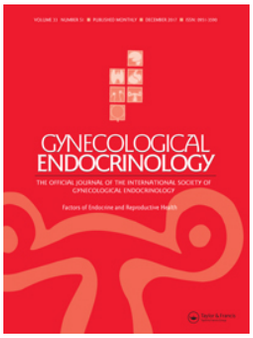

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Dienogest treatment after ovarian endometrioma removal in infertile women prior to IVF

Valeria Muller[a], Igor Kogan[a], Maria Yarmolinskaya[a], Dariko Niauri[b], Alexandr Gzgzyan[a,b] and Edward Aylamazyan[a,b]

[a]Department of Assisted Reproduction Technologies, FSBI D.O. Ott Research Institute of Obstetrics, Gynecology and Reproductology, Saint, Petersburg, Russia; [b]Department of Obstetrics, Gynecology and Reproductology, Faculty of Medicine, Saint-Petersburg State University, Russia

ABSTRACT

Background: Severe forms of genital endometriosis are known to be associated with infertility and its subsequent treatment failure. Both gonadotropin-releasing hormone analogs (a-GnRH) and dienogest have been suggested as additional hormone therapy for patients with endometriomas. However, the result of hormonal suppression before an in vitro fertilization (IVF) cycle remains undetermined.

Materials and methods: A prospective cohort study of 144 infertile women planning IVF after laparoscopic surgery of ovarian endometriomas was conducted at our department in 2012–2015. Patients were divided into three groups: group I ($N = 38$) with dienogest course, group II ($N = 70$) with a-GnRH group III ($N = 70$) without any hormonal therapy within 6 months preceding IVF.

Results: The study groups did not differ by removed endometriomas size and ovarian reserve indicators. The gonadotropin dose per Cycle was higher, while the number of retrieved oocytes was lower in group III patients ($p < .001$). In women with dienogest pretreatment, clinical pregnancy rate was 2.5 times (44.7% versus 16.7%, $p = .012$) and delivery rate – three times higher (36.8% versus 11.1%, $p = .013$) as compared with those from group III.

Conclusions: The present study confirms the necessity of pre-cycle medical interventions in women with ovarian forms of endometriosis undergoing IVF. We suggest dienogest to be possibly more efficient treatment option for this kind of patients.

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Dienogest; endometriosis; assisted reproduction; *in vitro* fertilization; IVF; GnRH agonist; endometrioma

Introduction

Infertility is one of the main clinical symptoms of genital endometriosis. Pregnancy in this subset of patients appears to be a difficult objective to achieve. This is due to high general incidence of the disease, its multifactorial influence on reproductive function, chronic course and elevated risks of recurrence and progression.

According to various estimates, the prevalence of ovarian forms is 17–44% among all stages of endometriosis [1]. Meanwhile, the pregnancy rate after assisted reproduction technologies (ART), particularly *in vitro* fertilization (IVF), in these patients is much lower than in those with mild forms of the disease [2,3]. It is generally assumed that the major causes of IVF failure in these women are the following: diminished ovarian reserve, impaired endometrial receptivity and low quality of embryos [4–6].

The use of prolonged courses of hormone therapy, as well as the timing of referring to IVF, is acclaimed to play an important role in the strategy of overcoming endometriosis-related infertility [7]. In this regard, gonadotropin-releasing hormone agonists (a-GnRH) have been continuously used for the purpose of suppression of the disease progression [2,8]. In recent years, papers have been published on the new approach to the management of endometriosis with a novel progestin – a derivative of 19-norsteroids – dienogest. The results of recent studies, conducted mainly in Europe and Japan, showed evidence of the comparable with a-GnRH effectiveness of dienogest for the treatment of endometriosis, including ovarian forms of the disease [1,9]. Nevertheless, at the present time, there is no general consensus on the type, duration and expedience of medical interventions preceding an IVF cycle for patients diagnosed with endometriosis-associated infertility.

Materials and methods

In order to analyze the efficacy of dienogest pretreatment, we performed a prospective cohort study of 144 infertile women of reproductive age, who planned to undergo IVF after the laparoscopic resection of ovarian endometriomas between January 2012 and December 2015 at ART department of D.O. Ott Research Institute of Obstetrics, Gynecology and Reproductology.

