Impact of ovarian endometrioma on oocytes and pregnancy outcome in in vitro fertilization

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Objective: To evaluate the effect of endometriosis and the presence of an ovarian endometrioma on outcomes of conventional in vitro fertilization (IVF).

Design: Retrospective study.

Setting: Reproductive Unit, Department of Obstetrics and Gynecology, Tokai University Hospital.

Patient(s): Group A: 80 cycles with ovarian endometriomas; group B: 248 cycles with endometriosis but without endometrial cysts at the time of oocyte retrieval; group C: 283 cycles undergoing IVF because of tubal factor without endometriosis.

Intervention(s): All conventional in vitro fertilization-embryo transfer (IVF-ET) with previous diagnostic laparoscopy. An endometrioma was diagnosed by direct aspiration at the time of oocyte retrieval.

Main Outcome Measure(s): Retrieved number of oocytes, fertilization rate, embryo quality, implantation rate, pregnancy rate, and live birth rate for all cases. In group A, the number of retrieved oocytes in relation to the volume of the endometrioma and affected laterality.

Result(s): Fewer oocytes were retrieved from groups A and B than from group C (P<.005). The number of retrieved oocytes was not dependent on the volume of endometrial cyst(s). Fertilization rates were similar among the groups. Group A had slightly but not significantly higher rates of morphologically good-quality embryos (group A: 67.2%, group B: 63.0%, group C: 58.1%), implantation (group A: 14.1%, group B: 11.7%, group C: 11.3%), and pregnancy (group A: 25.3%, group B: 22.3%, group C: 23.9%).

Conclusion(s) Endometriosis affects oocyte number but not embryo quality or pregnancy outcome, irrespective of the presence of an ovarian endometrioma. (Fertil Steril 2005;83:908–13. ©2005 by American Society for Reproductive Medicine.)

Key Words: Endometriosis, IVF, ovarian endometrioma, infertility, laparoscopy, retrieved oocytes, fertilization, embryo quality, implantation, pregnancy, live birth

Despite extensive studies, the cause and result relationship between endometriosis and infertility is not clearly understood. However, pelvic endometriosis is frequently found in infertile women: 55% of the 290 cases of diagnostic laparoscopy for infertility performed at our reproductive center between January 1999 and June 2003. Because of this high incidence, endometriosis is thought to be one of the major causes of clinical infertility.

Pelvic adhesion secondary to endometriosis is the most accepted reason for infertility, presumably via dysfunction of the fallopian tube (1) or ovary (2). In addition, several mechanisms of infertility have been proposed, such as immunologic defects (3) and altered characteristics of peritoneal fluid involving cytokines (4, 5) and macrophages (6), which would affect sperm and/or ova.

The presence of an ovarian endometrioma greater than 1 cm in diameter is classified as stage III (moderate) or more in the revised American Fertility Society (revised AFS) classification of endometriosis (7). The impact of an ovarian endometrioma on infertility remains controversial, despite the number of studies that have been performed (4, 6, 8–13, 14–26). The present study was undertaken to retrospectively analyze our records of in vitro fertilization-embryo transfer (IVF-ET) and to elucidate whether a pregnancy-related outcome is dependent on the presence of an ovarian endometrioma.

MATERIALS AND METHODS

We reviewed the medical records of IVF procedures performed at the Reproductive Unit of the Department of Obstetrics and Gynecology at Tokai University Hospital between March 1996 and December 2002. We analyzed 868 cycles, excluding those with intracytoplasmic sperm injection (ICSI). A total of 611 cycles were extracted and divided into three groups: 80 cycles (group A) had ovarian endometriomas that were aspirated and identified as “chocolate” cysts at the time of oocyte retrieval; 248 cycles (group B) did not have any cysts at the time of oocyte retrieval, but endometriosis was diagnosed by laparoscopy before IVF; 283 cycles (group C) undergoing IVF because of tubal factor

Received February 25, 2004; revised and accepted November 30, 2004.

