ASSISTED REPRODUCTIVE TECHNOLOGY

Controlled ovarian hyperstimulation: Does prolonged stimulation justify cancellation of in vitro fertilization cycles?

ITAT BAR-HAVA, RAKEFET YOELI, VERED YULZARI-ROLL, JACOB ASHKENAZI, JOSEF SHALEV, & RAOUL ORVIETO

Department of Obstetrics and Gynecology, Rabin Medical Center (Golda Campus), Petah Tikva, Israel, and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

Abstract

Background. In daily practice, assisted reproductive technology (ART) cycles are often cancelled under the assumption that a prolonged stimulation period lowers the likelihood of an appropriate ovarian response. The aim of the present study was to determine whether a prolonged cycle has an adverse effect on achievement of pregnancy.

Methods. The study sample included consecutive women enrolled in our ART unit between 1999 and 2001 who were treated with the mid-luteal long suppressive gonadotropin-releasing hormone protocol. Data were collected prospectively on a computerized database and evaluated at the end of the study. Prolonged stimulation was defined as a stimulation period of more than two standard deviations (SD) above the mean. Outcome was compared between patients who required prolonged stimulation and those who did not.

Results. A total of 1015 consecutive in vitro fertilization (IVF) cycles were performed with the mid-luteal long suppressive protocol during the study period. Thirty-four women required prolonged stimulation. No difference in clinical pregnancy rate was detected between women who received prolonged stimulation and those who did not (9/34, 26.5% vs. 291/981, 29.7%), despite the significantly fewer oocytes retrieved in the prolonged-stimulation group (7.1 ± 5.2 and 11.6 ± 6.7 (mean ± SD), respectively, \( p < 0.001 \)).

Conclusion. The likelihood of achieving pregnancy is not influenced by the length of stimulation. We recommend that IVF cycles should not be discontinued on the grounds of prolonged stimulation alone.

Keywords: Long/prolonged stimulation, cycle outcome, in vitro fertilization

Introduction

Controlled ovarian hyperstimulation (COH) is one of the main stages of assisted reproductive technology (ART) treatments. The average length of stimulation utilizing the long suppressive gonadotropin-releasing hormone agonist (GnRH-a) protocol is 10–12 days [1]. However, in daily clinical practice, women often need longer stimulation to achieve an appropriate ovarian response and to set the conditions required for human chorionic gonadotropin (hCG) administration for final oocyte maturation. It remains unclear if such prolonged stimulation is associated with a lower likelihood to conceive. The aim of the present retrospective observational study was to investigate the possible effect of prolonged ovarian stimulation on cycle outcome.

Material and methods

The study population comprised consecutive women enrolled in our ART unit between 1999 and 2001 who were treated with the mid-luteal long daily GnRH-a suppressive protocol. According to our unit's policy, the long suppressive protocol was provided only to patients with day 3 follicle-stimulating hormone (FSH) < 10 IU/L. For down-regulation, nafarelin (Synarel®; Teva Group, Netanya, Israel) or buserelin (Suprefact®; Aventis Pharma, Netanya, Israel) or triptorelin (Decapeptyl®; Ferring, Lapidot, Israel) was used, as decided by the physician. Criteria for downregulation were peripheral serum estradiol < 180 nmol/l, progesterone < 3 nmol/l, endometrial thickness < 5 mm, and absence of an ovarian cyst of > 15 mm on transvaginal ultrasound. Gonadotropins (either human...
menopausal gonadotropin, Pergonal®; Serono, Herzlia, Israel or FSH, Metrodin®; Teva Group) were then administered in variable doses, depending on the individual patient's previous response, and further adjusted according to serum estradiol levels and vaginal ultrasound measurements of follicular diameter, obtained every two or three days. If this was the first stimulation cycle, an initial dosage of 225 IU gonadotropins was used. Prolonged stimulation was defined as a stimulation period of more than two standard deviations (SD) above the mean. Women who did not respond at all, i.e., showed no ovarian response after 10 days of gonadotropin stimulation, were excluded from the study. The 10-day period was chosen because this is the average length of stimulation in our program (data not provided). A response was defined as the observation of at least one follicle measuring 14 mm in diameter on transvaginal scan within this 10-day period.

Our unit's ultrasound and hormonal surveillance methods, timing of hCG administration, and oocyte retrieval and sperm processing techniques are detailed elsewhere [2]. In brief, 10 000 IU hCG (Chorigon®; Teva-pharma, Natanya, Israel) is administered for final maturation of oocytes when at least one follicle of >17 mm is identified by transvaginal scan, combined with appropriate peripheral serum estradiol levels (around 600 pmol/l per oocyte). Oocyte collection is carried out 34–36 h later. Oocytes are fertilized conventionally or by intracytoplasmic sperm injection, according to the criteria of Bar-Hava and colleagues [3]. Embryo quality is graded before the transfer. The total number of embryos transferred is based on the individual woman's age and cycle number. For luteal phase support, patients receive either 50 mg progesterone intramuscularly (Gestone®; Ferring) daily or 600 mg micronized progesterone soft gel vaginal capsules (Utrogestan®; Besins Iscovesco, Petah Tikva, Israel) in three divided doses daily. Clinical pregnancy is defined as the presence of a gestational sac on transvaginal ultrasonography in association with rising β-hCG levels.

