FERTILITY AND STERILITY®
VOL. 74, NO. 1, JULY 2000

Published by Elsevier Science Inc.
Printed on acid-free paper in U.S.A.

Ovarian stimulation in in vitro fertilization with or without the "long" gonadotropin-releasing hormone agonist protocol: effect on cycle duration and outcome

Ron Beloosesky, M.D., Shahar Kol, M.D., Abraham Lightman, M.D., and Joseph Itskovitz-Eldor, M.D., D.Sc.

Department of Obstetrics and Gynecology, Rambam Medical Center, and Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel

Objective: To study the correlation between stimulation duration of IVF cycles, with and without GnRH agonist (GnRH-a), and cycle outcome.

Design: Retrospective analysis of data.

Setting: University-affiliated IVF clinic.

Patient(s): 998 IVF cycles in which long GnRH-a protocol was used, and 155 cycles with hMG only.

Intervention(s): IVF cycles.

Main Outcome Measure(s): Cycle outcome in number of oocytes and embryos, and pregnancy rate.

Result(s): The mean stimulation duration (±SD) was 9.6 ± 1.7 and 6.7 ± 1.0 for the GnRH-a and the hMG-only cycles, respectively ($P<0.01$). In the GnRH-a group, no statistically significant correlation between cycle duration and pregnancy rate was found. Interestingly, the patients treated for 9 days had the highest number of oocytes retrieved and the highest pregnancy rate. Stimulation duration was not affected by age in either protocol. GnRH-a cycles yielded a significantly higher number of oocytes and embryos compared to cycles without GnRH-a. The pregnancy rate was similar in both groups.

Conclusion(s): Stimulation duration in the long GnRH-a protocol group was significantly longer than in the hMG-only group. Stimulation duration was not affected by age. No statistically significant correlation was found between stimulation duration and cycle outcome in the long protocol group. (Fertil Steril® 2000;74: 166–8. ©2000 by American Society for Reproductive Medicine.)

Key Words: GnRH agonist, long protocol, controlled ovarian stimulation, IVF, stimulation duration

In the last decade, GnRH agonist (GnRH-a) "long protocols" have become routine in most IVF centers (1). In these protocols, induction of ovulation with hMG follows GnRH-a–induced pituitary suppression. The main reason for the use of GnRH-a in IVF is the complete suppression of the endogenous LH surge, thus reducing the cancellation rate due to premature luteinization. An improvement in pregnancy rates and fecundability without an associated increase in spontaneous abortion rates was noted. However, the time required for follicular growth and development and its effect on cycle outcome was not established.

GnRH antagonists are used in protocols that are based on starting ovarian stimulation in the early follicular phase; the antagonists are introduced when a spontaneous LH rise becomes imminent (2). GnRH antagonist–based controlled ovarian hyperstimulation protocols have renewed our interest in the dynamics of follicular recruitment, growth, and maturation, without prior pituitary down-regulation. Textbooks cite a rather general timetable, pointing to pregnancy usually being achieved with the administration of hMG for 7–12 days (3). Recently, a mean stimulation duration of 6 days was reported for protocols that used only hMG (or recombinant FSH) (4).

In our current study, we have determined the stimulation length with or without "long" GnRH-a, examined the correlation between the

Received October 19, 1999; revised and accepted January 24, 2000.

Reprint requests: Joseph Itskovitz-Eldor, M.D., Department of Obstetrics and Gynecology, Rambam Medical Center, POB 9602, Haifa, Israel 31096 (FAX: 972-4-8542503).

0015-0282/00/$20.00
PII S0015-0282(00)00574-4

number of stimulation days and the cycle outcome, and assessed whether the number of stimulation days correlates with the patient's age.

MATERIALS AND METHODS

Patients

During the years 1994 to 1996 we analyzed 998 consecutive cycles of IVF that used a GnRH-a long protocol. Only cycles that reached the stage of oocyte retrieval were included. These cycles were compared to 155 cycles in which the treatment did not use a GnRH-a, conducted between 1994–1996. These patients had been allocated randomly to treatment with one of two protocols: controlled ovarian hyperstimulation with or without long GnRH-a.

