

Comparison of gonadotrophin-releasing hormone analogues and human chorionic gonadotrophin for the induction of ovulation and prevention of ovarian hyperstimulation syndrome: a case-control study

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Gonadotrophin-releasing hormone analogue (GnRHa) has been suggested as an alternative to human chorionic gonadotrophin (HCG) for triggering ovulation, while preventing ovarian hyperstimulation syndrome (OHSS). Since a prospective, controlled study would be unethical at this point, we used a retrospective, case-self control approach to compare GnRHa with HCG in that context. A group of 16 in-vitro fertilization (IVF) patients who had severe OHSS in previous cycles, in which HCG was given to trigger ovulation, were studied in subsequent cycles in which GnRHa was used. Each GnRHa cycle (case) was compared to a previous HCG cycle that resulted in OHSS (self control). None of these subsequent cycles resulted in severe OHSS. The use of GnRHa did not affect the number of oocytes retrieved or their quality. Serum oestradiol concentrations on the day of ovulation triggering were significantly ($P < 0.01$) higher in the GnRHa cycles compared to HCG cycles. Exogenous progesterone and oestradiol were effective in maintaining relatively constant serum oestradiol and progesterone serum concentrations during the luteal phase. Pregnancy rate per cycle was similar in the two groups. In conclusion, the use of GnRHa to induce ovulation in IVF patients, who are at high risk for developing OHSS, effectively eliminates this risk without affecting other parameters of the stimulation cycle.

Key words: GnRH analogue/HCG/IVF-embryo transfer/ovarian hyperstimulation syndrome/ovulation induction

Introduction

Ovarian hyperstimulation syndrome (OHSS) remains the most serious complication related to gonadotrophin therapy for ovulation induction and assisted reproductive technologies. Since endogenous luteinizing hormone (LH) surge is usually absent or attenuated in patients treated with gonadotrophins, exogenous HCG is used to induce final oocyte maturation and ovulation (Schwartz and Jewelewicz, 1981). The longer half-life of HCG (>24 h), compared to that of LH, results in a sustained luteotrophic effect and the development of multiple functioning corpora lutea. These events are the hallmark of OHSS: hence HCG associated with high serum oestradiol

levels and multiple growing follicles is believed to play a key role in the pathogenesis of this syndrome.

It has been suggested that stimulation with low doses of gonadotrophins, the use of low dose mid-cycle HCG, avoiding HCG for luteal support, withholding embryo transfer and the use of albumin post-retrieval may prevent or minimize the risk of OHSS (Asch *et al.*, 1993; Shoham *et al.*, 1994), but all have proved to be of limited effectiveness.

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 induced LH surge by native LHRH was not always sufficient in terms of magnitude and duration to initiate the cascade of events leading to ovulation (Jewelewicz *et al.*, 1972; Keller, 1973; Nakano *et al.*, 1973; Breckwoldt *et al.*, 1974; Crosignani *et al.*, 1975; Letterie *et al.*, 1996).

The introduction of the more potent gonadotrophin-releasing hormone analogue (GnRHa) created a new strategy for ovulation induction. The sustained release of LH caused by these analogues can last for 24 h and leads invariably to ovulation. In 1988, we reported our preliminary results demonstrating the ability of GnRHa to reliably trigger pre-ovulatory LH and follicle stimulating hormone (FSH) surges and to induce oocyte maturation in patients undergoing ovarian stimulation for the purpose of in-vitro fertilization (IVF)-embryo transfer. The potential role of GnRHa in preventing OHSS was indicated for the first time in that report (Itskovitz *et al.*, 1988). Subsequent reports have also described the successful use of GnRHa in triggering LH surge and prevention of OHSS (Lanzone *et al.*, 1989; Gonen *et al.*, 1990; Emperaire and Ruffie, 1991; Imoedemhe *et al.*, 1991; Segal and Casper, 1992; Balasch *et al.*, 1994; Scott *et al.*, 1994; Shalev *et al.*, 1994). Since then we have used this approach in over 80 patients (Lewit *et al.*, 1995), 16 of whom have developed OHSS in previous cycles during which HCG was used. Since we believe it is unethical at this point to conduct a double-blind, controlled, prospective study comparing conventional (HCG) with GnRHa-triggered ovulation in patients at high risk for developing OHSS, this subset of patients allows a meaningful comparison, as each patient serves as her own control.

Materials and methods

Patients

The study group consisted of 16 women who developed severe OHSS in previous (control group A) IVF cycles (OHSS resulting from gonadotrophin treatment in, regular fertility clinic cycles was not included). In these cycles, ovulation was triggered with HCG (10 000 IU), fresh embryos were transferred in 11 cycles. Severe

Table I. Comparison of stimulation variables. Values are means \pm SD

| Group | Oestradiol on day of ovulation induction (pmol/l) | No. of oocytes retrieved | No. of HMG ampoules used |
|------------------------|---|--------------------------|--------------------------|
| A (HCG) | 16 969 \pm 8948 | 28 \pm 11 | 24 \pm 6 |
| B (GnRH _a) | 20 816 \pm 9568 ^a | 36 \pm 14 | 21 \pm 4 |

Numbers are mean \pm SD.

