

# Women with advanced-stage endometriosis and previous surgery respond less well to gonadotropin stimulation, but have similar IVF implantation and delivery rates compared with women with tubal factor infertility

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**Objective:** To investigate the response to controlled ovarian hyperstimulation and ART outcomes in women with advanced-stage endometriosis and previous surgeries at the Yale IVF program between 1996 and 2002.

**Design:** Retrospective case control study.

**Setting:** Academic medical center.

**Patient(s):** The study group consisted of 68 women who previously undergone laparoscopic surgery for advanced-stage endometriosis. The control group included 106 women with tubal-factor infertility. The women with endometriosis underwent 133 IVF-ET cycles and the control group 208 cycles.

**Intervention(s):** Controlled ovarian hyperstimulation and IVF-ET.

**Main Outcome Measure(s):** Response to gonadotropins, fertilization, cleavage, implantation, pregnancy, miscarriage, and live birth rates.

**Result(s):** Lower peak E<sub>2</sub> levels, higher total gonadotropin requirements, lower oocyte yield, and higher cancellation rates were found in women with endometriosis compared with tubal-factor control subjects. However, no differences were found in fertilization, cleavage, implantation, pregnancy, miscarriage, and delivery rates between the endometriosis and tubal-factor groups.

**Conclusion(s):** Women with advanced-stage endometriosis who have undergone previous surgery respond less well to gonadotropins than women with tubal-factor infertility. However, implantation, pregnancy, and delivery rates are similar, suggesting that embryo quality and uterine receptivity remains unaffected despite diminished ovarian reserve in women with endometriosis. (*Fertil Steril*® 2007;88:1568–72. ©2007 by American Society for Reproductive Medicine.)

**Key Words:** Endometriosis, infertility, IVF-ET, ovarian reserve, implantation, pregnancy

Although IVF-ET was initially developed as a treatment for tubal-factor infertility (1), it has become a successful treatment for patients with infertility for many indications, including male-factor and unexplained infertility (2). Patients with moderate or severe endometriosis may have anatomic distortion of the fallopian tube and ovary which may necessitate the use of IVF. However, even mild stages of endometriosis may have negative effects on oocyte development, embryogenesis, or implantation (3–7).

The impact of endometriosis on assisted reproductive technology (ART) outcomes is controversial (8–14). Several early studies suggested that pregnancy rates after IVF were

significantly lower in women with severe endometriosis than in those with minimal or mild endometriosis (9, 10). However, more recent larger studies have shown no difference in IVF pregnancy rates for women with stage III or IV disease (11–13).

Although pregnancy rates after surgery for endometriomas are satisfactory, there is concern that the mechanical removal of the pseudocapsule may impair ovarian reserve (15–17). Moreover, laparoscopic cystectomy before commencing controlled ovarian hyperstimulation (COH) does not appear to improve fertility outcomes compared with proceeding directly to IVF-ET (18). In fact, proceeding directly to IVF-ET in women with asymptomatic ovarian endometriomas may reduce the time to pregnancy, the costs of treatment, and the risk of surgical complications. The purpose of the present study was to compare IVF-ET outcomes in women with advanced-stage endometriosis who underwent surgical

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treatment of endometriomas to women with tubal infertility who underwent IVF during the same time period. We were specifically interested in examining the response to gonadotropins, embryo quality, and implantation rates.

## METHODS

A total of 174 women who had undergone IVF-ET treatment from 1996 to 2002 were retrospectively identified. The study group consisted of 68 women with stage III-IV endometriosis who had undergone laparoscopic cystectomy prior to IVF-ET. These women underwent 133 ART cycles, and none had any other known infertility factor besides endometriosis. The American Fertility Society Classification (1985) was used to grade the severity of endometriosis (19). The control group included 106 women with tubal infertility who underwent 208 cycles of ART treatment. All patient partners had a normal semen analysis according to the World Health Organization criteria. In both groups ICSI was performed if failed fertilization had occurred in previous IVF cycles.

