



Surgical treatment of endometriosis does not affect outcomes of IVF/ICSI patients: a retrospective single-institution experience

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Background: To compare outcomes of in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI) cycles in patients with stage I-II endometriosis with and without previous surgical treatment.

Methods: This is a retrospective cohort study of prospectively collected data from June 2006 to June 2016. Infertile women with stage I-II endometriosis and AMH ≥ 1 ng/mL, that had undergone IVF/ICSI in our center, were included. Patients were divided into two groups, group 1 consisting of women that had undergone surgical treatment of endometriosis and group 2, consisting of those without medical treatment only. Surgical excision could have been performed within the previous 24 months before the IVF/ICSI attempt. Only patients with endometriosis being the unique cause of infertility were included. Patients with endometriomas >3 cm were excluded from the present study. Primary outcomes were defined to be clinical pregnancy rate and live birth rate. Secondary outcomes were implantation rate, biochemical pregnancy rate, early miscarriage rate and twin pregnancy rate.

Results: There were overall 512 patients with stage I-II endometriosis that finally underwent IVF/ICSI and were included in the present study. Of these, 291 patients had been operated for endometriosis (group 1), while the rest 221 patients were treated conservatively (group 2). Clinical pregnancy rate, live birth rate as well as b-hCG (+) rate, implantation rate and twin pregnancy rate were comparable between study groups. Specifically, clinical pregnancy rate was 48.6% (n=141) vs. 41.1% (n=91), (P=0.11), while live birth rate was 41.5% (n=121) vs. 34.3% (n=76), (P=0.13).

Conclusions: The present study demonstrated that surgical treatment before IVF/ICSI in stage I-II endometriotic patients does not significantly affect the final reproductive outcome.

Keywords: Endometriosis; clinical pregnancy; surgery

Received: 01 October 2020; Accepted: 23 November 2020; Published: 25 March 2021.

doi: 10.21037/gpm-2020-es-03

View this article at: <http://dx.doi.org/10.21037/gpm-2020-es-03>

Introduction

Endometriosis is a gynecologic disease affecting 8–10% of reproductive-aged women (1). Although etiopathogenesis is still controversial, retrograde menstruation appears to be the prevalent mechanism facilitating the extra-uterine implantation of endometriotic implants (2,3). Mainly located in the pelvic cavity, endometriotic lesions may appear as superficial implants (IS), ovarian endometriomas

(OMA) and deep infiltrating endometriosis (DIE), which somehow defines also the stage of the disease (4–6).

As endometriosis is considered a cause of subfertility, the question whether a surgical treatment before the in vitro fertilization (IVF) attempt could have any beneficial effect in the final outcome of ART methods aroused. This is a rather unresolved issue. According to the guidelines of the European Society of Human Reproduction and Embryology (ESHRE) (7), there is limited evidence for

endometriosis surgery aiming at increased live birth rates. The main purpose of surgery for women suffering from endometriosis-related infertility ideally revolves around the restoration of normal pelvic anatomical relationships as well as the reduction of pelvic pain. In stage I-II endometriosis, particularly in asymptomatic cases presenting only with infertility, there is a controversy whether surgical treatment before IVF/intracytoplasmic sperm injection (ICSI) attempt should be given in order to optimize their results.

The aim of the present study was to compare outcomes of IVF/ICSI cycles in patients with stage I-II endometriosis with and without previous surgical treatment. We present the following article in accordance with the STROBE reporting checklist (available at <https://gpm.amegroups.com/article/view/10.21037/gpm-2020-es-03/rc>).

Methods

Study design and setting

This is a retrospective cohort study of prospectively collected data from June 2006 to June 2016 performed at the IAKENTRO IVF Centre, Thessaloniki, Greece. Clinical and laboratory outcomes of IVF/ICSI attempts were compared between patients with and without history of previous surgical treatment for endometriosis stage I-II. Patients whose elements were included in this study had provided written consent regarding anonymous usage of their health records for research purposes. Institutional review Board approved the present study.

Eligibility criteria

In this study, infertile women with stage I-II endometriosis and AMH ≥ 1 ng/mL, that had undergone IVF/ICSI in our center, were included. These patients were referred to our center for IVF by their treating doctors. Therefore, the diagnosis was set either by only diagnostic laparoscopy by their doctors or was based on ultrasound combined with blood markers, HSG and potentially MRI. Patients were divided into two groups, group 1 consisting of women that had undergone surgical treatment of endometriosis by our center and group 2, consisting of those without medical treatment only. Surgical excision could have been performed within the previous 24 months before the IVF/ICSI attempt. Only patients with endometriosis being the unique cause of infertility were included.