^a $P < 0.01$ compared to group A.

OHSS was diagnosed if a patient was hospitalized with enlarged ovaries (>10 cm), significant ascites (defined as fluid in the hepatorenal pouch), and/or any of the following signs: pleural effusion, haematocrit $>45\%$, oliguria (<600 ml/day), electrolyte imbalance. Subsequently, each patient underwent at least one cycle, during which ovulation was triggered with GnRH_a as a means to prevent OHSS (case, group B). A total of 22 such cycles was performed. Aetiologies of infertility included male factor ($n = 9$ couples), mechanical ($n = 4$ patients) and polycystic ovary syndrome ($n = 3$ patients).

Ovarian stimulation and cycle follow-up

In both groups, ovarian stimulation was initiated with FSH (Metrodin; Teva, Petach Tikva, Israel) human menopausal gonadotrophin (HMG, Pergonal; Teva) on day 3 of the cycle. In group A, ovarian stimulation was initiated after pituitary down-regulation with GnRH_a in eight patients. In group B, pituitary down-regulation with GnRH_a was not attempted, as it would render the pituitary unresponsive to the subsequent triggering dose. The number of growing follicles and their size, serum oestradiol, progesterone and LH levels were monitored on cycle day 3 (baseline) and then daily from cycle day 6 for both groups. None of the retrievals in group B was cancelled for premature spontaneous LH surge. In this group, LH surge was triggered with a single 0.2 mg dose of decapeptyl[®] (D-Trp₆-LHRH, Ferring, Malmö, Sweden) administered s.c. when at least two of the leading follicles reached a diameter of 16 mm. Oocytes were retrieved transvaginally 36 h later. Stripped oocytes prepared for micromanipulation procedures were used to obtain oocyte quality data. Micromanipulation (partial zona drilling, subzonal insemination and intracytoplasmic sperm injection) was performed in nine and 12 cycles in groups A and B respectively. The luteal phase was supported with daily injection of progesterone in oil (100 mg) in group A, while patients in group B were treated with oral oestradiol valerate (2–4 mg) in addition to daily injection of progesterone in oil (100 mg). Patient assessment, including vaginal sonography, was performed in mid-luteal phase to document the degree of ovarian hyperstimulation. Serum levels of β -HCG 11 days after embryo transfer were used to establish the presence of chemical pregnancy. Subsequently, sonography was used to detect the gestational sac and embryonic structures.

Statistical analysis

The statistical analysis was performed by the paired Student's *t*-test. In group B, four patients underwent two stimulation cycles. For these patients, the mean values of oestradiol, number of retrieved oocytes and number of HMG ampoules administered were used for the analysis. The level of significance was set at $P < 0.05$.

Results

As shown in Table I, mean oestradiol level on the day of LH surge was significantly higher in group B (case) compared to

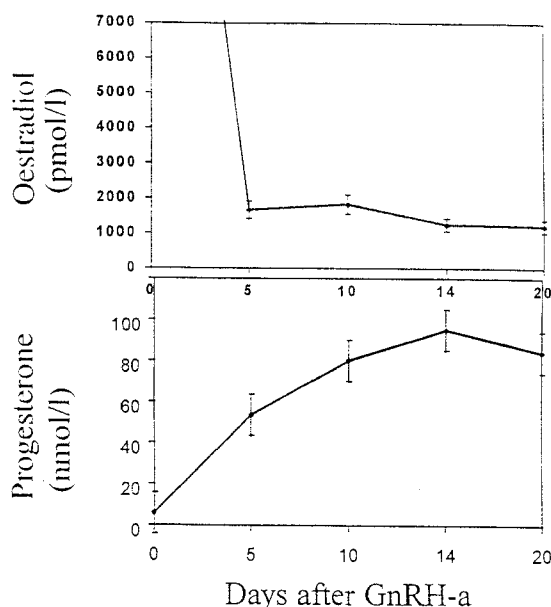


Figure 1. Serum concentrations (mean \pm SE) of oestradiol (upper panel) and progesterone (lower panel) during the luteal phase in group B [ovulation triggered by gonadotrophin-releasing hormone analogue (GnRH_a)].

Table II. Comparison of oocyte quality by numbers of oocytes showing particular attributes

| Group | Fractured zona | Atretic | Germinal vesicle | Polar body | Non-visible structure ^a | Total |
|------------------------|----------------|---------|------------------|------------|------------------------------------|-----------|
| A (HCG) | 6 (3) | 8 (4) | 10 (5) | 180 (84) | 10 (5) | 214 (100) |
| B (GnRH _a) | 11 (4) | 15 (6) | 19 (7) | 205 (80) | 7 (3) | 257 (100) |

Values in parentheses are percentages of total.

^aMetaphase I.

group A (control). The mean numbers of oocytes retrieved and HMG ampoules used were comparable in both groups.