Stimulation Protocols

GnRH Agonist–based Protocol

Triptorelin (Decapeptyl CR, 3.75 mg; Ferring, Malmo, Sweden) was administered intramuscularly during the midluteal phase. In anovulatory patients, triptorelin was administered on day 1 of spontaneous or induced withdrawal bleeding. E_2 levels of less than 150 pmol/L and P levels of less than 3 nmol/L confirmed the pituitary down-regulation 2 weeks later.

Stimulation was initiated during the first 2 days with urinary FSH (Metrodin, Teva, Petach-Tikva, Israel) and hMG (Pergonal, Teva, or Humegon, Organon, Oss, the Netherlands). The rest of the stimulation was done with hMG alone.

GnRH Agonist–free Protocol

Ovarian stimulation was initiated on day 3 of the cycle, after ascertaining that there was an adequate early follicular phase hormonal profile. During the first 2 days of stimulation, both urinary FSH and hMG were used. From stimulation day 3 onward, hMG was used exclusively.

Cycle Monitoring

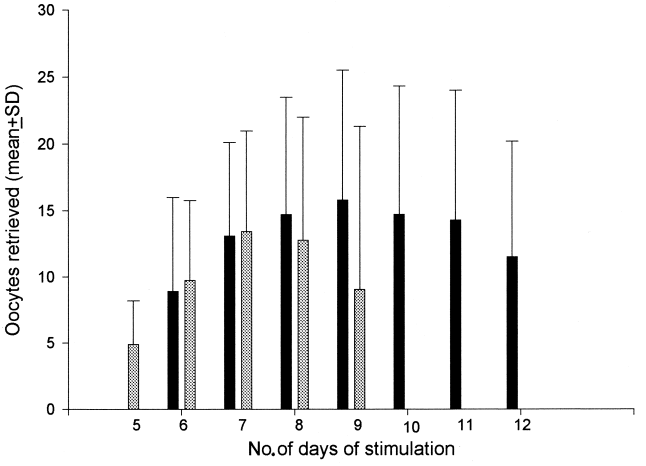
Transvaginal sonography every 2–3 days (or as required) together with serum E_2 levels were used for cycle monitoring. For hMG-only cycles, P and LH were also monitored. Human chronic gonadotrophin (5,000–10,000 IU, depending on the individual patient's response; hCG; Chorigon, Teva) was given when the leading follicles achieved a diameter of >16 mm; a transvaginal ultrasound–guided oocyte retrieval was scheduled 35 hours later. Intracytoplasmic sperm injection was done in male infertility cases. Embryos were transferred 2–3 days after the oocyte retrieval. Luteal phase support was given either by hCG (three doses of 2500 IU) or by daily intramuscular injection of P in oil (100 mg).

Clinical Pregnancy Confirmation

A pregnancy test was administered 12 days after the embryo transfer. If the test was positive, a transvaginal ultrasound study was performed 2 weeks later to confirm a clinical pregnancy.

FIGURE 1

Mean number of oocytes (±SD) retrieved according to number of stimulation days in two protocols. ■ = Long GnRH agonist (n = 998); ▨ = hMG only (n = 155).



Beloosesky. Duration of ovarian stimulation. Fertil Steril 2000.

Statistical Analysis of Data

The mean and standard deviation for the number of oocytes that had been retrieved and embryos obtained were calculated. Chi-square and Student's *t*-test analyses were used to determine the statistical significance.

RESULTS

Stimulation Length

Both groups (treated with or without GnRH-a) were similar in mean age (34.8 and 32.8 years, respectively) and distribution of IVF indications. In 93% of the GnRH-a–based cycles, stimulation duration ranged from 7–12 days. The mean stimulation duration (±SD) for this group was 9.6 ± 1.7 days. In contrast, in 88% of the hMG-only cycles, the stimulation duration ranged from 5–8 days. The mean stimulation duration for this group was 6.7 ± 1.0 days, significantly shorter than in the GnRH-a group ($P<.01$).

Oocytes Retrieved

GnRH Agonist–based Protocol

Overall, a mean (±SD) of 14.2 ± 9.2 oocytes was retrieved. The group stimulated for 9 days had the highest number of oocytes retrieved, 15.8 ± 9.7, compared with 14.7 ± 8.8, 14.7 ± 9.6, and 14.3 ± 9.7 oocytes in the groups stimulated for 8, 10, and 11 days, respectively (Fig. 1). The differences in this parameter between groups were not statistically significant.

