Use of oral contraceptives in women with endometriosis before assisted reproduction treatment improves outcomes

In women with endometriosis, including those with endometriomas, 6 to 8 weeks of continuous use of oral contraception (OC) before assisted reproduction treatment (ART) maintains ART outcomes comparable with the outcomes of age-matched controls without endometriosis. In contrast, ART outcomes are markedly compromised in endometriosis patients who are not pretreated with OC. Ovarian responsiveness to stimulation was not altered by 6 to 8 weeks' use of pre-ART OC, including in poor responders with endometriomas. (Fertil Steril® 2010;94: 2796–9. ©2010 by American Society for Reproductive Medicine.)

Key Words: ART, COH, controlled ovarian hyperstimulation, endometriomas, endometriosis, IVF, OC, oral contraceptives

Endometriosis, a disease of unknown origin, is accompanied by pain and infertility. Although the association of endometriosis and infertility is clinically recognized, the exact nature of the responsible mechanism is still debated. Current views favor a multifactorial phenomenon, with endometriosis affecting human reproduction at three distinct levels: the pelvic cavity, ovaries, and uterus (1).

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The pelvic effects of endometriosis are bypassed by assisted reproduction techniques (ART), but those exerted on the ovaries and uterus may affect oocyte quality and embryo implantation, respectively. It has been claimed that oocyte quality is altered by endometriosis, particularly when endometriomas are present (1–3). It is indeed plausible that various direct inflammation-related effects linked to endometriomas impact on the nearby follicles and affect oocyte quality.

In the uterus, numerous alterations of the eutopic endometrium have been described in cases of endometriosis. These include an activation of prostaglandin ($PG\text{-}E_2$) production through cytokines produced by macrophages (4) as well as, ultimately, inflammation-mediated CYP19A1 (aromatase) expression and estradiol (E_2) production (5, 6). In endometriosis, the eutopic endometrium is also the site of an increase in macrophages, dendritic cells, and neurotrophic factors (7, 8). Moreover, there is also mounting evidence that an overt resistance to progesterone occurs in endometriosis (9), as seen in labor (10). These endometrial anomalies, both morphologic and functional, can be temporarily corrected by suppressing ovarian function with the use of gonadotropin-releasing hormone (GnRH) agonists (11) or oral contraceptives (OC) (12).

Prior studies in women with endometriosis have indicated that 3 to 6 months of treatment with a GnRH agonist before ART can improve outcomes (13, 14). If this beneficial effect results from ovarian suppression rather than from lowering E_2 levels only, a shorter course of OC might be similarly effective, with fewer side effects. We tested this simple hypothesis in a pilot two-center trial that compared ART outcomes from January 2008 to October 2009 in women with or without endometriosis (controls). In the study population, endometriosis was diagnosed either surgically or by ultrasound images of single or multiple endometriomas at the time of oocyte retrieval (15). The controls consisted of women in whom endometriosis was neither diagnosed nor suspected.

Patients from both centers (groups 1 and 2) received similar treatment protocols and were evaluated following similar

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guidelines, with the exception of the OC treatment. The women of group 1 used OC before ART for 1 to 3 weeks (control population) or continuously for 6 to 8 weeks (endometriosis population). The women of group 2 (both control and endometriosis populations) received no OC pretreatment.

Patient characteristics, controlled ovarian hyperstimulation (COH) characteristics, and the results obtained in groups 1 and 2 are detailed in Table 1. Briefly, the clinical pregnancy rates were similar for the controls in both groups (P=.12), but there were slight demographic differences. The women controls in group 1 were 34.7 ± 4.4 years of age, which was slightly younger than the controls in group 2 (35.6 ± 3.0 years) (P=.03). Likewise, baseline levels of follicle-stimulating hormone (FSH) were slightly but statistically significantly lower (P=.001) in the group 1 controls (6.7 ± 2.1) compared with group 2 controls (7.8 ± 3.3). There were no differences between the endometriosis patients of either group. The antimüllerian hormone levels were similar in controls and endometriosis patients. Likewise, there were no differences in the proportion of GnRH agonist long, GnRH-agonist short, or GnRH-antagonist protocols used between groups 1 and 2 (data not shown). The GnRH-agonist long protocol was the standard protocol used in the majority (>75%) of endometriosis and control patients of groups 1 and 2. The GnRH-agonist short (16) and GnRH-antagonist protocols were used in the remaining cases.

