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ORIGINAL PAPER

The Impact of Endometriosis on *In Vitro* Fertilization Outcome

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ABSTRACT

Introduction: *Endometriosis is a common inflammatory disease and a major cause of infertility through various mechanisms.*

Material and method: *We conducted a retrospective study in infertile women with endometriosis who underwent* in vitro *fertilization (IVF) in order to evaluate the particularities and outcome of ovarian stimulation.*

Results: *A total of 59 patients aged 24-40 years were included. Clinical characteristics of the studied group revealed dysmenorrhea in 66.66% of cases, previous ovarian surgery in 57.89% and primary infertility in 78.94%. The most used protocol was the short one with antagonist (64.91%), followed by the long protocol with agonist (22.80%), and Dual-stim protocol (12.28%). The number of ovarian stimulation days varied between 8-14 days. The total number of oocytes obtained ranged between 0-12. Standard IVF was performed in 40.35% of cases and FIV-ICSI in 59.64% of cases; 78.94% of patients were able to obtain an embryo and blastocysts were obtained in 42.10% of cases. All patients aged under 35 obtained at least one viable embryo. Fresh or frozen single embryo transfer was furtherly performed with a day 3 embryo or a blastocyst. Fresh embryo transfer was mainly performed with day 3 embryos (60.46%). The overall biochemical pregnancy rate in the studied lot was 35.59%. The biochemical pregnancy rate was 40% in the group of patients aged under 35 and 35.13% in the group aged over 35 years.*

Conclusion: *Women with endometriosis are a special category of poor ovarian response mainly due to the decline in ovarian reserve and inferior IVF results are expected due to a lower number of retrieved oocytes, lower fertilization rates, poor embryo quality and altered endometrial receptivity.*

Keywords: endometriosis, infertility, IVF, pregnancy, ovarian stimulation.

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ABBREVIATIONS

IVF: *in vitro* fertilization
ICSI: intracitoplasmatic sperm injection
AMH: antimullerian hormone
AFC: antral follicle count
FSH: follicle-stimulating hormone
BMI: body-mass index
LH: luteinizing hormone
ESHRE: European Society of Human Reproduction and Embryology
GnRH: gonadotropin-releasing hormone

INTRODUCTION

Endometriosis is a common inflammatory disease defined by the presence of endometrial-like tissue outside the uterine cavity, which affects nearly 10-15% of the female population. The proliferation of endometriotic implants is estrogen-dependent, being thus mainly encountered in reproductive-aged women; nevertheless, clinical manifestations and relapses can also occur after menopause (1-3).

Symptoms in endometriosis can vary greatly from almost asymptomatic patients with deep infiltrating lesions to severe manifestations in patients with superficial peritoneal implants or small endometriotic cysts. This lack of correlation between symptoms and disease severity often leads to late diagnosis and management. Notwithstanding, certain hallmark symptoms lead the clinician to the diagnosis: chronic pelvic pain, dysmenorrhea, dyspareunia, infertility, but also urinary or intestinal symptomatology according to the location of endometrial implants. Rare sites of endometriotic lesions, including the lungs, brain or umbilicus, have been reported in the literature (2, 4, 5).

Proper diagnostic with complete mapping of lesions is crucial in the preoperative evaluation with the aim of a "one stop-shop" surgery, especially when dealing with infertility. Transvaginal sonography associated with MRI is mandatory, but when deep infiltrating endometriosis is suspected, sonovaginography with gel offers a better representation of the posterior pelvic compartment (6).

Endometriosis is a major cause of infertility through various mechanisms. One of them is the altered anatomy, with pelvic adhesions leading to impaired oocyte release and pick-up, altered tubal motility and transport of the embryo. The peritoneal fluid of women with endometriosis contains high concentrations of prostaglandins, macrophages, cytokines, interleukins, TNFα, reactive oxigen species. This immune alteration leads to hormonal imbalance, ovulatory disfunction and altered sperm mobility, directly affecting the woman's reproductive function (2, 7, 8). Diminished ovarian reserve assesed by AMH and AFC is due to direct impact of the endometrioma or is iatrogenously induced by repeated cystectomies. Consequently, endometrosis is associated with diminished ovarian reserve, poor response to ovarian stimulation, low quality oocytes and embryos, altered endometrial receptivity, and low spontaneous or IVF-obtained pregnancy rates (2, 8, 9). ❑

MATERIAL AND METHOD

We conducted a retrospective study among women diagnosed with endometriosis who underwent IVF procedures in the Department of Human Assisted Reproduction of "Prof Dr Panait Sirbu" Clinical Hospital of Obstetrics and Gynecology, Bucharest, Romania, between January 2020 - December 2021. The aim was to evaluate the particularities and outcome of ovarian stimulation in infertile women with endometriosis.

Inclusion criteria comprised age 18-40 years and endometriosis diagnosed after laparoscopy. Exclusion criteria were age < 40 years, IVF with donated oocytes, sperm donation, and history of major diseases with impact on fertility (cancer, cardiovascular or psychiatric disease).

