The impact of rescue in vitro fertilization converted from high-response gonadotropin intrauterine insemination cycles in terms of implantation and pregnancy rates as compared with matched controls

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Objective: To determine whether conversion of high-response gonadotropin/intrauterine insemination (IUI) cycles to "rescue" in vitro fertilization (IVF) yields a higher implantation and pregnancy rate as found in matched IVF controls.
Design: A prospective study with a retrospective controlled section.
Setting: Baskent University Department of Obstetrics and Gynecology.
Patient(s): Thirty-two patients switched from high response gonadotropin/IUI cycles to "rescue" IVF, 202 women with polycystic ovaries (PCO), and 452 women without PCO from the IVF database.
Intervention(s): High-response gonadotropin/IUI cycles were converted to IVF to avoid cycle cancellation and high-order multiple pregnancies.
Main Outcome Measure(s): Clinical parameters and characteristics of controlled ovarian hyperstimulation and intracytoplasmic sperm injection results.
Result(s): The pregnancy rate was 78.1% in the rescue IVF group: 66.3% and 58.2% in the PCO and non-PCO groups, respectively. Clinical pregnancy rates and ongoing pregnancy rates also tended to be higher in the rescue IVF group but the difference was not statistically significant. The main difference between the groups was in the implantation rate: 37.5% in the rescue IVF group, which was greater than that of the PCO and non-PCO groups (27.58% and 24.46%, respectively).
Conclusion(s): Our study demonstrates that conversion of gonadotropin IUI cycles in patients with excessive follicles to IVF is a safe, effective strategy. Implantation rates are higher than those in hyper-responder and normal responder IVF patients. (Fertil Steril® 2009;92:137–42. ©2009 by American Society for Reproductive Medicine.)

Key Words: Rescue IVF, implantation, GnRH antagonist, IUI

In unexplained and mild male factor subfertility, stimulated or unstimulated intrauterine insemination (IUI) is generally indicated as the first-line treatment. Because the success rate of IUI is low, many couples for whom IUI has been unsuccessful will subsequently require in vitro fertilization (IVF) treatment. Whether IVF should be the primary treatment for these patients is still a subject of debate (1–2).

It has been suggested that ovarian stimulation in IUI cycles might improve the monthly pregnancy rate by simply increasing the number of oocytes available for fertilization and implantation (3). Although this treatment modality may increase pregnancy rates, supernumerary follicles in high responders expose the women to the risk of multiple pregnancy and ovarian hyperstimulation syndrome (OHSS), especially in gonadotropin cycles. Accordingly, monitoring the cycle and adjustments of the dose of gonadotropins and cancellation of the cycle when necessary are important in this treatment modality. High estradiol (E_2) levels and the number of follicles have generally been used as indications for canceling a cycle (4).

After the marketing of gonadotropin-releasing hormone (GnRH) antagonists, it became practical and possibly safer to convert stimulated IUI cycles to IVF instead of canceling cycles. It has been demonstrated that the probability of live birth after ovarian stimulation for IVF does not depend on the type of analogue used for pituitary suppression (5). Although conversion of IUI to IVF eliminates the canceling of cycles, which has been a frustrating problem for both the patient and clinician, literature on the effectiveness of this strategy has been scarce (6–8). In our prospective study with a retrospective controlled part, we examined whether these patients have as high a pregnancy rate as matched IVF controls. For this purpose, we divided the control group into hyper-responders and normal responders, and we compared the cycle characteristics and IVF outcomes accordingly.

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MATERIAL AND METHODS

This study was conducted from February 2005 to July 2007 in Baskent University Department of Gynecology and Obstetrics, Division of Reproductive and Endocrinology Unit. The study was approved by the Ethical Committee of Baskent University. A total of 32 out of 2401 cycles (1.33%) with an excessive numbers of follicles during gonadotropin IUI cycles that were converted to IVF ("rescue" IVF) were included in the study. Indications for stimulated IUI were unexplained or male factor infertility, which also included women with polycystic ovary syndrome (PCOS). In our department, anovulatory women with PCOS are not routinely scheduled for IUI cycles unless it occurs along with male factor infertility. There were six women diagnosed with hypogonadotropic hypogonadism with male factor infertility. Unexplained infertility was defined as a normal hysterosalpingography, normal midluteal phase progesterone levels ($\geq$3 ng/mL), and a normal seminal fluid analysis (by World Health Organization criteria) with a failure to conceive spontaneously after at least 12 months of unprotected intercourse.

