In vitro fertilization and embryo transfer in seminatural cycles for patients with ovarian aging

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Objective: To investigate whether seminatural cycle is a reasonable management for ovarian aging patients.
Design: Prospective study.
Setting: ART Unit, Clamart, France.
Patient(s): Seventy-five women, 158 cycles.
Intervention(s): Infertile women who presented with ovarian aging (defined as low ovarian reserve and characterized by cycle day 3 high FSH, high E_2, and/or low inhibin B and/or previous cycle cancellations due to poor ovarian response to COH) were studied. Patients were offered up to three cycles. Treatment was scheduled as follows. From cycle day 8 onward the selection of the dominant follicle was monitored by ultrasound and hormonal measurements. When the dominant follicle appeared, patients received GnRH antagonist and, thereafter, hMG to support further follicular development.
Main Outcome Measure(s): Implantation rate and clinical pregnancy.
Result(s): Twenty-eight of 158 cycles were cancelled (17.7%). Oocyte pickups were performed in 119 (75.3%) cycles, 91 (57.6%) mature oocytes were retrieved, and 67 (42.4%) embryos transferred. Nineteen clinical pregnancies were obtained; the cumulative pregnancy rate per patient, after 3 cycles, was 35.2%.
Conclusion(s): Use of a seminatural cycle is a reasonable management for patients with ovarian aging who have ovulatory menstrual cycles. It achieves a high implantation rate (28.3%). (Fertil Steril® 2005;84:875–80. ©2005 by American Society for Reproductive Medicine.)

Key Words: In vitro fertilization, poor ovarian response, low ovarian reserve, ovarian aging, seminatural cycle

Initial attempts at in vitro fertilization were done on natural cycles (1). This approach was quickly replaced by controlled ovarian hyperstimulation (COH), which proved to be more effective. Unfortunately, poor response to COH due to ovarian status defects is not rare. It represents from 9% to 24% cancellation rate in IVF-ET cycles (2).

However, the lack of a uniform definition of this group of patients makes it difficult to compare treatment outcomes reported in different studies (3). Poor responders can be divided in two main groups (4). The first group includes those with low ovarian reserve, identified on cycle day 3 with presence of high FSH, high E_2, and/or low inhibin B (5–8). The second group includes those with a poor response to previous ovarian stimulation, despite evidence of normal ovarian reserve. Nonetheless, the definition of "poor response to ovarian stimulation" remains controversial. It has been defined as small number of follicles after adequate ovarian stimulation, with a cut-off point varying from 2 to 4 follicles (9–12), and/or low peak E_2 levels (500–600 pg/mL) (13, 14). The presence of this second group confirms the limited value of endocrine markers of ovarian reserve reported above to identify the poor responders. For this reason, some authors are investigating other predictors of ovarian reserve, such as antimüllerian hormone (15, 16) and total number of antral follicles on cycle day 3 (17–20).

Because of the high incidence of cancellation rate, due to partial or complete lack of ovarian response to COH, of patients with ovarian aging, some investigators have suggested the use of natural cycle IVF-ET instead (21, 22).

To optimize the effectiveness of natural cycle we recently proposed to control the dominant follicle to prevent spontaneous rupture by the administration of a GnRH antagonist together with mild gonadotropic support (23). We decided to examine the usefulness of IVF-ET using this form of seminatural cycle for this heterogeneous group with ovarian aging.

MATERIALS AND METHODS

Subjects

Between January 2001 and January 2004, in the Unit of Reproductive Medicine, Antoine Béclère Hospital, Clamart, France, we prospectively studied 75 infertile women, 25–37 years of age, who had a poor prognosis with COH.

Women who had either low ovarian reserve (LR) or previous cancellation cycles due to poor ovarian response (PR) to COH were included in this study. The LR group was

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characterized on cycle day 3 by FSH ≥10 UI/L, E_2 ≥60 pg/mL, and/or inhibin B <45 pg/mL, and the PR group was characterized by <5 follicles despite adequate ovarian stimulation with mean daily gonadotropin dose of 250 IU and evidence normal ovarian reserve.

The inclusion criteria were as follows: ovulatory menstrual cycles occurring every 25–35 days, age <38 years, adequate visualization of both ovaries in transvaginal ultrasound scans, and any cause of infertility, male or female, amenable to IVF treatment. The cancellation criteria were: inadequate follicular growth (defined as the absence of increase in follicular diameter after two ultrasound scans) and the evidence of a premature ovulation confirmed by elevation of LH (value three times the basal LH value determined on day 2 of the menstrual cycle). Patients were offered up to 3 cycles of treatment. The causes of infertility in the study group were male factor 55.7%, tubal factor 17.5%, idiopathic 15.8%, and endometriosis 10.9%.

