a result of endometrial dysfunction or combined with poor oocyte or embryo quality [(3)].

Considering the presence of controversies in data on the effect of endometriosis on the results of ICSI treatment, we decided to perform this study.

AIM OF THE WORK

The main objective of this retrospective study was to compare the pregnancy outcome of ICSI cycles in women with endometriosis and tubal factor infertility as control.

PATIENTS AND METHODS

A retrospective, database-searched, case-control study was conducted. Data were extracted from the database of a private IVF center from July 2016 to June 2018. The data collected included age, BMI, duration and type of infertility, antral follicle count, basal serum E2, FSH, LH and AMH, ovarian stimulation protocol, dosage of gonadotropin, days of stimulation, endometrial thickness and number of follicles on day of HCG, oocytes retrieved number, MII oocyte number, number of transferred embryo and implantation, chemical and clinical pregnancy outcome. **The study was approved by the Ethics Board of Al-Azhar University and an informed written consent was taken from each participant in the study.**

The study group comprised of 40 women with endometriosis having no other known infertility factor besides endometriosis while the control group consisted of 40 women with tubal-factor infertility.

Inclusion criteria:

They were women were age < 40 years, minimum 2 years of infertility, regular menstrual cycle, normal concentrations of prolactin, free thyroxin and thyroid–stimulating hormone (TSH). Diagnosis of the two groups had previously been confirmed by laparoscopy. All patients in both groups underwent a routine infertility work-up.

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Exclusion criteria

(1) Patients older than 40 years at the onset of the controlled ovarian hyperstimulation (COH) cycle.
(2) Poor ovarian reserve with a day 3 b-FSH concentration of more than 12 IU/L and serum AMH of <0.7 ng/ml.
(3) Patients with other known factors for infertility besides the endometriosis and tubal pathology, such as polycystic ovarian syndrome, uterine malformation, underlying immune conditions, and paternal abnormalities. The standard long GnRH agonist protocol was started by pituitary desensitization with daily administration of 1 mg leuprolide acetate subcutaneously (Lucrin®; Abbot, Hoofddorp, Netherlands) and began in the mid luteal phase of the menstrual cycle onward till the day of hCG injection. At days 1 and 2 of ovarian stimulation, 2 ampoules/day of human menopausal gonadotrophin (hMG, Merional®; IBSA, Institute Biochimique SA, Lugano, Switzerland) were administered) intramuscular together with 2 ampoules of FSH (Fertinorm®; Serono). At days 3, 4 and 5 of ovarian stimulation, 1 ampoule/day of FSH and hMG was administered to each patient. Beginning on day 6, FSH and hMG were administered on an individual basis according to serum oestradiol and transvaginal ovarian ultrasound scans. Ovarian ultrasound scans were performed using a 5.0–9.0 MHz multi-frequency transvaginal probe (Mindray DP-5). (hCG) intramuscular administration (10,000 IU, Choriomon, IBSA, Institute Biochimique SA) were the presence of two or more follicles >19 mm and serum estradiol >800 pg/ml. Leuprolide acetate and gonadotrophins were discontinued from the day of hCG administration. The luteal phase was supported with daily intramuscular injection of 50 mg of progesterone along with vaginal supplementation of 400 mg micronized progesterone (Cyclogest 400mg ®Actavis plc.Dublin, Ireland) starting on the day of oocyte retrieval and continued for 16 days after Oocyte retrieval.

Oocyte preparation:

Oocyte retrieval under general anesthesia, using ultrasound–guided transvaginal approach was scheduled 34–36 h after hCG administration. The cumulus–corona cells were initially removed by exposure to Flushing's medium (Medicult, Copenhagen, Denmark) and 80 IU hyaluronidase (Sigma Chemical Company, St Louis, MO, USA) for up to 1 min. After removing the corona cells, only metaphase II oocytes were injected.

ICSI procedure:

For injection, a motile and morphologically normal spermatozoon was immobilized and aspirated tail first into the tip of the microinjection pipette. The metaphase II oocyte was held by the holding pipette with the polar body at the 12 or 6 o'clock position. The injection pipette was pushed through the zona pellucida and into the ooplasm at the 3 o'clock position. A single spermatozoon was injected. The injection pipette was withdrawn and the oocyte was released from the holding pipette. After microinjection the oocytes were incubated in 20 ml microdrops of IVF medium under lightweight mineral oil.