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without endometriosis, which was previously diagnosed by laparoscopy. Group C acted as the control group. These groups were compared for differences in retrieved number of oocytes, fertilization rate, embryo quality, implantation rate, pregnancy rate, and live birth rate. The institutional review board approved this study.

In our IVF procedure, the overall cancellation rate was 6.5%. The rules for cancellation were: [1] when we could detect a follicle no larger than 16 mm in diameter, even after ovarian stimulation of more than 2 weeks, or [2] when serum estradiol levels remained less than 100 pg/mL, even after ovarian stimulation of more than 2 weeks. The standard ovarian stimulation protocol is a daily bolus administration of human menopausal gonadotropin (hMG) (150–300 IU for 10–21 days) under a short protocol of gonadotropin-releasing hormone agonist (GnRH-a). Oocyte retrieval was performed at approximately 36 hours after human chorionic gonadotropin (hCG) administration via a stainless steel needle (30-cm long, 18 or 19 gauge; Hakko Shoji Co. Ltd., Tokyo, Japan) under transvaginal ultrasound guidance.

At the time of oocyte retrieval, the suspected endometrioma was aspirated with a single puncture. We examined the aspirated material for cytological diagnosis, and no malignancy was evidenced in all cases. In our study, ovarian endometriomas were diagnosed primarily by the appearance of aspirated fluid because the pathologist indicated that the cytological materials were not enough to diagnose whether the cysts were endometriosis or not. If the aspirated fluid of the cyst was chocolate-colored, dense, and mucous, then the cyst was diagnosed as an endometrioma. Alternatively, when the fluid was pale, serous, and not thick, it was from a functional cyst that may have been induced by a previous ovarian hyperstimulation regimen.

The material aspirated from the cyst was kept separate from the retrieved oocytes to avoid contamination of the culture medium. Retrieved oocytes were suspended and inseminated in human tubal fluid (HTF) medium, supplemented with 10% Serum Substitute Supplement (Irvine Scientific, Santa Ana, CA), and cultured under 5% O2, 5% CO2, and 90% N2 at 37°C. Embryos were graded from 1 to 5 (grade 1 being the best quality), according to the symmetry of the blastomeres and the presence or absence of fragmentation under an inverted microscope (27). In this study, we defined embryos of grade 1 or 2 as “good quality.” Transcervical intrauterine ET was performed 48 or 72 hours following oocyte retrieval. Luteal-phase support was provided with intravaginal progesterone (150–300 mg/day).

Pregnancy was diagnosed based on the rising concentration of serum hCG levels, which was tested 14 days after oocyte retrieval. Clinical pregnancy was determined by the presence of a gestational sac by vaginal ultrasound examination.

In group A, the number of retrieved oocytes was analyzed in relation to the volume of an endometrioma and affected laterality.

**Statistical Analysis**

The results were analyzed using one-way analysis of variance (ANOVA) with a post hoc test using Fisher’s Protected Least Significant Difference (PLSD). Statistical significance was set at P<.05. Values are expressed as mean ± SD.

**RESULTS**

The IVF outcomes for the three groups are summarized in Table 1. There were no significant differences in age or BMI among the three groups. Cases were grouped into A, B, or C according to a diagnosis of “presence of endometrioma,” “endometriosis without endometrioma,” or “infertility for tubal factor,” respectively. Thus, group A included all recurrent cases of stage III and IV endometriosis; 50% of group A included recurrent endometriomas in stage III and IV endometriosis, even after laparoscopic treatment; the rest of group A included newly developed endometriomas, which were not found on the previous laparoscopy. Group B included cases of stage III and IV endometriosis without recurrence after laparoscopic treatment; 12.2% and 13.0% of group B were in stage III and IV, respectively. Group B also included cases of mild and minimal endometriosis; 47.5% and 27.3% of group B were in stage I and II endometriosis, respectively.