Inclusion criteria to the study were the following: female age from 23 to 42 years; infertility; surgical treatment of endometrioid ovarian cysts performed $\leq$4 months before the recruitment to the study; absence of endometriomas or other ovarian cysts at the start of stimulation; basal follicle stimulating hormone (FSH) < 12.0 IU/L and antimullerian hormone (AMH) blood level ≥ 0.5 ng/mL (both measured at the start of stimulation); controlled ovarian stimulation (COS) in IVF protocol with recombinant FSH (Puregon, N.V. Organon, Oss, Netherlands, or Gonal-F, Merck Serono S.A., Darmstadt, Germany) and GnRH antagonists (Orgalutran, N.V. Organon, Oss, Netherlands or Cetrotide, Merck Serono S.A., Darmstadt, Germany). Subjects with body mass index (BMI) ≥ 30 kg/m^2; uterine fibroids $\geq$2 cm

CONTACT Igor Kogan ikogan@mail.ru Department of Assisted Reproduction Technologies, FSBI D.O. Ott Research Institute of Obstetrics, Gynecology and Reproductology, Saint, Petersburg, Russia

in diameter and/or deforming the uterine cavity; III/IV stage of adenomyosis diagnosed at ultrasound; general contraindications to COS or gestation were excluded.

Participants were randomly divided into three groups: group I included 38 patients who received dienogest (Visanne, Bayer Pharma, AG, Germany) at the dose of 2 mg daily for 6 months prior to IVF protocol; group II consisted of 70 women who were prescribed with 6 injections of a-GnRH (triptorelin 3.75 mg, Diphereline, Ipsen Pharma, France) once every 28 d before the cycle; group III studied 36 subjects without any hormone therapy preceding an IVF attempt.

Ovarian stimulation was initiated on menstrual cycle days 2–3; the starting dose of gongadotropins was 225 IU for each group. GnRH antagonist was administered when the leading follicle reached a diameter of 14 mm. When at least three follicles or a single follicle (in patients with "poor" response) were registered to be 17 mm, an ovulation trigger (Pregnyl, N.V. Organon, Oss, Netherlands) was injected and transvaginal oocyte pick up (OPU) was performed 35–36 h later. Retrieved cumulus–oocyte complexes (COCs) were fertilized either by conventional insemination or by intracytoplasmatic sperm injection with regard to the sperm quality. Embryo transfer (ET) to the uterine cavity was carried out on day 3 of *in vitro* cultivation. Evaluation of the quality was performed using morphology: 6 or 8-cell Grade A (Van Steiterghem A., 1995) cleavage-stage embryos were considered to be of a top quality.

The major outcome of the study was clinical pregnancy (defined by the embryo heart beat registration at transvaginal ultrasound at 6–7 weeks of gestation) rate, measured per ET (CPR). As all patients were followed up to the delivery, live birth rate (LBR) per ET was also registered. Secondary outcomes included total dose of recombinant FSH (r-FSH), duration of stimulation, number of follicles with a diameter of ≥14 mm at the time of ovulation triggering; number of COCs retrieved during OPU; good-quality embryo rate on the third day of development; cycle cancelation rate. Approval of the protocol was granted by the local Ethics Committee.

Statistical data analysis was performed using the package of programs "Statistica version 10.0" (StatSoft Inc., Tulsa, OK). Descriptive statistics were reported as mean ± standard error of mean or median and range (LQ; UQ) according to the distribution. The comparison between two groups was done using Mann–Whitney tests for non-parametric statistics and by Chi-square (χ^2) or two-sided Fisher's exact test – for proportions and categorical factors. The significance level (p-level) was set at .05 for all statistical tests.

Results

Patients from all of the studied groups were comparable in mean age, BMI, and average duration of infertility (data not shown). The maximum diameter of previously removed endometriomas ranged from 1 to 10 cm among the subjects. The incidence of endometriomas of ≥3 cm in diameter was registered in more than 50%, bilateral ovarian damage – in more than 40% of cases and was equally distributed between the studied groups (Table 1).

Ovarian reserve indicators did not differ between the subjects: AMH level was 1.12 ± 0.41, 1.33 ± 0.75, and 1.07 ± 0.59 ng/mL in group I, II, and III, respectively ($p = .387$); FSH level was 8.89 ± 4.89, 7.79 ± 3.01 and 8.71 ± 2.96 IU/L ($p = .447$); antral follicle count on day 1 of COS was 6.7 ± 2.9, 6.9 ± 2.9, and 5.6 ± 2.4 ($p = .387$).

Regarding IVF protocol characteristics, no significant differences in the duration of COS were determined. However, the mean dose/cycle of r-FSH was statistically higher in patients without any suppressive treatment after laparoscopic surgery (Table 2). In contrast, the median number of follicles with a diameter of ≥14 mm, as well as the number of COCs obtained during OPU, was significantly lower in women from group III compared to those who received dienogest or a-GnRH prior to IVF attempt. The average number of A-class embryos on the third day of development in participants, preliminary treated with dienogest

Table 1. Characteristic of previously removed endometriomas in women undergoing IVF.