Patients underwent ovarian stimulation with long agonist protocol or short antagonist protocol according to clinical and paraclinical characteristics (age, AMH, AFC, FSH, records of previous stimulation protocols). The Dual-stim protocol was used in case of a very low ovarian response after a short antagonist protocol. Types and doses of gonadotropins were chosen according to AMH, AFC, BMI and the addition of LH activity was done mainly in women >35 years. Fresh or frozen single embryo transfer was performed with day 3 or day 5 embryos. Luteal phase support was offered to all patients in a personalised manner with progesterone (vaginal, injectable), estradiol, low dose aspirin,

low molecular weight heparin, corticosteroids, vitamins.

The statistical analysis was performed using Microsoft Office Excel 2016. ❑

RESULTS

A total of 476 couples underwent *in vitro* fertilization procedures in the Human Assisted Reproduction Department of "Prof Dr Panait Sirbu" Clinical Hospital of Obstetrics and Gynecology, Bucharest, Romania, between January 2020 and December 2021. After applying the inclusion and exclusion criteria, 57 patients (11.97%) diagnosed with endometriosis with 79 embryo transfers were enrolled in this study.

The clinical characteristics of the studied group are listed in Table 1.

The ovarian reserve was objectively measured by AMH before starting the ovarian stimulation. Patients with previous history of ovarian surgery had an AMH between 0.1-2.83 ng/mL, with an average of 0.83 ng/mL, while those with no history of ovarian surgery had an AMH between 0.12-4.79 ng/mL, with an average of 1.66 ng/mL. Correlating patients' age with the AMH value, we found an average AMH of 1.79 ng/mL in patients aged under 35 and 1.23 ng/mL in those aged over 35.

The most used ovarian stimulation protocol was the short one with antagonist (64.91%), followed by the long protocol with agonist (22.80%) and the Dual-stim protocol (12.28%).

TABLE 1. Clinical characteristics of the studied group

Clinical characteristic		Value (No/Percentage)
Age	<29 years	4 (7.01%)
	30-34 years	16 (28.07%)
	35-40 years	37 (64.91%)
BMI	< 20 kg/m^2	17 (29.82%)
	20-25 kg/m^2	27 (47.36%)
	> 25 kg/m^2	13 (22.80%)
AMH	<1 ng/mL	20 (35.08%)
	1-2 ng/mL	21 (36.84%)
	>2 ng/mL	16 (28.07%)
Dysmenorrhea		38 (66.66%)
Primary infertility		45 (78.94%)
Secondary infertility		13 (22.80%)
History of ovarian surgery		33 (57.89%)

The number of ovarian stimulation days varied between 8-14 days. The majority of patients required 10-12 days of gonadotropin administration.

The correlation between the IVF protocol and the number of stimulation days revealed that 10-12 days were adequate in 23 cases of short antagonist protocol and in nine cases of long agonist protocol. Less than nine days of stimulation were sufficient only in the short antagonist protocol. Over 13 days of stimulation were almost equally distributed among these two protocols.

The total number of oocytes obtained ranged between 0-12. Four patients did not obtain any oocytes. The majority of patients (61.40%) obtained between 1-5 oocytes and only 31.57% of patients obtained between 1-5 mature oocytes. No patient retrieved over 10 mature oocytes; the maximum number of 9 was obtained in two patients.

Correlating the number of oocytes with the AMH value, the patients who did not obtain any oocytes had an AMH between 0.1-0.83 ng/mL. The maximum number of oocytes was obtained in patients with an AMH over 1.5 ng/mL.

Standard IVF was performed in 40.35% of patients and FIV-ICSI in 59.64% of cases; 78.94% of patients were able to obtain at least one embryo, either a day 3 one or a blastocyst. Most of the patients (57.89%) obtained between 1-3 embryos (Figure 1). Blastocysts were obtained in 42.10% of cases.

Fresh or frozen single embryo transfer was furtherly performed with a day 3 embryo or a blastocyst. Fresh embryo transfer was mainly performed with day 3 embryos (60.46%), while frozen embryo transfer was carried out with blastocysts for the most part (25.58%).

All patients under 35 years of age obtained at least one viable embryo for transfer. In the patient group aged over 35, 32.43% of subjects did not reach an embryo transfer.

The cancellation rate due to either a lack of oocytes upon retrieval or failed fertilization was 7.01% and 10.52%, respectively.

The overall biochemical pregnancy rate in the studied lot was 35.59%. In this group, biochemical pregnancy was obtained after a fresh embryo transfer in 76.19% of cases. The bio-

