Is the endometriosis recurrence rate increased after ovarian hyperstimulation?

Thomas M. D'Hooghe, M.D., Ph.D., Bénédicte Denys, M.D., Carl Spiessens, Ph.D., Christel Meuleman, M.D., and Sophie Debrock, Ph.D.

Leuven University Fertility Center, Department of Obstetrics and Gynecology, University Hospital Gasthuisberg, Leuven, Belgium

Objective: To test the hypothesis that the cumulative endometriosis recurrence rate (CERR) after fertility surgery for endometriosis stage III or IV is increased in women exposed to very high E_2 levels during ovarian hyperstimulation (OH) for IVF when compared with women exposed to less high E_2 levels during OH for intrauterine insemination (IUI).
Design: Retrospective cohort study including infertility patients with endometriosis stage III or IV.
Setting: Leuven University Fertility Center, between 1990 and 2001.
Patient(s): Patients (n = 67) with endometriosis stage III (n = 45) or IV (n = 22) who underwent pelvic reconstructive surgery and subsequently started fertility treatment with either IVF only (n = 39), both IVF and IUI in different cycles (n = 11), or IUI only (n = 17).
Intervention(s): Life table analysis was used to calculate the CERR.
Main Outcome Measure(s): The CERR based on histologic or cytologic proof of disease recurrence.
Result(s): At 21 months after the start of OH the overall CERR was 31% and was significantly lower in patients treated with IVF only (7%) or women treated with both IVF and IUI in different cycles (43 %) than in those treated with IUI only (70%). At 36 months after the start of OH, the overall CERR was 63%.
Conclusion(s): In contrast to our hypothesis, the results from this study showed that the CERR is lower after ovarian hyperstimulation for IVF than after lower-dose ovarian stimulation for IUI, suggesting that temporary exposure to very high E_2 levels in women during OH for IVF is not a major risk factor for endometriosis recurrence in women treated with assisted reproductive technology. (Fertil Steril® 2006;86:283–90. ©2006 by American Society for Reproductive Medicine.)

Key Words: Endometriosis recurrence, ovarian hyperstimulation, moderate to severe endometriosis

Endometriosis can be considered as an estrogen-dependent disease, because it is rarely observed before menarche and usually disappears after menopause. It is well known that moderate to severe (1, 2) endometriosis can be a recurrent disease, both after cessation of medical suppressive treatment and after surgical treatment (3–5).

Recurrences of endometriosis after surgery can be explained by incomplete surgery, persistence and growth of microscopic endometriosis, the development of new lesions, or a combination of these factors. However, it is not known whether temporary and repeated exposure to high E_2 levels during controlled ovarian hyperstimulation (COH) for IVF contributes to the recurrence of endometriosis.

Some case reports suggest indeed that OH may lead to a higher recurrence rate of endometriosis. About 10 years ago (6), a rare coincidence of ureteral endometriosis and ovarian stimulation with hMG was described in a patient with a history of a surgically removed endometriotic cyst. Symptoms occurred 10 days after her first IVF attempt. Furthermore, four cases of severe digestive complications due to the rapid growth of sigmoid endometriosis were reported under OH with hMG (7). In that study, all four patients underwent a laparoscopy where endometriosis of revised American Fertility Society/American Society for Reproductive Medicine (rAFS) stage IV was found and treated before the onset of COH. Symptoms occurred after one to seven cycles (mean 3.5 cycles) of COH for IVF. The mean E_2 concentration was 2,383.75 ± 187.94 pg/mL when the bowel symptoms started.

These case reports suggest that repeated ovarian hyperstimulation during IVF may stimulate the growth of endometriotic lesions and lead to recurrence of endometriosis. However, no prospective controlled cohort studies are available to support this hypothesis.

In this retrospective cohort study we tested the hypothesis that the cumulative endometriosis recurrence rate (CERR) after fertility surgery for stage III and IV endometriosis is increased in women exposed to very high E_2 levels during OH for IVF when compared with a control group of women exposed to less high E_2 levels during OH for intrauterine insemination (IUI). As a second outcome variable, we measured the CERR after fertility surgery for moderate or deep

Received January 10, 2006; revised and accepted January 17, 2006.
Reprint requests: Thomas M. D'Hooghe, M.D., Ph.D., Department of Obstetrics and Gynecology, University Hospital Gasthuisberg, Herestraat 6, 3000 Leuven, Belgium (FAX: 32-16-344368; E-mail: thomas.dhooghe@uz.kuleuven.ac.be).

endometriosis in infertile patients before the start of IVF or IUI.

