Gynecol. Endocrinol. 9 (1995) Suppl. 4, 13–17

The use of GnRH analogs for induction of the preovulatory gonadotropin surge in assisted reproduction and prevention of the ovarian hyperstimulation syndrome

N. Lewit, S. Kol, D. Manor and J. Itskovitz-Eldor

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

Key words: GONADOTROPIN-RELEASING HORMONE ANALOG, OVARIAN HYPERSTIMULATION SYNDROME, OVULATION INDUCTION, LUTEINIZING HORMONE SURGE, *IN VITRO* FERTILIZATION

ABSTRACT

Ovarian hyperstimulation syndrome (OHSS) remains a potential severe complication of the use of gonadotropin therapy in ovulation induction and assisted reproduction technologies. In 1988, we reported preliminary results which demonstrated the ability of gonadotropin-releasing hormone analogs (GnRH-a) to trigger ovulation, and to prevent subsequent OHSS. In this report, we summarize our experience of 73 treatment cycles involving 44 high responders (i.e. patients with a previous history of severe OHSS, or with high estradiol levels (> 13 200 pmol/l) on the day of triggering the luteinizing hormone (LH) surge).

In spite of the high estradiol levels (mean 24 202 pmol/l) and the large number of oocytes (mean 32.4), none of our patients developed severe OHSS. Luteal support with progesterone and estradiol valerate was necessary to maintain adequate serum levels of these hormones. Without such support, a precipitous decline in levels of estradiol and progesterone was observed. We believe that the use of GnRH-a instead of human chorionic gonadotropin (hCG) for the induction of ovulation allows for safe ovarian stimulation without exposing the patient to the risk of OHSS.

INTRODUCTION

Ovarian hyperstimulation syndrome (OHSS) is the most serious complication related to gonadotropin therapy for ovulation induction and assisted reproduction technologies. In patients treated with gonadotropins, the luteinizing hormone (LH) surge is usually absent or attenuated and, therefore, exogenous human chorionic gonadotropin (hCG) is used to induce final oocyte maturation and ovulation[1].

The longer half-life of hCG (more than 24 h), compared to that of LH, results in a sustained luteotropic effect and the development of multiple functioning corpora lutea. These events are the hallmark of OHSS, hence hCG is considered to have a key role in the pathogenesis of this syndrome. Until recently, hCG was the only effective

Correspondence: Dr N. Lewit, Rambam Medical Center, Department of Obstetrics and Gynecology, POB 9602, Haifa 31096, Israel

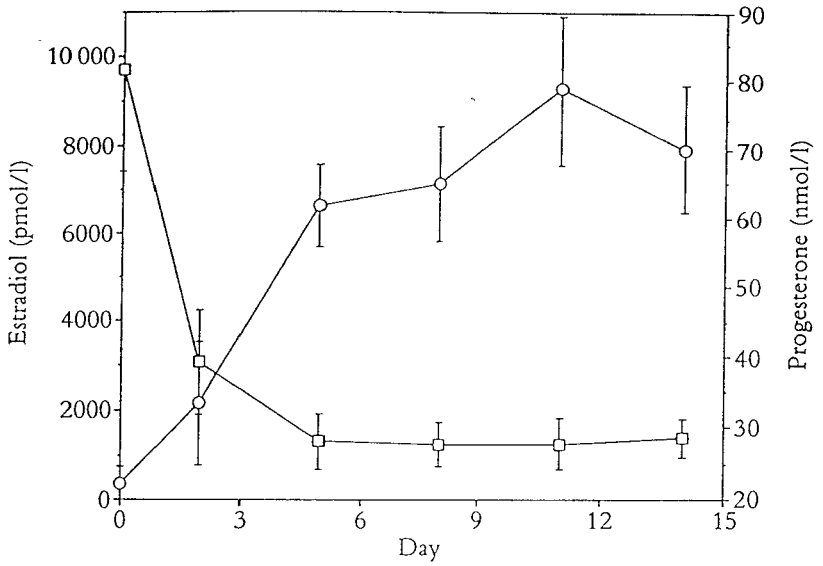

Figure 1 Serum levels (mean ± standard error) of estradiol (open squares) and progesterone (open circles) are presented for the luteal phase ($n = 73$). Throughout the luteal phase, fairly constant hormone levels were maintained. Day 0, day of gonadotropin-releasing hormone analog (GnRH-a) administration

method to induce ovulation in gonadotropin-stimulated cycles. Since the mid-1970s, several authors have reported the use of native luteinizing hormone-releasing hormone (LHRH) for the induction of ovulation, with limited success. Apparently, the LH surge induced by native LHRH was not always sufficient in terms of magnitude and duration to cause the cascade of events leading to ovulation[2–6]. The introduction of the more potent gonadotropin-releasing hormone analogs (GnRH-a) created an alternative solution to this problem. The sustained release of LH caused by these analogs can last for 24 h and leads invariably to ovulation.