A long protocol was used for COH. Briefly, GnRH agonist leuprolide acetate (1.0 mg/day Lupron; TAP Pharmaceuticals, Waukegan, IL) was administered starting in the luteal phase of the previous cycle. After pituitary desensitization ( $E_2$  level  $<50$  pg/mL) was achieved, the dose of GnRH agonist was reduced to 0.5 mg/day and ovarian stimulation commenced. Recombinant FSH and/or hMG (Pergonal or Metrodin; Serono Laboratories, Norwell, MA) were used at doses ranging between 225 IU/day and 450 IU/day, in accordance with body mass index, patient age, size and number of follicles, and  $E_2$  levels. Human chorionic gonadotrophin (10,000 IU IM Profasi; Serono Laboratories, Randolph, MA) was administered when at least two follicles reached a mean diameter of 18 mm and the serum  $E_2$  concentration was  $>500$  pg/mL. Transvaginal oocyte retrieval was scheduled 35–36 hours after hCG injection. Embryo transfers were performed 3–5 days later under ultrasound guidance. Pregnancies were diagnosed by a rising concentration of serum  $\beta$ -hCG, which was tested 14 days after ET. Clinical pregnancies were confirmed by the presence of a gestational sac on vaginal ultrasound examination during the 5th week.

This study was approved by the Human Investigation Committee of Yale University School of Medicine (HIC #12590). Data are expressed as mean  $\pm$  SD or percentages as required. Statistically significant differences were performed with Fisher exact test, Yates corrected  $\chi^2$ , or Student  $t$  test, as appropriate. All statistical calculations were performed with Sigmasat for Windows 2.0 (Systat Software Inc., San Jose, CA). Statistical significance was defined as  $P < .05$ .

## RESULTS

Patient characteristics and ovarian stimulation parameters are shown in Table 1. Women in the two groups were comparable in terms of age, body mass index, day 3 FSH, type of

gonadotropin used, length of the stimulation phase, and quality of their partner's sperm. However, women with tubal-factor infertility required fewer ampules of gonadotropins and attained higher peak  $E_2$  levels than women with endometriosis. Moreover, the number of follicles on the day of hCG and the number of follicles with diameter  $\geq 15$  mm were significantly higher in women with tubal factor than endometriosis. Finally, cycle cancellation rates were significantly higher for women in the endometriosis group.

The total number of oocytes retrieved, the number of mature oocytes, the number of embryos one day after retrieval, and the number of cleaved embryos on day 3 were significantly higher in women with tubal factor than in women with endometriosis (Table 2). No significant differences were found between the groups with regard to the fertilization rate or cleavage rate. A similar number of embryos were transferred in each group.

Pregnancy outcomes are presented in Table 3. Implantation rates, clinical pregnancy rates, and live birth rates were comparable between the two groups. There were no significant differences in miscarriage rates between women with tubal-factor infertility and those with endometriosis. Moreover, no differences were found in fertilization, cleavage, implantation, pregnancy, miscarriage, and delivery rates between the endometriosis and tubal factor groups compared with first-cycle patient results.

## DISCUSSION

A number of retrospective studies have examined IVF-ET outcomes in women with endometriosis. A reduced response to gonadotropins, lower oocyte yield, and poor clinical pregnancy rates per cycle have all been described (19). In addition, lower implantation rates, assessed by the number of visible gestational sacs per embryo transferred, have been reported in women with severe endometriosis compared with women with tubal-factor infertility (7).

In the present study, all patients with advanced-stage endometriosis had previously undergone surgical treatment. We found a detrimental relationship between endometriosis with previous ovarian surgery and ovarian reserve. Despite similar day 3 FSH levels in women with endometriosis compared with women with tubal-factor infertility, women with endometriosis required significantly higher dosages of gonadotropins, achieved lower peak  $E_2$  levels, and yielded fewer oocytes. Moreover, women with endometriosis had higher cycle cancellation rates.

Similar results have been reported by Ho et al. (20). That group compared oocyte yield from each ovary in 38 IVF cycles from 32 patients who had undergone unilateral cystectomy for an endometrioma. They reported significantly fewer follicles and significantly fewer oocytes from the ovary previously operated on compared with the "normal" ovary. In contrast, Canis et al. (21) compared the IVF outcomes of patients who had laparoscopic cystectomy for endometriosis

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