GnRH Agonist–free Protocol

Overall, a mean (±SD) of 10.7 ± 7.6 oocytes was retrieved, which was significantly less than seen in the GnRH-a–based protocol ($P<.01$).

Embryos Obtained

GnRH Agonist–based Protocol

Overall, 5.9 ± 4.7 embryos were obtained. The number of embryos obtained was 5.1 ± 3.5, 5.8 ± 5.0, 6.1 ± 4.7, 6.3 ± 4.9, 6.4 ± 4.7, and 5.2 ± 4.7 for the groups stimulated for 7, 8, 9, 10, 11, and 12 days, respectively. These differences were not statistically significant.

GnRH Agonist–free Protocol

Overall, 4.9 ± 2.8 embryos were obtained, significantly lower than the GnRH-a-based protocol ($P<.01$).

Pregnancy Rate

GnRH Agonist–based Protocol

The 9-day stimulation group had the highest clinical pregnancy rate per retrieval (26.8%). The pregnancy rate was 24.2%, 19.2%, 19.6%, 17.5%, and 23.5% for the groups stimulated for 7, 8, 10, 11, and 12 days, respectively. These differences were not statistically significant.

GnRH Agonist–free Protocol

The mean clinical pregnancy rate (±SD) was 28.3%. This rate was not statistically different from the pregnancy rate observed with the GnRH-a–based protocol.

Age and Stimulation Duration

For both protocols, there was no difference in the number of stimulation days between the different age groups. It was 10.11, 9.84, 9.51, 9.64, 9.54, and 10.17 days for GnRH-a–based protocol, and 6.16, 7.1, 6.55, 6.87, 6.54, and 7 for the hMG-only cycles for the age groups 20–24, 25–29, 30–34, 35–39, 40–44, and 45–49 years, respectively.

DISCUSSION

GnRH agonists have been extensively used in IVF stimulation cycles. The primary goal of this use is prevention of the threat of untimely LH rise. Starting ovarian stimulation with exogenous gonadotropins after quiescence has been reached has the potential advantage of increasing the homogeneity of follicular recruitment, although at the cost of increased hMG consumption. However, no data are available as to the duration of ovarian stimulation under these circumstances.

Our results show that in 64% of GnRH-a–based cycles, the stimulation period ranged from 8–10 days. Patients treated for 9 days had the largest number of oocytes retrieved (15.8) and the highest clinical pregnancy rate (26.8%), although this was not statistically significant. Starting ovarian stimulation without prior pituitary down-regulation shortens the cycle duration significantly (6.7 days), without a significant effect on the cycle outcome. By day 3 of the cycle, the cohort of growing follicles is already established. In fact, follicular recruitment is a late luteal phase event, which is abolished in long GnRH-a–based protocols. Under these circumstances, follicular recruitment is achieved by exogenously administered hMG, resulting in a higher number of oocytes obtained (14.2) compared to an hMG-only protocol (10.7). However, the pregnancy rate did not differ significantly between the two groups.

Interestingly, the patient's age had no effect on stimulation duration, in spite of the well-established shortening of the natural follicular phase length during the fourth and fifth decade of life. It is tempting to speculate that GnRH-a–induced ovarian quiescence neutralizes the ovarian and pituitary factors that govern age-related changes in follicular phase dynamics.

References

1. FIVNAT 1995 evaluation. Contracept Fertil Sex 1996;24:694–9.
2. The ganirelix dose-finding study group. A double-blind, randomized, dose-finding study to assess the efficacy of the gonadotrophin-releasing hormone antagonist ganirelix (Org 37462) to prevent premature luteinizing hormone surges in women undergoing ovarian stimulation with recombinant follicle stimulation hormone (Puregon). Hum Reprod 1998; 13:3023–31.
3. Speroff L, Glass RH, Kase GN. Clinical gynecologic endocrinology and infertility. 6th ed. Baltimore: Lippincott Williams & Wilkins, 1999: 1112–35.
4. Jansen CAM, van Os HC, Out HJ, Coelingh Bennink JT. A prospective randomized clinical trial comparing recombinant follicle stimulating hormone (Puregon) and human menopausal gonadotrophins (Humegon) in non-down-regulated in-vitro fertilization patients. Hum Reprod 1998; 13:2995–9.