In 1988, we reported our preliminary results demonstrating the ability of GnRH-a to trigger the preovulatory LH/follicle-stimulating hormone (FSH) surge and induce oocyte maturation in patients undergoing ovarian stimulation for the purpose of *in vitro* fertilization–embryo transfer (IVF–ET). The potential role of GnRH-a in preventing OHSS was indicated for the first time in this report[7]. Subsequent reports have also suggested the use of GnRH-a for prevention of OHSS[8–17]. However, the data published to date describe relatively small series of patients, and lack matched case–control groups.

PATIENTS AND METHODS

The present study was conducted in a group of IVF patients highly prone to developing OHSS. Forty-four women underwent 73 treatment cycles, 23 of which were regular IVF cycles and 50 of which were micromanipulation cycles (partial zona dissection, subzonal insemination, intracytroplasmic sperm injection). The study group consisted of two types of high responders: 16 women (22 cycles) who had developed severe OHSS in previous IVF cycles, and 28 patients (51 cycles) who had estradiol levels > 13 200 pmol/l on the day of LH surge triggering.

Ovarian stimulation was initiated with FSH/human menopausal gonadotropin (hMG) on day 3 of the cycle. The number of growing follicles and their size and serum estradiol, progesterone and LH levels were monitored on cycle day 3 (baseline) and then daily from cycle day 6. Luteinizing hormone surge was triggered by a single 0.2-mg dose of Decapeptyl® (D-Trp_6-LHRH, Ferring, Malmo, Sweden) administered subcutaneously when at least two of the leading follicles reached a diameter of 16 mm. Oocytes were retrieved transvaginally 36 h later.

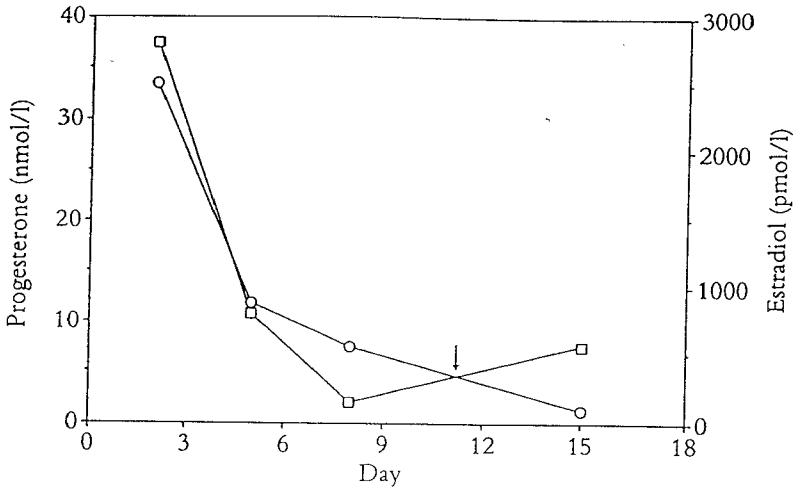

Figure 2 A representative cycle in which luteal support was withheld due to lack of fertilization. Serum levels of estradiol (open squares) and progesterone (open circles) declined rapidly 3 days after oocyte retrieval. Note was made of a short luteal phase (9 days). Day 0, day of gonadotropin-releasing hormone analog (GnRH-a) administration; arrow indicates time of withdrawal bleeding

RESULTS

Mean (± standard deviation) estradiol level on the day of LH surge was 24 202 ± 9213 pmol/l (median, 23 525, range 6200–53 660).. The mean number of oocytes retrieved was 32.4 ± 10.7 (median 32, range, 15–71).