Briefly, four grades of embryos were defined: Grade 1, embryos had blastomeres of equal size and no cytoplasmic fragmentation; Grade 2, embryos had blastomeres of equal or unequal size and cytoplasmic fragmentation of less than 20% of the embryo surface; Grade 3, embryos had blastomeres of equal or unequal size and 20-50% overall cytoplasmic fragmentation; and Grade 4, embryos had blastomeres of equal or unequal size and cytoplasmic fragmentation of more than 50% of the embryo surface. and Fertilization was assessed 18 h after injection. Only the embryos with high quality were transferred to the uterus 48-72 hours after oocyte retrieval using ultrasound–guided transvaginal approach.

Outcomes measures: Primary outcomes included implantation rate, chemical and clinical pregnancy rate. While, Secondary outcomes were COH, such as dosage and duration of gonadotropins, the number of oocytes retrieved, endometrial thickness and E2 level on the day of hCG, fertilization rate and the number of transferred embryos. Clinical pregnancy was determined by observation of gestational sac and presence of cardiac pulsation on transvaginal ultrasound scan 5-7 weeks after transfer.

Statistical analysis

Recorded data were analyzed using the statistical package for social sciences, version 20.0 (SPSS Inc., Chicago, Illinois, USA). Quantitative data were expressed as mean± standard deviation (SD). Qualitative data were expressed as frequency and percentage.

The following tests were done:

- Independent-samples t-test of significance was used when comparing between two means.
- Chi-square (x^2) test of significance was used in order to compare proportions between two qualitative parameters.
- The confidence interval was set to 95% and the margin of error accepted was set to 5%. The p-value was considered significant as the following:
- Probability (P-value)
- P-value <0.05 was considered significant.
- P-value <0.001 was considered as highly significant.
- P-value >0.05 was considered insignificant.

RESULTS

In the current study, there was no statistically significant difference between the two groups in mean age, body mass index, type and duration of infertility, antral follicle count and basal E2, FSH, LH, AMH.

Also, there were no statistically significant differences between the two groups in duration of down-regulation, total dose of Gonadotropin administered, duration of stimulation, estradiol levels at HCG administration, endometrial thickness or number of follicles. Our data demonstrated that, no statistically significant difference between the two groups in percentage of metaphase II oocyte, number of embryo transferred, implantation rate and chemical and clinical pregnancy rates, suggesting that embryo quality and uterine receptivity remains unaffected despite the number of oocyte retrieved and fertilization rate were significantly lower in endometriosis group.

Table (1): Baseline characteristics

	Endometriosis (N =40)	Tubal factors (N =40)	P-value	Sig.
Age (years)	32.7±3.5	31.9±3.7	0.166	NS
BMI (kg/m^2)	24.3±3.5	25.1±4.2	0.178	NS
Primary infertility (%)	70 (28/40)	72.5 (29/40)		
Secondary infertility (%)	30 (12/40)	27.5 (11/40)	0.805	NS
Duration of infertility (years)	5 .17	5.22	0.919	S
AFC	11.1±5.1	10.9±2.8	0.722	NS
AMH	2.9±1.4	2.7±0.5	0.382	NS
Basal serum E2 (pg/mL)	45.2±1.3	45.3±2.4	0.242	NS
Basal serum FSH (mIU/mL)	6.9±1.1	6.3±1.9	0.652	NS
Basal serum LH (mIU/mL)	5.3±1.4	5.02±.4	0.442	NS

Baseline characteristics in women with endometriosis compared with women with tubal infertility. Where appropriate, Data are expressed as mean ±SD. Average age of the patients was 32 years (in the group of women with endometriosis 32.7±3.5, the youngest patient was 25 and the oldest 38 years old; in the group with tubal infertility 31.9±3.7, the youngest patient was 22 and the oldest 39 years old). There was no statistically significant difference in mean age, body mass index, type and duration of infertility, antral follicle count and basal E2, FSH, LH, AMH between the studied groups.

Table (2): Ovarian stimulation characteristics

Ovarian stimulation characteristics in women with endometriosis compared with women with tubal infertility. Where appropriate, data are expressed as mean ±SD.