An informed consent was obtained from all women, and this study received the approval of our internal Institutional Review Board.

Study Protocol

On day 3 of a spontaneous cycle, a blood sample was drawn to determine the baseline levels of E_2, FSH, LH, and progesterone. A baseline ultrasound scan was also done the same day to identify the possible presence of ovarian cysts. The second hormonal and ultrasound control took place on cycle day 8. Subsequent controls were performed every second day until the day of hCG administration, when the follicular diameter was predicted to be ≥16 mm.

The dominant follicle was defined by serum E_2 levels >100 pg/mL and by a diameter >12 mm measured by ultrasound scan (24). Once the follicular dominance was established, GnRH antagonist was administered to prevent ovulation and to complete follicular maturation before oocyte pickup (OPU). The GnRH antagonist was used in one of two ways: either a single SC dose of 3 mg cetrorelix acetate (Cetrotide; Serono, Boulogne, France) or a daily SC injection of 0.25 mg cetrorelix until the day of hCG (Gonadotropin Chorionique "Endo"; Organon, Saint-Denis, France) administration. The choice between the two forms of antagonist administration was made by the individual physician. On the same day as the GnRH antagonist, 150 IU hMG (IM) (Menopur; Ferring, Gentilly, France) was started and given daily until the IM administration of 5,000 IU of hCG, when the follicular diameter reached ≥16 mm and the serum E_2 level was >150 pg/mL (25).

Oocyte pickup was performed 36 h after of hCG administration. The oocyte retrieval was performed without anesthesia (26). The follicle was aspirated with a syringe under vaginal ultrasound guidance and a flushing with 3 mL of physiological saline solution was done (Tyrode; Eurobio, Courtaboeuf, France). ICSI was used only in the presence of male factor (<500,000 progressive spermatozoons).

For all transfers we systematically associated an assisted hatching. The zona pellucida was refined without rupture (27) by using a heat source without contact (Laser Fertilase MTG; Medical Technology [MTG], Altdorf, Germany). All embryo transfers were performed two days after oocyte retrieval using a classic Frydman catheter (CCD, Paris, France). The luteal phase was supported with 600 mg micronized progesterone (Estima Gé; Effik, Bièvres, France) administered daily (200 mg in the morning and 400 mg in the evening) by vaginal route, starting on the day of ET until the 12th day after ET, when a pregnancy test was done. When the pregnancy test was positive, progesterone administration was continued for nine weeks. The clinical pregnancy was confirmed by ultrasonographic evidence of a gestational sac five weeks after ET.

Statistics

The results are expressed as means ± SE. We assessed the differences between the groups with Fisher's exact test. The statistical assessement used Stat View software (Abacus Concepts, Berkeley, CA). $P<.05$ was considered statistically significant.

RESULTS

The population included in this study was not homogeneous. The patients were divided into two groups, LR and PR, according to the presence or not of low ovarian reserve (on cycle day 3 serum FSH ≥10 UI/L, E_2 ≥60 pg/mL, and/or inhibin B <45 pg/mL). Their characteristics are presented in Table 1.

A total of 158 cycles of IVF using seminatural cycles was started. The results for the LR and PR groups are given in Table 2. The two groups were similar with regard to all the parameters listed in Table 2. However, the LR group trended to cancel more cycles than the PR group (20.8% vs. 14.8%). In contrast, there was a lower failed oocyte recovery rate in the LR group than in the PR group, but this was not statistically significant.

Including both groups, a total of 28 cycles (14.3% LR vs. 21% PR) had to be cancelled. In 10 of these cycles an LH surge was observed (6 cycles LR and 4 cycles PR). The other 18 cycles were cancelled owing to inadequate follicular growth (10 cycles LR and 8 cycles PR). In 11 cycles, hCG was administered but OPU was not undertaken owing to absence of a dominant follicle at ultrasound that preceded OPU. OPU was performed in 119 cycles (75.3%), in 25 of which an oocyte was not recovered (21%). There was no statistically significant difference in serum E_2 levels ($P=.51$), follicular diameter ($P=.11$), and the day of hCG administration ($P=.67$) between the cycles in which an oocyte was recovered (239.1 ± 107.0 pg/mL, 17.4 ± 1.2 mm, and 12.4 ± 3.0 days, respectively) or was not recovered