MATERIALS AND METHODS

Patient Recruitment

The database of the Leuven University Fertility Center was searched in June 2001 for all patients with a previous history of surgically treated endometriosis stage III or IV, who underwent IUI, IVF, or a combination of both between February 1990 and June 2001. Institutional Review Board approval was not needed, because this was a retrospective study based on electronic patient files. Staging of endometriosis followed the standard rAFS classification system (1, 2). We identified 74 women who had received pelvic reconstructive surgery for endometriosis before entering our program of medically assisted reproduction using artificial reproductive techniques (ARTs) including IUI and/or IVF.

Controlled Ovarian Stimulation

In our IUI program, patients were stimulated with either clomiphene citrate (50–100 mg per day on days 3–7 of the cycle) or gonadotropins (75 to 150 IU FSH/LH per day, starting on day 2 of the cycle) and monitored using gynecologic ultrasound and hormonal analysis (E_2, P, LH). An injection of 10,000 IU hCG was given when one or two mature follicles of at least 17 mm diameter were documented, at a median E_2 level of 331 (range 114–1,241) pg/mL (Table 1). When three or more follicles were present, the patient was offered a selective aspiration of some follicles, with the goal to conserve one (at most two) follicles to prevent higher-order multiple pregnancies.

In our IVF program, COH was performed as follows. In the previous cycle an oral contraceptive pill was given for 25 days (Cilest; Janssen-Cilag, Berchem, Belgium), followed by pituitary down-regulation with busereline acetate (600 μg daily; Suprefact; Hoechst, Frankfurt, Germany) from day 21 onwards. Daily injections of hMG (Humegon [Organon, Oss, The Netherlands] or Menopur [Ferring, Copenhagen, Denmark]) were started on the second day after the subsequent menstruation, followed by monitoring using ultrasound and hormonal analysis as mentioned above. Final follicular maturation was induced with 10,000 IU hCG (Pregnyl; Organon) when at least three follicles of 17 mm or more were present.

Ultrasound-guided oocyte aspiration was performed 36 hours later. Luteal supplementation was given either by 1,500 IU hCG, every three days, starting on the third day after oocyte retrieval, or by vaginal progesterone (600 mg/day; Utrogestan; Piette International, Drogenbos, Belgium) when there was an increased risk for hyperstimulation syndrome (E_2 level >3500 pg/mL at the time of hCG injection, or patients with polycystic ovarian syndrome).

In freeze-thaw cycles, the endometrium was prepared using COH with a low dose (75 IU) of hMG (Humegon or Menopur). Monitoring and hCG injection was performed as described above for IUI cycles.

Post-ART Recurrence Study

The study group included patients exposed to at least one cycle of IVF and consisted of two subgroups: women treated with IVF alone (n = 39) and women treated with both IVF and IUI in different cycles (n = 11) (Table 1). The control group (IUI only; n = 17) consisted of women treated with IUI after minimal ovarian hyperstimulation with gonadotropins or clomiphene citrate, with a median E_2 level of 331 pg/mL at the time of hCG injection (Table 1).

The CERR was calculated from the first cycle of OH for IUI or IVF. Patients entered the study at the time of their first

TABLE 1

Recurrence of endometriosis after treatment with ART according to type of treatment and to median E_2 levels per cycle (post-ART recurrence study).

	Study group					Control group
	IVF alone		Combination of IUI and IVF			IUI alone
	IVF OPU	IVF cryo	IUI	IVF OPU	IVF cryo	IUI
Patients	39	(7)[a]		11	(1)[b]	17
Total cycles	101	11	28	21	1	50
Median E_2 level/cycle (pg/mL)	1838	691	454	1140	463	331
Range	532–5479	441–1,333	53–1,097	52–2,807		114–1,241

Note: OPU = ovum pick up.

[a] Seven out of 39 patients undergoing IVF ovum pick up cycles additionally received one or several cryo cycles.

[b] One out of 11 patients undergoing IVF ovum pick up cycles additionally received a cryo cycle.

D'Hooghe. Endometriosis recurrence after ovarian hyperstimulation. Fertil Steril 2006.