In group 1, all patients received an OC preparation containing 0.03 mg of ethinyl E_2 (EE) and 0.125 mg of levonorgestrel (Minidril; Codepharma Laboratories, Boulogne, France), starting on day 2 of the menstrual cycle. In anovulatory patients, OC was started either randomly after verifying that serum progesterone was low (<1.5 ng/mL) or after withdrawal bleeding was induced with progestin. Pre-ART use of OC was continued for 1 to 3 weeks in controls, and 6 to 8 weeks in patients with endometriosis. In the GnRH-agonist long protocol, triptorelin (0.05 mg daily, Decapeptyl; Beaufour-Ibsen-Pharma, Boulogne France) was initiated 5 days before the scheduled stop of the OC treatment, as previously reported elsewhere (17). The FSH/human menopausal gonadotropin (hMG) protocol was initiated 6 days after stopping the OC treatment, irrespective of when menses occurred. With the GnRH-agonist short protocol (poor responders) (15), triptorelin (0.05 mg/day) and FSH/hMG were initiated 4 and 6 days after OC discontinuation, respectively. Finally, in the GnRH antagonist protocol, FSH/hMG was initiated 6 days after stopping OC treatment. The GnRH-antagonist ganirelix (0.25 mg/day, Orgalutran; Schering-Plough Pharmaceuticals, Courbevoie, France) was initiated when one or more ovarian follicles were ≥14 mm and/or the E_2 level was ≥400 pg/mL, but never before day 6 of COH.

In group 2, patients received either a long GnRH-agonist, short GnRH-agonist, or GnRH-antagonist protocol, following criteria similar to those used in group 1. In the GnRH-agonist long protocol, 0.05 mg/day of triptorelin was initiated on cycle day 23 or after progestin administration in anovulatory women. In the short GnRH-agonist protocol, 0.05 mg/day of triptorelin were initiated on cycle day 2 of natural or induced menses, and FSH/hMG was started 2 days later. Finally, in the antagonist protocol, FSH/hMG was initiated on cycle day 2 of spontaneous or induced menses.

The results are summarized in Table 1. No differences were found in the COH parameters when comparing the control patients of similar age of groups 1 and 2. This included the total FSH/hMG used (totFSH), the number of oocytes retrieved, and the FSH/hMG used per oocyte obtained (FSH/o). Likewise, no differences in the clinical pregnancy rate (CPR) were found when comparing the controls of group 1 (35%/retrieval) and group 2 (32.5%/retrieval) (P=.67).

The response to COH was markedly but similarly altered in patients with stage III–IV endometriosis of groups 1 and 2, as compared with their respective controls. This alteration was particularly marked in women with endometriomas in whom the FSH/o was 165% that of controls (P=.001).

In group 1, women aged ≤37 and ≥38 years with endometriosis (including women with endometriomas) had similar a CPR compared with same-age controls. In group 2, the findings were strikingly different. Although the results for the controls of group 2 were similar to those of group 1 (P=.67), the CPR declined sharply for the women with endometriosis, particularly when endometriomas were present. In these latter patients, the CPR of 12.9%/retrieval was statistically significantly lower than the findings for controls in the same study group (32.5%) and for the group 1 women with endometriosis (35.0%) (P=.01).

Our data indicate that pre-ART use of OC for 6 to 8 weeks is beneficial in endometriosis. In severe endometriosis, including with endometriomas, pre-ART treatment with OC obtained a CPR similar to that of unaffected women of similar age.

Remarkably, 6 to 8 weeks of OC treatment before ART did not further alter the already compromised ovarian response to COH encountered in women with endometriomas. The amount of gonadotropin required in the women with endometriomas of group 1 who were pretreated with OC for 6 to 8 weeks (3,163 ± 1,350 IU) actually tended to be lower than in the women of group 2 who did not receive OC treatment (3,677 ± 1,590 IU).

Our findings suggest that 6 to 8 weeks of OC treatment before ART may be as effective as suppressing ovarian function with a GnRH agonist for 3 to 6 months for optimizing ART outcome in endometriosis (13, 14). Our data do not permit a direct comparison to a GnRH agonist, but it is reasonable to postulate that 6 to 8 weeks of OC use will generate fewer side effects than are found with GnRH agonists.

The mechanisms responsible for the beneficial effects from pre-ART treatment with either GnRH agonist (13, 14) or OC are still elusive. However, our findings and those of Surrey et al. (13) parallel the observations that ovarian suppression with either GnRH agonist (11) or OC (12) corrects the endometrial alterations seen in endometriosis. This therefore suggests that GnRH agonist or OC treatment may improve ART outcomes in endometriosis through an endometrial effect.

An alternative explanation for the benefits of OC use before ART (6 to 8 weeks) may be an effect on oocyte quality. Ovarian suppression may indeed soothe the inflammation associated with ovarian endometriosis. We obtained fewer embryos for women with endometriomas in group 2 (2.8 ± 2.5) as compared with their counterparts in group 1 who were pretreated with OC before ART (5.2 + 3.6; P=.01), which also supports this argument.

There is a lingering fear that ovarian suppression using a GnRH agonist or OC diminishes ovarian responses to COH, particularly in poor responders (18). To the contrary, our data suggest that 6 to 8 weeks of OC use before ART did not reduce the COH