Significantly fewer oocytes were retrieved from group A (4.40 ± 2.99) and group B (4.48 ± 2.81) than from group C (5.34 ± 2.99). In group A, the mean volume aspirated from the endometrial cyst at oocyte retrieval was 17.9 ± 24.5 mL, ranging from 1–123 mL. Figure 1A depicts the relationship between the volume aspirated from the endometrial cyst and the number of retrieved oocytes. In the case of a unilateral endometrioma, the number of retrieved oocytes from the affected side was plotted against that from the healthy side (Fig. 1B). In 94.5% of the cases, at least one ovum was retrieved from the side of endometriosis, and 58.8% of 246 retrieved oocytes came from the affected side.

No statistical differences were noted among the three groups with regard to fertilization rate, embryo quality, implantation rate, pregnancy rate, and live birth rate (Table 1).

**DISCUSSION**

The general protocol for infertility treatment calls for the treatment of detected endometriosis lesions during diagnostic laparoscopy: We electrocoagulate peritoneal lesions, such as blueberry spots, separate adhesive lesions surrounding the reproductive organs, and remove endometrial cysts in conjunction with other methods, such as aspiration, electrocoagulation of the intraluminal area, and/or alcohol fixation. If the adhesion is too severe to be treated, IVF-ET is immediately indicated. Otherwise, after treatment during diagnostic
laparoscopy, treatments such as hormonal therapy, induction of ovulation, and intrauterine insemination are initiated. If these treatments are unsuccessful, IVF-ET is indicated.

To date, we have experienced acceptable IVF outcomes in patients with endometriosis. However, some authors have reported poor IVF-ET outcomes with endometriosis (9–13). In this study, we retrospectively analyzed our IVF-ET records in an attempt to confirm whether endometriosis has an impact on IVF-ET outcome and whether pregnancy-related outcomes are dependent on the presence of an ovarian endometrioma.

After an ovarian endometrioma is diagnosed by laparoscopy, we typically perform electrosurgery to resect the cyst, as mentioned previously. Therefore, recruiting such cases for elucidation of the adverse effects of an ovarian endometrioma is difficult. However, in this study, endometrial cysts were confirmed by direct aspiration during oocyte retrieval. For comparison, groups B and C were used as control groups. Group B represented endometriosis cases without endometrial cysts. Comparison between groups A and B clearly illustrated the adverse effects of an endometrioma on IVF outcome. In addition, cases in group C were confirmed as being endometriosis-free by previous laparoscopy; these cases acted as an absolute control.

Several confounding variables may interfere with the interpretation of the IVF statistics: the number of times for the same case, the surgical technique used, the delay between the IVF cycle and the surgery, the medical treatment used in between, and the regimens used for the stimulation. In our study, the first IVF cycle was 65.5% of all cases, with no statistical difference in distribution among the groups (62.5%, 64.5%, and 67.1% of group A, B, and C, respectively). We found no difference in the number of retrieved oocytes between the first and subsequent IVF cycles. As for the surgical technique used in group A (n = 50), 16 and 9 cases were after electrocoagulation and cystectomy, respectively. The average delay between the IVF cycle and the surgery was 15.0 ± 13.4 (mean ± SD) months, and there was no statistical difference among the three groups. In the analyzed cases, there were no cases of medical treatment after the surgery.

For the regimens used for the ovarian stimulation, we usually (in 90% of the cases) used the standard protocol as described in MATERIALS AND METHODS, where the total dosage of hMG was 2,730 ± 1,230 (mean ± SD) IU/cycle; there was no statistical difference in the number of cases with the standard protocol or the total dosage of hMG among the three groups. As with the rest of the standard protocols with GnRH-a in this study, protocols without GnRH-a were used, where clomiphene-hMG-hCG, clomiphene-hCG, and natural-hCG were 7, 2, and 1%, respectively. In conjunction with the fact that the analyzed cases were almost evenly distributed in each fiscal year, there was no difference in the method of IVF used among the three groups. In other words, the analyzed cases conducted their IVF programs with similar doses of medication under similar protocols.