A total of 2332 oocytes were retrieved from 73 cycles. Of these oocytes, 76.2% were in metaphase II, 5.4% were in metaphase I, 6.7% had a germinal vesicle and 11.7% were atretic or had fractured zonae. Fertilization and cleavage rates were 53.2 and 82.9% in the IVF cycles, and 35.7 and 84.7% in the micromanipulation cycles, respectively. The luteal phase was supported with daily injection of progesterone in oil (100 mg) and oral estradiol valerate (2–4 mg). Under these conditions, the serum levels of progesterone and estradiol remained fairly constant throughout the luteal phase, and ranged between 75 and 130 nmol/l for progesterone and 1000 and 2000 pmol/l for estradiol. Figure 1 depicts the serum levels (mean ± standard error) of estradiol and progesterone during the luteal phase. In three cycles where fertilization did not occur, luteal support was not given, resulting in a sharp decline in serum levels of estradiol and progesterone and a short luteal phase which lasted 9–10 days. Figure 2 depicts a representative cycle for which luteal support was withheld.

The 73 cycles resulted in 63 embryo transfers and 13 clinical pregnancies (four from freeze–thawed embryos). Eight pregnancies were from regular IVF cycles (pregnancy rate of 26.3% per embryo transfer and 34.8% per cycle). Five pregnancies resulted from micromanipulation cycles (pregnancy rate of 11.3% per embryo transfer and 10% per cycle). Two of the IVF pregnancies were spontaneously aborted. None of the patients developed signs of moderate or severe OHSS. Vaginal sonography in the luteal phase revealed moderate ovarian enlargement and, in some cases, a small amount of pelvic fluid. The corpora lutea were usually reduced in size and irregularly shaped.

DISCUSSION

Ovarian stimulation and retrieval of mature oocytes were successfully accomplished in 73 cycles in patients at high risk for developing OHSS, yet not a single case of severe OHSS was observed. Wada and co-workers[18] have reported their experience with similar high-risk patients. In their study of 78 women with serum estradiol levels greater than 13 200 pmol/l (mean 19 100) on the day of hCG injection, 21 (27%) had OHSS, and six (8%) had the severe form of the syndrome. Notably, ovarian stimulation started after pituitary down-regulation with GnRH-a, all embryos were cryopreserved and GnRH-a was continued in the luteal phase. Given the clinical details of our study group (i.e.

the number of treatment cycles, serum estradiol levels, number of oocytes retrieved and the history of previous OHSS), one would have expected at least six cases of severe OHSS.

A prospective, randomized, double-blind, controlled study on a group of high-risk patients similar to our study group would provide ultimate proof for the efficacy of this method. However, for ethical reasons, such a study could not possibly be conducted. Nevertheless, our results strongly suggest that the midcycle use of GnRH-a instead of hCG for the induction of oocyte maturation and ovulation permits a safe ovarian stimulation without exposing the patient to the risk of OHSS.

A possible explanation for prevention of OHSS by GnRH-a relies on its mechanism of action: an initial 'flare up' effect triggering the LH surge followed by down-regulation of pituitary GnRH receptors. The latter may result in abnormal LH secretion during the early luteal phase, reduced LH support for the corpora lutea, reduced ovarian steroidogenesis and early luteolysis[8,19]. The rapid and profound decline in activity of the corpora lutea is probably the key event in the prevention of OHSS[20]. It should be noted that GnRH-a would not be effective for triggering an adequate LH surge in cycles where GnRH-a down-regulation is used to prevent a spontaneous LH surge or premature luteinization. The future availability of GnRH antagonist is expected to eliminate this limitation. The 'ideal' protocol for controlled ovarian stimulation would use GnRH antagonist instead of GnRH-a for pituitary suppression, while the preovulatory LH/FSH surge would be induced with a single dose of GnRH-a.