	Endometriosis (N =40)	Tubal factors (N =40)	P-value	Sig.
Days of stimulation	10.1±1.6	9.9±1.9	0.466	NS
Total Gonadotropin dose (IU)	3453±982	3480±1213	0.874	NS
E2 on day of hCG (pg/mL)	2600.1±61	2304.9±524	0.408	NS
Endometrial thickness on day of hCG (mm)	8.44±1.65	8.72±2.015	0.315	NS
No. of follicles on day of hCG	8.09±4.3	10.04±5.4	0.117	NS

There were no statistically significant differences between the groups in duration of down-regulation, total dose of Gonadotropin administered, duration of stimulation, estradiol levels at hCG administration, endometrial thickness or number of follicles.

Table (3): IVF laboratory parameters

IVF laboratory parameters in women with endometriosis compared with women with tubal infertility. Where appropriate, data are expressed as mean±SD.

	Endometriosis (N =40)	Tubal factors (N =40)	P-value	Sig.
No. of retrieved oocytes	6.2±3.6	7.9±5.5	0.016	S
No. of MII oocytes (%)	69.5	69.3	0.944	NS
Fertilization rate (%)	64.8	70.2	0.044	S
No. of transferred embryo	2.4±1.1	2.68±1.2	0.276	NS
No. of retrieved oocytes	**6.2±3.6**	**7.9±5.5**	**0.016**	**S**
No. of MII oocytes (%)	69.5	69.3	0.944	NS
Fertilization rate (%)	64.8	70.2	0.044	S
No. of transferred embryo	2.4±1.1	2.68±1.2	0.276	NS

The number of oocyte retrieved and fertilization rate were statistically significantly lower in endometriosis group when compared to tubal group, but we did not find any statistically significant difference in the percentage of metaphase II oocyte or mean number of embryo transferred.

Table (4): Clinical outcomes

	Endometriosis (N =40)	Tubal factors (N =40)	P-value	Sig.
Implantation rate (%)	38/96 (39.6%)	50/108 (46.3%)	0.123	NS
Chemical pregnancy rate	**19 (47.5)**	22 (55)	0.389	NS
Clinical pregnancy rate	19(47.5)	21(52.5)	0.431	NS

Clinical outcomes in women with endometriosis compared with women with tubal infertility. Data are expressed as mean ±SD.

There were no statistically significant differences between two groups in implantation rate, chemical pregnancy rate, and clinical pregnancy rate.

DISCUSSION

The exact mechanism by which endometriosis impairs fertility remains elusive and it is most likely a multifactorial effect. In moderate or severe endometriosis, patients may have anatomic distortion of the fallopian tubes or significant damage to the ovaries. In these situations, it is clear how fertility may be adversely affected. The mechanism of fertility impairment associated with milder forms of endometriosis is less apparent [(4)].

There is molecular evidence that endometriosis has a negative impact on the ovaries, although the exact pathophysiology concerning endometriosis-associated subfertility is not known. The negative impact on the tuboovarian unit can be directly by distorting the anatomy, indirectly by invoking inflammation or by oxidative damage with poorer-quality oocytes [(5)].

Many patients with endometriosis and infertility will require some assistance to conceive. The assisted reproductive technologies and, more specifically, in vitro fertilization (IVF/ICSI) represent the most successful means of achieving conception in endometriosis patients struggling with infertility. This approach bypasses anatomic distortion, potential compromise in tubal function, and aberrations in the peritoneal environment associated with this disease [(2)].

The effect of endometriosis on the success rates of IVF treatment remains an issue of some debate. One of the main problems has been a variety of conflicting studies either demonstrating a negative impact of endometriosis or no impact at all. There have been two primary theories for the proposed poor outcome after IVF in patients with endometriosis. First, the oocyte quality is poor, resulting in lower fertilization rates. Second, implantation is impaired either as a result of endometrial dysfunction or combined with poor oocyte or embryo quality [(3)].

In this study, we tried retrospectively to analyze the ICSI records of 40 women with endometriosis as a study group and 40 women with tubal factor infertility as a control group, in an attempt to confirm whether endometriosis has an impact on ICSI outcome.

In the current study, there was no statistically significant difference between the two groups in mean age, body mass index, type and duration of infertility, antral follicle count and basal E2, FSH, LH, AMH. Also, there were no statistically significant differences between the two groups in duration of down-regulation, total dose of Gonadotropin administered, duration of stimulation, estradiol levels at HCG administration, endometrial thickness or number of follicles.