In the present study, the cycle outcome of the patients who required prolonged stimulation (study group) was compared with that of patients with a shorter stimulation period (control group). All pertinent clinical data were collected prospectively on a computerized database and evaluated at the end of the study. The following variables were assessed: patient age, duration of follicular stimulation, number of oocytes retrieved, fertilization rates, number of embryos transferred and pregnancy rate. Only clinical pregnancies were considered for analysis.

For statistical analysis, SPSS 11.0 for Windows software (SPSS Inc., Chicago, IL, USA), Student's t test and the $\chi^2$ test were used as appropriate. A p value of less than 0.05 was considered significant.

Results

A total of 1015 consecutive in vitro fertilization (IVF) cycles utilizing the mid-luteal long daily GnRH-a suppressive protocol were performed from 1999 to 2001. Patient age ranged from 21 to 45 years. Thirty-four patients required prolonged stimulation. Average length of the stimulation period was 16.9 days in the study group and 9.8 days in the control group ($p < 0.0001$). While the prevalence of polycystic ovary syndrome (PCOS) was significantly higher in the control than in the study group (26.5% vs. 3.9%, $p < 0.01$), no between-group differences were observed in the prevalences of mechanical or male infertility.

No significant differences between the study and control groups were noted in mean patient age (34.3 ± 4.6 vs. 32.9 ± 5.4 years), mean fertilization rate (per designated oocytes) (52% vs. 50%) and mean number of embryos transferred (1.9 ± 1.5 vs. 2.2 ± 1.7) (mean ± SD).

Furthermore, the difference in implantation and pregnancy rates between the women who needed prolonged stimulation (4.5% and 26.5%, respectively) and those who did not (3.2% and 29.7%, respectively) was not statistically significant. This finding held true despite the significantly fewer oocytes retrieved in the patients who needed prolonged stimulation (7.1 ± 5.2 vs. 11.6 ± 6.7, $p < 0.001$) (mean ± SD).

Discussion

Although the average length of the typical ovarian stimulation period in COH with the long protocol is 10–12 days [1], many women require longer stimulation to achieve an ovarian response. We sought to determine if prolonged stimulation reduces oocyte quality or interferes with endometrial function, thereby lowering the likelihood of pregnancy and warranting cancellation of the cycle. Our study demonstrated that prolonged (>95th percentile) stimulation, especially in PCOS patients, did not lower clinical pregnancy rates, even though the women who required prolonged stimulation had a lower response, as evidenced by the significantly lower number of oocytes retrieved in that group (7.1 ± 5.2 vs. 11.6 ± 6.7, $p < 0.001$). This finding may suggest that the time it takes for the ovaries to reach an appropriate state to receive hCG is irrelevant to the outcome of the cycle. Furthermore, we speculate that the need for prolonged stimulation is associated with the patients' underlying infertility, and that the infertility is overcome once a high-quality embryo is placed in the uterine cavity, regardless of the length of time its endometrial lining was stimulated until that point. It should be remembered that these results apply when an ovarian response is observed (defined in our study as at least one follicle measuring 14 mm in diameter) at some
point during stimulation (defined here as within 10 days). If these criteria are met, our data suggest that the stimulation be continued.

Interestingly, there was no difference in mean patient age between the women who needed prolonged ovarian stimulation and those who did not. Beloosesky and colleagues [4] studied the correlation between stimulation duration of IVF cycles, with and without GnRH-a, and cycle outcome. Only cycles that reached the stage of oocyte retrieval were included. Similar to our finding, in the long protocol subgroup, there was no correlation between stimulation duration and cycle outcome. However, it should be emphasized that these authors did not focus specifically on the patients who needed prolonged stimulation. They suggested that the GnRH-a-induced ovarian quiescence in the long protocol may neutralize the ovarian and pituitary factors that govern the age-related changes in follicular phase dynamics, particularly the shortened natural follicular phase in the fourth and fifth decades of life (as seen in our low-responder group as well). Nevertheless, it should be noted that others reported contrary results of a negative correlation between patient age and response rate [5]. Further support for our findings may be derived from studies demonstrating that although the various stimulation protocols differ in length, they are similar in other parameters, such as number of oocytes and fertilization and pregnancy rates [6,7].

The main limitation of our study is that the sample size (34 in the study group) may have been too small statistically. In order to demonstrate a difference of 5% in pregnancy rates at a power of 80% and a of 5% using the uncorrected \( \chi^2 \) test, 548 study subjects would be needed. In order to detect a 10% difference, 119 study subjects would be needed. With the sample size in the present study, we were able to demonstrate a difference of more than 16%—i.e., 26% in the control group and 9% in the prolonged stimulation study group. Nevertheless, the 26.5% pregnancy rate justifies completion of the cycle in women who need prolonged stimulation.

In summary, this observational study demonstrates that the length of stimulation in the long protocol apparently does not affect the likelihood of achieving pregnancy, as evidenced by the similar clinical pregnancy rates in the patients with and without prolonged stimulation (26.5% and 29.7%, respectively). Despite the small sample size, the 26.5% clinical pregnancy rate justifies continuation of the cycle. We recommend that IVF cycles associated with prolonged stimulation should not be cancelled on these grounds alone.

References