Size and location of ovarian endometriomas	Group I (dienogest), $N = 38$ (%)	Group II (a-GnRH), $N = 70$ (%)	Group III (no treatment), $N = 36$ (%)	p Level
Unilateral	23 (60.5)	37 (52.9)	20 (55.6)	$\chi^2 = 0.586$ $p = .746$
Bilateral	15 (39.5)	33 (47.1)	16 (44.4)	
Diameter ≤3 cm	13 (34.2)	31 (44.3)	13 (36.1)	$\chi^2 = 1.287$ $p = .525$
Diameter >3 cm	25 (65.8)	39 (55.7)	23 (63.9)	

Table 2. Main characteristics of IVF protocol in women after surgical treatment of ovarian endometriomas.

IVF pararmeters	Group I (dienogest), $N = 38$	Group II (a-GnRH), $N = 70$	Group III (no treatment), $N = 36$	p Level
r-FSH dose, IU/cycle	1800 (1500;2350)	1862.5 (1350;2475)	2650 (1800;3050)	pI–II = .800 pII–III = .001 pI–III = .002
Duration of stimulation, days	9 (8;10)	9 (8;10)	9 (8;10)	$p = .4314$
Number of follicles ≥14 mm on ovulation triggering day	5.5 (4;8)	6 (3;10)	3 (2;6)	pI–II = .981 pII–III = .006 pI–III = .002
Number of COCs retrieved	4.5 (3;7)	5 (2;8)	2 (1;4)	pI–II = .810 pII–III = .003 pI–III < .001
Number of A-class embryos	2.5 (1;5)	2 (0;5)	1 (0;2)	pI–II = .59 pI–III = .01 pII–III = .04

significantly exceeded this parameter in subjects with only surgical management of ovarian endometriomas (group III).

In women who did not receive any hormone therapy after laparoscopy, cycle cancelation rate was 4.5 times higher than that in females prescribed with dienogest and two times higher than in patients with a-GnRH pre-cycle administration. The main reason for the protocol discontinuation in this subset of patients was ineffective ovarian stimulation: 8.3% of women showed no response to COS, while in 15.2% of subjects from group III, no COCs were obtained during OPU.

In women, who had a prolonged course of dienogest prior to IVF, clinical pregnancy rate was 2.5 times (44.7% versus 16.7%, $p = .012$) and live birth rate – three times higher (36.8% versus 11.1%, $p = .013$) than in patients without any hormone therapy after surgical interventions. Meanwhile, no differences were found when comparing IVF outcomes in group II (a-GnRH) and group III subjects: 34.3% (24/70) versus 16.7% (6/36) for CPR ($p = .345$) and 28.6% (20/70) versus 11.1% (4/36) for LBR ($p = .234$) respectively.

Discussion

Overcoming infertility with IVF in women with endometriosis, especially after surgical treatment of the ovarian forms of the disease, is a challenging task in contemporary assisted reproduction. This is related to the variety of causes: diminished ovarian reserve, poor response to stimulation, impaired quality of reproductive cells, and endometrial receptivity in this population of patients. All of the mentioned factors expectedly reduce the effectiveness of infertility management with IVF and lead to the repeatedly unsuccessful treatment attempts.

One of the aspects for optimizing IVF outcomes in patients with endometriosis is a prolonged (3–6 months) pre-cycle suppressive hormone therapy [8]. The results obtained in the present study confirm the importance of this statement as both the quality and the quantity parameters of the protocol were improved in females with either a-GnRH or dienogest administration as opposed to the women without any medical intervention after surgical resection of ovarian endometriomas.

In the prospect of suppressive treatment of genital endometriosis, GnRH analogs have repeatedly proved its effectiveness. It is well known that a-GnRH cause the desensitization of the pituitary gland, suppress the production of gonadotropins and dominant follicle growth, and thus, restrain the development of heterotopic lesions. The effect of a-GnRH on molecular level is being implemented via the reduction of concentrations of the tissue inhibitors of metalloproteinase-1 and proinflammatory mediators (interleukin-1β, vascular endothelial growth factor), which play an important role in the invasion process of endometriotic heterotopies and its proliferative activity. In addition, GnRH agonists induce cell apoptosis by increasing the expression of proapoptotic proteins (Bax, FasL) and decreasing antiapapthotic activity (Bcl-2) [10]. However, there is a concern regarding the possible influence of prolonged a-GnRH administration on endometrial receptivity, especially on the expression of implantation factors, such as αvβ3 integrin [6,12].

Another controversy of treatment with GnRH analogs is related to its negative effects associated with induced hypoestrogenemia: bone mineral density loss, hot flashes, and vaginal dryness [12]. Due to these side actions of the drug many patients "remember" the treatment with a-GnRH and do not always agree to repeat it, showing a decreased rate of adherence to the therapy. At this point, dienogest may serve as an alternative prescription due to the absence of a pronounced antigonadotropic effect and significant suppression of ovarian function. The drug is proposed to have a better compliance and, as the results of the current study showed, might be beneficial for improving IVF outcomes: clinical pregnancy and live birth rates.