Our data demonstrated that, no statistically significant difference between the two groups in percentage of metaphase II oocyte, number of embryo transferred, implantation rate and chemical and clinical pregnancy rates, suggesting that embryo quality and uterine receptivity remains unaffected despite the number of oocyte retrieved and fertilization rate were significantly lower in endometriosis group.

It might be difficult to generalize our data and simply compare ours with those of other reports. We could not clearly identify the exact reason for the low number of oocytes retrieved, although many authors have reported that endometriosis can reduce the ovarian reserve to decrease the number of oocytes retrieved.

It is interesting to note that whereas many of the earlier studies suggested negative impact of endometriosis on ICSI outcome, more recent studies demonstrated minimal or no impact.

Simon *et al.*[(6)] supported the concept of impaired implantation in a retrospective comparison with patients with tubal infertility. Women with endometriosis have a poor IVF outcome in terms of reduced pregnancy rate per cycle, reduced pregnancy rate per transfer, and reduced implantation rate. Interestingly, Results from oocyte donations showed that patients who received embryos derived from

endometriotic ovaries showed a significantly reduced implantation rate as compared to the remaining groups. All these observations suggest that infertility in endometriosis patients may be related to alterations within the oocyte, which in turn result in embryos with decreased ability to implant.

From the results of a case–control study from the Yale University IVF-ET program, **Arici *et al.*** [7] retrospectively studied 35 patients undergoing 89 cycles of IVF treatment. It has been suggested that the presence of endometriosis impairs implantation. The implantation rate in women with a diagnosis of endometriosis was 3.9% compared with 7.2% and 8.1% in those with unexplained and tubal factor infertility, respectively. Abnormal implantation, which may be secondary to endometrial dysfunction or embryotoxic environment, is a factor in endometriosis-associated subfertility.

Mı´nguez *et al.* [8] assessed the impact of endometriosis on ICSI outcome. They have retrospectively evaluated 980 ICSI cycles, comparing the results of women with and without endometriosis. A total of 101 cycles was identified in which various degrees of endometriosis were involved, and in the remaining 879 cycles, male infertility was the only cause of infertility. Ejaculated spermatozoa were microinjected in all cycles. There was a significant reduction in the number of oocytes retrieved from women with endometriosis as compared to those without endometriosis. However, there were no significant differences in either fertilization or pregnancy and implantation rates between women with or without endometriosis. They concluded that the presence of endometriosis in patients undergoing ICSI because of severe male infertility does not affect fertilization, pregnancy and implantation rates, although significantly fewer oocytes are retrieved from patients with endometriosis. This observation raises the question of whether ICSI can overcome an apparent defect which may be present in oocytes derived from endometriosis patients and which may result in embryos of lower quality.

A meta-analysis by **Barnhart *et al.*** [9] on Twenty-two published studies proposed that the chance of achieving pregnancy was lower for endometriosis patients compared to those with tubal-factor infertility. Multivariate analysis also demonstrated a decrease in fertilization and implantation rates, and a significant decrease in the number of oocytes retrieved for endometriosis patients. The inferior IVF/ICSI outcomes of endometriosis women may result from decreasing number of retrieved oocytes.

Suzuki *et al.* [10] evaluated the effect of endometriosis and the presence of an ovarian endometrioma on outcomes of conventional in vitro fertilization (IVF) in a retrospective study. Group A: 80 cycles with ovarian endometriomas; group B: 248 cycles with endometriosis but without endometrial cysts at the time of oocyte retrieval; group C: 283 cycles undergoing IVF because of tubal factor without endometriosis. Fewer oocytes were retrieved from groups A and B than from group C. The number of retrieved oocytes was not dependent on the volume of endometrial cyst(s). Fertilization rates were similar among the groups. They concluded that endometriosis affects oocyte number but not embryo quality or pregnancy outcome, irrespective of the presence of an ovarian endometrioma.

Matalliotakis *et al.* [11] investigated the response to controlled ovarian hyperstimulation and ART outcomes in women with advanced-stage endometriosis and previous surgeries at the Yale IVF program between 1996 and 2002 in retrospective case control study. The study group consisted of 68 women who previously undergone laparoscopic surgery for advanced stage endometriosis. The control group included 106 women with tubal-factor infertility. The women with endometriosis underwent 133 IVF-ET cycles and the control group 208 cycles. Women with advanced-stage endometriosis who have undergone previous surgery respond less well to gonadotropins and required higher dosages than women with tubal-factor infertility. However, implantation, pregnancy, and delivery rates are similar; suggesting that embryo quality and uterine receptivity remains unaffected despite diminished ovarian reserve in women with endometriosis.