Our data presented in Table 1 show a relatively low number of oocytes retrieved and relatively low pregnancy

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<td><strong>IVF outcomes for the groups.</strong></td>
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*Note: Values are mean ± SD. IVF = in vitro fertilization; BMI = body mass index; ET = embryo transfer.*  
*a Embryos were graded from 1 to 5 according to the classification of Veeks and defined as “good quality” when the embryo was 1 or 2 grade; 80 cycles had ovarian endometriomas that were aspirated and identified as “chocolate” cyst(s) at the time of oocyte retrieval (group A); 248 cycles did not have cysts at the time of oocyte retrieval, while endometriosis was diagnosed by laparoscopy or laparotomy before IVF (group B); 283 cycles had tubal factor without endometriosis, as diagnosed by previous laparoscopy (group C).*
rates compared with other reports. It might be difficult to generalize our data and simply compare ours with those of other reports. We could not clearly identify the exact reason for the low number of oocytes retrieved. However, as analyzed in Table 1, the age of patients was approximately 35, which is relatively higher than that in other similar hospitals in Japan. For our reproductive unit in Tokai University Hospital, other hospitals mentioned above were the main source for patients, who were introduced to us after some treatment there for their infertility. Thus, the patients analyzed in this study were not always young or new cases; these factors might contribute to the low number of retrieved oocytes.

FIGURE 1

Number of oocytes retrieved against endometrioma volume. (A) The number of retrieved oocytes from the ovary affected by the endometrioma is shown against the endometrial cyst volume. Values are mean ± SEM. (B) In the case of a unilateral endometrioma, the number of retrieved oocytes is plotted for each side. In 94.5% of the cases, at least one ovum was retrieved from the side of endometriosis, and 58.8% of 246 retrieved oocytes came from the affected side.

rates when comparing patients with and without endometriosis (14–20). Alternatively, adverse effects of endometriosis on oocyte and embryo quality, as well as on implantation rates, have been reported by several investigators (9–13). Barnhart et al. recently performed a meta-analysis on the effects of endometriosis on IVF; they found that the “pregnancy rate is almost one-half that of women with other indications for IVF” and that “the effect of endometriosis is not exclusively on the receptivity of the endometrium but also on the development of the oocyte and embryo” (24). In our study, significantly fewer oocytes were retrieved from the endometriosis groups (group A and group B) than from the nonendometriosis group (group C). Although the fertilization rate was slightly, but not significantly, lower in the endometriosis groups (group A and group B), the depressive effects of endometriosis on oocyte development are consistent with the meta-analysis.

Our data demonstrated that the number of retrieved oocytes as well as the number of transferred embryos is depressed in the case of endometriosis, but, interestingly, the presence of an ovarian endometrioma did not necessarily enhance such adverse effects. However, the similar outcomes seen in groups A and B might be attributable to the fact that all our cases underwent laparoscopic treatment. In other words, the original adverse effects of endometriosis might be modified or reduced by laparoscopic treatment, and thus our data may support the efficacy of laparoscopic procedures because IVF (28–32). We may therefore conclude that following laparoscopic treatment, an ovarian endometrioma has no additional negative effects on oocyte development.

In group A, oocytes were retrieved from the side of the endometrioma despite the large volume of the cysts (Fig. 1A). Excluding cases in which both sides were affected, the number of oocytes retrieved from the ultrasonographically healthy side was similar to that from the side of the endometrioma (Fig. 1B). These data confirm that the endometrioma does not suppress oocyte maturation and retrieval, even on the affected side.

Our results suggest that endometriosis does not affect embryo quality and the related parameters of pregnancy, as indicated by the fertilization rate, embryo quality, implantation rate, pregnancy rate, and live birth rate, independent of an ovarian endometrioma. However, our results also demonstrate that endometriosis, even after diagnostic laparoscopy with treatment when necessary, clearly affects the number of oocytes, irrespective of the presence of an ovarian endometrioma.

Acknowledgments: The authors thank Ms. Yoshimi Fujita and Ms. Kei Mori from the Teaching and Research Supporting Center of Tokai University School of Medicine for their assistance in editing this manuscript.

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