REFERENCES

1. Schwartz, M. and Jewelewicz, R. (1981). The use of gonadotropins for induction of ovulation. *Fertil. Steril.*, **35**, 3–12
2. Jewelewicz, R., James, S. L., Finster, M., Dyrenfurth, I., Warren, M. P. and Vande Wiele, R. L. (1972). Gestation after ovulation induction with menopausal gonadotropins and pituitary luteinizing hormone. *Obstet. Gynecol.*, **40**, 1–5
3. Nakano, R., Mizuno, T., Kotsuji, F., Katayama, K., Washio, M. and Tojo, S. (1973). 'Triggering' of ovulation induction after infusion of synthetic luteinizing hormone releasing factor (LRF). *Acta Obstet. Gynecol. Scand.*, **52**, 269–72
4. Keller, P. J., (1973). Treatment of anovulation with synthetic luteinizing hormone-releasing hormone. *Am. J. Obstet. Gynecol.*, **116**, 698–705
5. Breckwoldt, M., Czygan, P. J., Lehman, F. and Bettendorf, G. (1974). Synthetic LH-RH as a therapeutic agent. *Acta Endocrinol. (Copenh.)*, **75**, 209–20
6. Crosignani, P. G., Trojsi, L., Attanasio, A., Tonani, E. and Donini, P. (1975). Hormonal profiles in anovulatory patients treated with gonadotropins and synthetic luteinizing hormone-releasing hormone. *Obstet. Gynecol.*, **46**, 15–22
7. Itskovitz, J., Boldes, R., Barlev, A., Erlik, Y., Kahana, L. and Brandes, J. M. (1988). The induction of LH surge and oocyte maturation by GnRH analog (buserelin) in women undergoing ovarian stimulation for *in vitro* fertilization. *Gynecol. Endocrinol.*, 2(Suppl. 2), 165
8. Itskovitz, J., Boldes, R., Levron, J., Erlik, Y., Kahana, L. and Brandes, J. M. (1991). Induction of preovulatory luteinizing hormone surge and prevention of ovarian hyperstimulation syndrome by gonadotropin-releasing hormone agonist. *Fertil. Steril.*, **56**, 213–20
9. Lanzone, A., Fulghesu, A. M., Apa, R., Caruso, A. and Mancuso, S. (1989). LH surge induction by GnRH agonist at the time of ovulation. *Gynecol. Endocrinol.*, **3**, 213–20
10. Gonen, Y., Balakiar, H., Powell, W. and Casper, R. F. (1990). Use of gonadotropin-releasing hormone agonist to trigger follicular maturation for *in vitro* fertilization. *J. Clin. Endocrinol. Metab.*, **71**, 918–22
11. Imoedemhe, D. A. G., Sigue, A. B., Pacpaco, E. L. A. and Olazo, A. B. (1991). Stimulation of endogenous surge of luteinizing hormone with gonadotropin-releasing hormone analog after ovarian stimulation for *in vitro* fertilization. *Fertil. Steril.*, **55**, 328–32
12. Emperaire, J. C. and Ruffie, A. (1991). Triggering ovulation with endogenous luteinizing hormone may prevent ovarian hyperstimulation syndrome. *Hum. Reprod.*, **6**, 506–10
13. Segal, S. and Casper, R. F. (1992). Gonadotropin-releasing hormone agonist versus human chorionic gonadotropin for triggering follicular maturation in *in vitro* fertilization. *Fertil. Steril.*, **57**, 1254–8
14. van der Meer, S., Gerris, J., Joostens, M. and Tas, B. (1993). Triggering of ovulation using a

gonadotropin-releasing hormone agonist does not prevent ovarian hyperstimulation syndrome. *Hum. Reprod.*, **8**, 1628–31

15. Scott, R. T., Bailey, S. A., Kost, E. R., Neal, G. S., Hofmann, G. E. and Illions, E. H. (1994). Comparison of leuprolide acetate and human chorionic gonadotropin for the induction of ovulation in clomiphene citrate-stimulated women. *Fertil. Steril.*, **61**, 872–9
16. Balasch, J., Tur, R., Creus, M., Buxanderes, R., Fabregues, F., Ballesca, J. L., Barri, P. N. and Vanrell, J. A. (1994). Triggering of ovulation by a gonadotropin releasing hormone agonist in gonadotropin-stimulated cycles for prevention of ovarian hyperstimulation syndrome and multiple pregnancy. *Gynecol. Endocrinol.*, **8**, 7–12
17. Gerris, J., De Vits, A., Joostens, M. and Van Royen, E. (1995). Triggering of ovulation in human menopausal gonadotropin-stimulated cycles: comparison between intravenously administered gonadotropin releasing hormone (100 and 500 μg) GnRH agonist (buserelin 500 μg) and human chorionic gonadotropin (10 000 IU). *Hum. Reprod.*, **10**, 56–62
18. Wada, I., Matson, P. L., Troup, S. A., Hughes, S. Buck, P. and Lieberman, P. A. (1992). Outcome of treatment subsequent to elective cryopreservation of all embryos from women at risk of the ovarian hyperstimulation syndrome. *Hum. Reprod.*, **7**, 962–6
19. Khoury, C., Itskovitz-Eldor, J. and Bar-Ami, S. (1994). Induction of maturation of cumulus–oocyte complex by gonadotropin releasing hormone analogue is associated with lower progesterone secretion. *J. Clin. Endocrinol. Metab.*, **79**, 1001–7
20. Itskovitz-Eldor, J., Levron, J. and Kol, S. (1993). Use of gonadotropin-releasing hormone agonist to cause ovulation and prevent the ovarian hyperstimulation syndrome. *Clin. Obstet. Gynecol.*, **36**, 701–10