To further confuse the issue, several subsequent studies have refuted the effect of endometriosis on implantation or pregnancy rates.

Geber *et al.* [12] suggested that implantation and pregnancy rates are similar in women with minimal to mild disease as in those with moderate to severe endometriosis. They compared patients with endometriosis to those with male factor, unexplained and tubal factor infertility. The implantation rates and clinical pregnancy rates were not statistically different between the four groups. Of interest, the stage of endometriosis had no impact on the outcome.

In one of the largest series, **Olivennes *et al.*** [13] compared 214 patients with endometriosis undergoing 360 cycles of IVF treatment to a control group of 111 patients with tubal factor infertility. There were no differences in the pregnancy rates between the two groups. The pregnancy rates among subgroups of patients with pure endometriosis,

endometriosis, and tubal factor or endometriosis and other factors were also similar.

The study of **Nejad *et al.*** [14] in comparison of women with endometriosis and women with tubal infertility a retrospective study was carried out in patients with endometriosis (n=80) and tubal infertility (n=57) after treatment with IVF/ICSI. The main outcome measures were ovarian responsiveness, quality of oocytes, implantation, pregnancy and ongoing pregnancy rates. No differences were found in the age, body mass index, duration of infertility, mean number of ampoules of hMG, duration of hMG injection, number of MII oocytes, number of embryo transferred, and rates of implantation, pregnancy, ongoing pregnancy and twin birth between women with endometriosis and tubal infertility and also between women with stages I/II or those with stages III/IV disease with women with tubal factor infertility. Their results suggest that endometriosis does not seem to have adverse effect on outcome of IVF/ ICSI as compared with tubal infertility.

The 2012 Clinic Summary [15] Report of the Society for Assisted Reproductive Technology reflects no real differences in implantation or pregnancy rates when comparing the subgroup of patients with endometriosis to the aggregate of patients with all diagnoses undergoing IVF in the United States.

In a retrospective cohort study by **Dong *et al.*** [16], they investigated the impact of endometriosis on the IVF/ICSI outcomes. A total of 1027 cycles of patients undergoing IVF/ICSI treatment, 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. 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.

Singh *et al.* [4] retrospectively analyzed two groups consisted of 78 women diagnosed with advanced stage endometriosis and the control group included 100 women with tubal-factor infertility. There was no significant difference in mean age, body mass index and percentage of patient with primary infertility, day 2 FSH, LH, AMH, antral follicle count, percentage of patients with pre-menstrual proliferative or hyperplastic endometrium between two groups. However, the combined ovarian volume was significantly higher in endometriosis group. Women with endometriosis undergoing IVF-ET had a significantly lower oocyte yield and lower fertilization rate in comparison with tubal-factor infertility.

Endometriosis is still an insufficiently explained condition. Numerous controversies still surrounding this complex disease indicate an obvious need for further clinical studies, meta-analysis and explanation of its pathophysiologic mechanisms. Should a consensus be reached on a precise methodology, future studies would definitely be more informative and results easier to use in clinical practice.

CONCLUSION

This study showed that the presence of endometriosis in patients undergoing ICSI does not affect pregnancy outcome, although significantly fewer oocytes retrieved from patients with endometriosis, and lower fertilization rate. ICSI can be considered as an effective approach for managing endometriosis-associated infertility.

RECOMMENDATIONS

The question of whether the presence of endometriosis affects the outcome of women undergoing ICSI has not been resolved. Endometriosis is still an insufficiently explained condition. Numerous controversies still surrounding this complex disease indicate an obvious need for further clinical studies, meta-analysis and explanation of its pathophysiologic mechanisms. Should a consensus be reached on a precise methodology, future studies would definitely be more informative and results easier to use in clinical practice.

Our study may have its limitations. First, it is a retrospective study. Second, the database does not reflect disease stage, past therapy or presence of ovarian endometrioma. We were unable to determine whether patients with severe disease may have different outcome. We were also unable to determine whether there was heterogeneity among tubal' factor patients in terms of presence or absence of hydrosalpinix, a possible confounding factor.

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