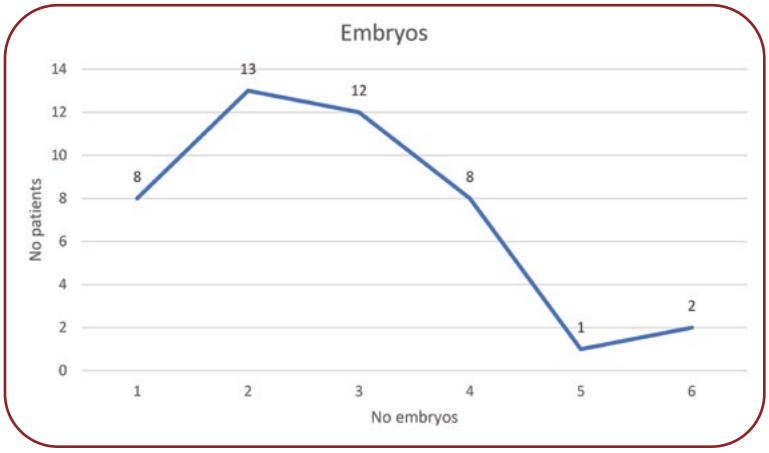

FIGURE 1. Patient distribution according to the number of embryos

chemical pregnancy rate was 40% in patients aged under 35 and 35.13% in those over 35 years of age.

Analysing the type of ovarian stimulation protocol used in patients who obtained a biochemical pregnancy, the short antagonist protocol was used in 66.66% of cases, the long agonist protocol in 23.80% of cases and the dual-stim protocol in 9.52% of cases. Correlating with the proportion in which each protocol was overall used, pregnancy was achieved in 37.83% of patients with the short antagonist protocol, 38.46% of those with the long agonist protocol and 28.57% of subjects with the dual-stim protocol. ❑

DISCUSSION

Endometriosis is a chronic inflammatory disease with major impact on ovarian reserve and subsequently, on the reproductive function. Early diagnosis and proper surgical management in specialized centers could offer patients the chance to obtain a pregnancy.

Surgical treatment in endometriosis causes a degree of injury to the remaining ovarian tissue during the resection of endometriomas, which further accentuates the decrease in ovarian reserve. For this reason, for the preservation of fertility, an individualized approach is recommended depending on each patient's age, preoperative ovarian reserve and desire to obtain a pregnancy in the short- or long-term.

The impact of ovarian surgery is primarily reflected in the ovarian reserve, which is objectified by measuring the level of postoperative AMH. In 2020, a meta-analysis evaluated the AMH level in patients with endometriotic ovarian cyst after surgery and reported a decline in AMH of up to 38%. The AMH level of women with endometriomas naturally declines, even in the absence of surgery, up to 26.4% in just six months (1, 10). Low levels of AMH were also noted in our study among patients aged under and over 35 years (1.79 ng/mL vs 1.23 ng/mL), but especially with a notable difference between patients with or without history of ovarian surgery (0.86 ng/mL vs 1.48 ng/mL).

In vitro fertilization is recommended in women with endometriosis and age >35 years, low ovarian reserve, documented tubal obstruction, failure in obtaining a spontaneous pregnancy, and altered semen parameters of the male partner. According to the ESHRE endometriosis guideline from February 2022, the treatment with GnRH agonist prior to ovarian stimulation during IVF procedure in order to improve live birth rate is no longer recommended. Hormone suppression therapy should not be prescribed postoperatively to women wishing to conceive naturally, but it can be offered to those who do not want to conceive in the near future (11).

When it comes to ovarian stimulation protocols, both the long agonist and short antagonist ones can be recommended to women with endometriosis according to patients' characteristics and doctor's experience. In the past, the long agonist protocol was mainly used in women with endometriosis because of the poor ovarian reserve, but nowadays it is rather disregarded since it requires more stimulation days and higher doses of gonadotropins (11, 12). In our study, the short antagonist protocol was the most commonly used (64.91%) due to its convenient use, greater acceptance from patients, lower cost and less chance of ovarian hyperstimulation syndrome.

Several meta-analyses comparing the IVF outcome of women with endometriosis with a control group revealed a lower number of oocytes retrieved, mature oocytes and embryos and a higher cancellation rate (1, 13, 14). In our study, we also encountered a rather high cancellation rate of 10.52% due to lack of fertilization in the absence of notable male pathology which indirectly explains the poor quality of the oocytes.

In 2020, a meta-analysis of 21 studies found no statistical difference in implantation rate be-

tween the long agonist protocol and the short antagonist protocol, but noticed a significant difference in the number of ovarian stimulation days in favour of the short antagonist protocol (7). Recent studies have shown no significant difference in implantation and clinical pregnancy rates when comparing the outcome of ovarian stimulation protocols (11). The biochemical pregnancy rates in our study were similar in terms of the ovarian stimulation protocol.

The implantation rate, biochemical pregnancy rate and live birth rate in women with endometriosis show no statistical difference *versus* those without the disease, as revealed by several systematic reviews. In the literature, biochemical pregnancy rate ranges from 28.3% to 35%, which is similar to our study (13-16). ❑

CONCLUSION

Endometriosis is a chronic inflammatory disease directly linked with infertility associated mainly with poor ovarian reserve. *In vitro* fertilization procedures in these patients require higher doses of gonadotropins and a longer stimulation period, no matter of the ovarian stimulation protocol. Nevertheless, infertile women with endometriosis are a special category of poor ovarian response because, although inferior IVF outcome is expected due to lower fertilization rates, poor embryo quality and altered endometrial receptivity; however, pregnancy rates are similar to those of women without the disease. ❑

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