Male factor subfertility for IUI was defined as total progressive motile sperm count (TPMSC) greater than 5 million. According to the Turkish Ministry of Health's in vitro fertilization and intracytoplasmic sperm injection (IVF/ICSI) program, patients whose partners have a total progressive motile sperm count lower than 5 million are eligible to undergo IVF/ICSI cycles.

Women with secondary amenorrhea who had lower follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels ($<$1.5 nmol/L) were diagnosed with hypogonadotropic hypogonadism.

The women in the case-matched group were selected from the retrospective database of our IVF unit. Only the patients within their first IVF cycle, conducted by our unit, were included in the study. The women older than 35 years and those with day-3 FSH levels greater than 10 mIU/L and fewer than six oocytes retrieved during oocyte pickup were excluded from the study.

The standard stimulation protocol for gonadotropin IUI cycles was as follows. Patients underwent a baseline ultrasound on cycle day 2 or 3. If there were no cysts $\geq$2 cm, they began to take single doses of 75 or 150 IU of FSH starting on the evening of cycle day 3. Ultrasound monitoring was performed on day 6 of stimulation. Blood tests were performed as indicated. (We used E_2 monitoring according to number of follicles greater than 10 mm. In cycles with more than two dominant follicles, serial E_2, LH, and progesterone measurements were performed.) The goal was to obtain two or three follicle of 16 to 18 mm at the time of human chorionic gonadotropin (hCG) administration.

According to our clinical approach, high response was defined as $\geq$4 follicles measuring $\geq$14 mm in diameter during stimulation for IUI. Those patients whose parameters were high ($E_2 \geq 1500$ pg/mL or $\geq$4 mature follicles) were offered cycle cancellation or conversion to IVF as options. Nearly all patients who were offered this option proceeded with conversion to IVF.

On the day of hCG administration, 10,000 IU of hCG was scheduled, and oocyte pickup was carried out 35 to 36 hours later. If a delay of 1 to 2 days was planned, a GnRH antagonist (Orgalutran; Organon, Istanbul, Turkey) was added to the stimulation regimen. When at least three follicles had reached 17 mm, hCG administration was scheduled as previously described.

In IVF patients, ovarian down-regulation was initiated with 1 mg daily of leuprolide acetate (Lucrin; Abbott France SA, Rungis, France), beginning on the 21st day of the preceding menstruation. After ovarian suppression had been achieved, the dose was reduced to 0.5 mg until the day of hCG administration. If there were no cysts $\geq$2 cm and the E_2 concentration was $<$50 pg/mL, gonadotropin stimulation with 150–225 IU of gonadotropin was performed, with E_2 monitoring commencing on the morning of stimulation day 5. Ultrasound and blood E_2 monitoring continued until hCG administration criteria were met, with at least three follicles having a maximum diameter of $>$17 mm.

Transvaginal ultrasound-guided oocyte retrieval was performed 35 to 36 hours after the hCG injection. Oocyte pickup was performed with a 17-gauge needle for oocyte retrieval under sedation with propofol (propofol 1%; Fresenius Kabi AG, Bad Homburg, Germany). The oocyte–corona complexes were denuded, and ICSI was performed after 2 hours of incubation; embryos were transferred on day 3. Our clinical policy is to use ICSI routinely in all patients. The embryo transfer policy depends on the number and quality of the embryos developed. The transfer protocol was individualized for poor-grade embryos up to four embryos. All patients had luteal support with 90 mg of progesterone intravaginally (Crinone 8% gel; Serono, Randolph, MA) daily after embryo transfer. Clinical pregnancy was defined as the presence of at least one gestational sac with detectable fetal cardiac activity by transvaginal ultrasonography. Hospitalized OHSS was defined as hematocrit levels over 45 and abdominal discomfort together with moderate ascites and/or thrombocytosis, and leucocytosis.

The patients diagnosed as poor responders (fewer than six oocytes at pickup) and potential poor responders (FSH $>$10 mIU/L and antral follicle count $<$6) were excluded from the study. The control group was divided into two according to sonographic criteria: women with polycystic ovaries (PCO) and women without PCO. At least one ovary with $>$12 antral follicles was used to diagnose PCO on the ultrasonography.

The data of group 1, rescue IVF (n = 32), were compared with those of the two subgroups within the IVF group: group 2, PCO (n = 202), and group 3, and non-PCO (n = 452). Baseline parameters compared among the study groups included the following: age, body mass index, and duration of infertility; serum levels of FHS, LH, and E_2 on day 3 of