All surgically treated patients had undergone

postoperatively GnRH agonists for 6 months followed by contraceptives or just contraceptives. The typical laparoscopic technique used was enucleation, leaving the ovary incision open and burning with bipolar all the superficial sites that are seen during the laparoscopy. No stitches are used.

Patients with endometriomas >3 cm were excluded from the present study. The limit of 3 cm was set based on the guidelines of the international endometriosis Congress held in Montpellier, France, on 2011, in which it was proposed as the maximum limit of potential surveillance, above which further laparoscopy should be performed.

Protocols

All cases were stimulated using a standard fixed 6th day antagonist protocol as described elsewhere (Prapas *et al.*). Briefly, multiple follicle development was induced with 225–300 IU/day of recombinant human FSH (Gonal-f, Serono Pharmaceuticals; Puregon, Organon) or highly purified urinary FSH (Metrodin; Serono Pharmaceuticals). The criterion for use of recombinant or purified urinary FSH was the patient's insurance financial coverage. Daily gonadotropin-releasing hormone (GnRH) antagonist 0.25 mg (Orgalutran, Organon) from stimulation day 6 through the evening prior to the day of triggering ovulation was administered. Final stage of oocyte maturation was triggered with 10,000 IU of HCG (Profasi, Serono Pharmaceuticals; Pregnyl, Organon) or ovitrelle and transvaginal, ultrasound-guided follicular aspiration was performed 34–36 h later. Progesterone supplementation (200 mg vaginal suppositories t.i.d. or vaginal crème daily) was given, beginning on the day of oocyte retrieval. The laboratory techniques and the culture media have been described previously. Briefly, ICSI was used to fertilize all oocytes 4–6 h after retrieval and a maximum of two good quality embryos were transferred on day 5 blastocyst stage. All cases in the study had at least one good quality embryo according to the Veeck criteria (8).

Study outcomes

Epidemiological characteristics and cycle characteristics were recorded for all patients included in the present study. Primary outcomes were defined to be clinical pregnancy rate and live birth rate. Secondary outcomes were implantation rate, biochemical pregnancy rate, early miscarriage rate and twin pregnancy rate. Pregnancies were

confirmed by radioimmunoassay for serum β -hCG levels 14 days after embryo transfer. If the β -hCG test was positive, progesterone administration continued up to 12 gestational weeks. Meanwhile transvaginal ultrasound control 12 days after positive β -hCG test were performed. Clinical pregnancy was defined as a distinct intrauterine gestational sac with a positive fetal heartbeat reported on transvaginal ultrasound. Biochemical pregnancy was considered a temporal increase of β -hCG levels without sonographic findings and miscarriage as a clinical pregnancy loss before 12th gestational week. Live birth rate was defined as the delivery of an alive newborn. Implantation rate was defined as the number of gestational sacs diagnosed in the ultrasound out of the total number of embryos transferred.

Statistical analysis

Independent samples *t*-test was used for the comparison of means of continuous variables, while the chi-squared test was used for testing for independence between categorical variables. Odds ratios were also calculated when the chi-squared test was used. Statistical significance was defined at $P < 0.05$. IBM SPSS 24.0 (IBM Corp., Armonk, NY) was the software of choice for data analysis.

Sample size was defined to be that of all eligible patients during the period of retrospective study cohort. No study of potential bias was set in the scope of present manuscript.

Results

Participants

There were overall 512 patients with stage I-II endometriosis that finally underwent IVF/ICSI and were included in the present study. Of these, 291 patients had been operated for endometriosis (group 1), while the rest 221 patients were treated conservatively (group 2). There were another 86 patients identified during the study period that were excluded, of which in 42 patients cycle was stopped, 23 patients had coexistent infertility cause and other 9 patients had endometriomas over 3 cm. All patients included had at least one good quality embryo transferred.

Study outcomes

Clinical pregnancy rate, live birth rate as well as β -hCG (+) rate, implantation rate and twin pregnancy rate were

comparable between study groups. Specifically, clinical pregnancy rate was 48.6% ($n=141$) *vs.* 41.1% ($n=91$), ($P=0.11$), while live birth rate was 41.5% ($n=121$) *vs.* 34.3% ($n=76$), ($P=0.13$). Implantation rates were 24.6% *vs.* 23.5% ($P=0.56$), overall pregnancy rate was 51.3% *vs.* 46.6% ($P=0.23$) and twin pregnancy rate was 19.7% *vs.* 17.6% ($P=0.45$).