Several pato-genetic mechanisms may explain the above-mentioned findings. First, it has been suggested that dienogest possess anti-inflammatory qualities: decreases the activity of macrophages and intraleukin-1 expression, indirectly affecting follicular growth. In connection with our results, the gonadotropin dose per cycle was lower, while the quantity of retrieved oocytes and, consequently, the quality of embryos was higher in subjects prescribed with dienogest as apposed to the women without any hormone treatment prior to IVF.

Second, the effect of the drug can also be implemented on endometrial level. It is already known that in patients with endometriosis, the sensitivity of eutopic endometrium to steroid hormones is impaired due to the disturbance of expression of its receptors: increased activity of estrogen (ER, isoform α) and decreased – of progesterone receptors (PR, isoform B), which result to the state of "progesterone resistance". This might be one of the reasons for the violation of endometrial secretory transformation, implantation failure, or its pathology after ET [11]. A recent study by Hayashi et al. (2012) has demonstrated that dienogest may improve this progesterone resistance in endometrial tissue by increasing the relative expression of PR-B/PR-A ratio and decreasing the ERβ/ERα isoform ratio [12] and, therefore, might have a positive impact on the pregnancy outcome.

In conclusion, to the best of our knowledge, this is the first study which attempted to evaluate the effectiveness of IVF protocol after different types of hormone therapy of endometriosis. We draw the attention to the importance medical suppression of cycles in women previously diagnosed with ovarian forms of the disease. Furthermore, we suggest dienogest being an alternative, possibly more compliant and efficient treatment option for this subset of patients. However, further research is required in order to develop a consensus for the management of infertile women, who are planning to undergo an IVF cycle after surgical treatment of severe forms of genital endometriosis.

Disclosure statement

The authors report that they have no conflict of interest. No funding was required for this study.

References

1. Surrey ES. Endometriosis and assisted reproductive technologies: maximizing outcomes. Semin Reprod Med 2013;31:154–63.
2. Dunselman GA, Vermeulen N, Becker C, et al. ESHRE guideline: management of women with endometriosis. Hum Reprod 2014;29:400–12.
3. Stern JE, Luke B, Tobias M, et al. Adverse pregnancy and birth outcomes associated with underlying diagnosis with and without assisted reproductive technology treatment. Fertil Steril 2015;103:1438–45.
4. Cohen J, Ziyyat A, Naoura I, et al. Effect of induced peritoneal endometriosis on oocyte and embryo quality in a mouse model. J Assist Reprod Genet 2015;32:263–70.
5. Kitajima M, Dolmans MM, Donnez O, et al. Enhanced follicular recruitment and atresia in cortex derived from ovaries with endometriomas. Fertil Steril 2014;101:1031–7.
6. Ruan HC, Zhu XM, Luo Q, et al. Ovarian stimulation with GnRH agonist, but not GnRH antagonist, partially restores the expression of endometrial integrin beta3 and leukaemia-inhibitory factor and improves uterine receptivity in mice. Hum Reprod 2006;21:2521–9.

7. Somigliana E, Arnoldi M, Benaglia L, et al. IVF-ICSI outcome in women operated on for bilateral endometriomas. Hum Reprod 2008;23:1526–30.
8. Sallam HN, Garcia-Velasco JA, Dias S, Arici A. Long-term pituitary down-regulation before *in vitro* fertilization (IVF) for women with endometriosis. Cochrane Database Syst Rev 2006;25:CD004635.
9. Strowitzki T, Faustmann T, Gerlinger C, Seitz C. Dienogest in the treatment of endometriosis-associated pelvic pain: a 12-week, randomized, double-blind, placebo-controlled study. Eur J Obstet Gynecol Reprod Biol 2010;151:193–8.
10. Bilotas M, Baranˆao RI, Buquet R, et al. Effect of GnRH analogues on apoptosis and expression of Bcl-2, Bax, Fas and FasL proteins in endometrial epithelial cell cultures from patients with endometriosis and controls. Hum Reprod 2007;22:644–53.
11. Muller V, Makhmadalieva M, Kogan I, et al. Ectopic pregnancy following in vitro fertilization: meta-analysis and single-center experience during 6 years. Gynecol Endocrinol 2016;32:69–74.
12. Hayashi A, Tanabe A, Kawabe S, et al. Dienogest increases the progesterone receptor isoform B/A ratio in patients with ovarian endometriosis. J Ovarian Res 2012;5:31.