Discussion

The present study demonstrated that surgical treatment before IVF/ICSI in stage I-II endometriotic patients does not significantly affect the final reproductive outcome.

The impact of surgery on the final reproductive outcome of endometriosis patients treated with IVF/ICSI has been an issue of controversy. Furthermore, this impact may be related to the stage of endometriosis. Although In DIE, there has been a unique prospective study, where Bianchi *et al.* (9) reported that extensive laparoscopic excision of DIE resulted in a 2.45-fold increase of clinical pregnancy rate, other relative studies of retrospective nature, reported controversial results as to whether actually IVF outcomes may be improved by a surgical treatment in endometriosis patients. Capelle *et al.* observed that surgery for DIE before IVF did not result in improvement of pregnancy and birth rates (10). In contrary, Centini *et al.* observed that non-surgically treated DIE affected negatively cumulative pregnancy rates, especially when DIE was associated with endometriomas (82.5% patients operated *vs.* 69.4% non-operated) (11).

The review of literature about the impact of surgery in stage I-II endometriosis patients on the final outcome of an IVF/ICSI attempt, leads to similar conclusions with our work. First of all, no prospective RCT has yet been published answering the question whether previous surgical treatment improves pregnancy outcomes in IVF/ICSI patients with endometriosis I–II stage. Furthermore, most of the studies have set DIE in the center of their interest and not the stage I-II endometriosis as the present work. The available published studies are observational and not large enough to allow conclusions. Our work has shown that although a cystectomy, before an IVF attempt, in these patients should not considered as malpractice, there is no evidence supporting that such a strategy should be the gold standard.

A plausible explanation why a surgical procedure does not alter significantly IVF rates actually lies in the nature of endometriosis disease itself. Indeed, endometriosis-

related infertility is not caused by mechanical manner but mainly because of the general inflammatory and immune-deregulating nature of the disease. This has been also proven by studies such as that of Xu *et al.* (12). In this study, authors compared levels of various immune factors (e.g., peripheral blood T-cell subsets CD3, CD4, and CD8) 1 day before and 3 days after surgical operation. They demonstrated no significant alteration of the increased levels of these factors after surgical treatment, therefore indicating that nature of the disease is multimodal and mainly related to a general immune dysregulation and not so much on mechanic reasons. Therefore, they concluded that the immune function of patients with endometriosis is mildly affected by laparoscopic surgery and recover rapidly, which may be one of the reasons for quick recovery of patients after laparoscopy for endometriosis

Another important aspect for patients with endometriosis surgically treated before IVF/ICSI concerns the optimal interval to perform the ART method after surgery. Specifically, even if no consensus exists about cystectomy necessity before IVF, it is common conclusion that IVF should performed within the next 9–12 months at maximum after the operation (13). Otherwise, risk of endometriosis recurrence is increased and thereafter potential benefit of operation is diminished.

This study is not devoid of limitations. The retrospective character of the study may be considered as basic drawback. However, it is one amongst few studies to include exclusively stage I-II patients as well as a relative increased number of patients.

In conclusion, surgical treatment does not have significant impact on IVF/ICSI reproductive outcomes of patients with stage I-II endometriosis. However, in case surgery is performed, IVF should not delay for more than 9–12 months. Further prospective RCTs should performed in order to assess the actual impact surgery may have on patients with all various stages of endometriosis.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editor (Andrea Tinelli) for the series “Endometriosis Surgery” published in *Gynecology and Pelvic Medicine*. The article has undergone external peer review.

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at <https://gpm.amegroups.com/article/view/10.21037/gpm-2020-es-03/rc>

Data Sharing Statement: Available at <https://gpm.amegroups.com/article/view/10.21037/gpm-2020-es-03/dss>

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at <https://gpm.amegroups.com/article/view/10.21037/gpm-2020-es-03/coif>). The series “Endometriosis Surgery” was commissioned by the editorial office without any funding or sponsorship. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Institutional Review Board of IAKENTRO (No. 04/03.06.2016) and patients whose elements were included in this study had provided written consent regarding anonymous usage of their health records for research purposes.

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doi: 10.21037/gpm-2020-es-03

Cite this article as: Petousis S, Prapas Y. Surgical treatment of endometriosis does not affect outcomes of IVF/ICSI patients: a retrospective single-institution experience. *Gynecol Pelvic Med* 2021;4:4.