A total of 214 stripped oocytes for group A and 257 for group B were assessed for their quality. As shown in Table II, oocyte quality was comparable in both groups.

Luteal support in group B resulted in serum levels of progesterone and oestradiol that remained fairly constant throughout the luteal phase, and ranged between 53–130 nmol/l for progesterone and 1000–1800 pmol/l for oestradiol. Figure 1 depicts the serum concentrations (mean \pm SE) of oestradiol (upper panel) and progesterone (lower panel) during the luteal phase of group B. These values were not obtained for group A.

The 16 control cycles (group A) resulted in three clinical pregnancies (one from frozen-thawed embryos), a pregnancy rate of 19% per cycle. The 22 case cycles (group B) resulted in four clinical pregnancies (two from frozen-thawed embryos), a pregnancy rate of 18% per cycle.

None of the group B patients developed signs of severe OHSS as defined above. 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 with GnRHa in 22 cycles in patients who developed OHSS in previous cycles, during which HCG was used to induce ovulation, yet not a single case of severe OHSS was observed. The clinical and hormonal profiles of the cycles during which GnRHa was used were even more ominous as far as the potential risk for the subsequent development of OHSS. Specifically, serum oestradiol levels, generally considered as a characteristic predictor of OHSS, were significantly higher in these cycles compared to HCG-triggered cycles. Moreover, GnRHa-triggered cycles produced more oocytes compared to HCG-triggered cycles, although the difference was not statistically significant. We believe that the treating physicians felt confident despite reaching very high levels of oestradiol, knowing that ovulation would be triggered with GnRHa, and thereby eliminating the risk for OHSS altogether. This feeling of confidence is based on extensive experience of >80 cycles, in which not a single case of severe OHSS was observed (Lewit *et al.*, 1995). The oocytes retrieved proved to be of similar quality, suggesting that GnRHa does not affect the process of oocyte maturation. The pregnancy rates also appeared to be similar, if somewhat low. However, the small number of cycles, and the use of older micromanipulation techniques (partial zona drilling, subzonal insemination) should be borne in mind, and additional cycles should be analysed for meaningful conclusions regarding the impact of GnRHa on pregnancy rates.

Shalev *et al.* (1995) have used 0.1 mg decapeptyl to induce ovulation in 24 patients, two of whom developed moderate OHSS. In this study patients at high risk of developing OHSS were excluded. The same group of investigators (Shalev *et al.*, 1994) have also used 0.5 mg of the same GnRHa preparation to induce ovulation in 12 patients who were at high risk of developing severe OHSS, and none of these patients developed the syndrome. It should be mentioned that mild to moderate symptoms (e.g. abdominal pain) or signs (e.g. enlarged ovaries), on which the diagnosis of OHSS can be established, are merely a reflection of controlled ovarian stimulation, thus in this context, clinically significant OHSS may well be defined by the criteria listed above. Based on these data, we suggest that 0.2 mg decapeptyl is probably the lowest effective dose in the context of OHSS prevention. Induction of ovulation per se can be accomplished by even lower doses of GnRHa as demonstrated by Shalev (1995).

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, based on the extensive body of evidence, albeit not derived from randomized studies, and on our own extensive experience, we feel that for ethical reasons, such a study could not possibly be conducted. Nevertheless, our series of patients, in which each patient served as her own control, strongly suggests that the mid-cycle use of GnRHa instead of HCG for the induction of oocyte maturation and ovulation permits safe ovarian stimulation without exposing the patient to the risk of OHSS. We, on our part, have adopted this approach to all our 'high risk' patients.

A possible explanation for the prevention of OHSS by GnRHa relies on its mechanism of action: an initial 'flare up' that induces LH and FSH surges, 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 (Itskovitz *et al.*, 1991; Van der Meer *et al.*, 1993; Khoury *et al.*, 1994; Gerris *et al.*, 1995). The rapid and profound decline in the activity of the corpora lutea is probably the key event in the prevention of OHSS (Itskovitz *et al.*, 1993), and is supported by several observations: (i) an abrupt fall in oestradiol and progesterone levels was recorded in the first days of the luteal phase in cases where luteal support was not given (Lewit *et al.*, 1995); (ii) a consequent short luteal phase lasting 9–10 days (Lewit *et al.*, 1995); (iii) reduced progesterone production by cumulus and granulosa cells obtained from women treated with midcycle GnRHa for the induction of LH surge was observed (Khoury *et al.*, 1994). Additional experiments are warranted to explore other possible mechanisms of action.

It is important to note that GnRHa would not be effective for triggering an adequate LH surge in cycles where GnRHa down-regulation is used to prevent a spontaneous LH surge or premature luteinization. We believe that this limitation will be circumvented with the clinical introduction of a GnRH antagonist. The future protocol for ovarian stimulation would probably use GnRH antagonist instead of GnRHa for pituitary suppression, while a pre-ovulatory LH/FSH surge would be induced with a single dose of GnRHa.

In summary, the comparison of the two strategies for ovulation triggering (HCG and GnRHa) in the same patients clearly shows the advantage offered by the latter in eliminating the risk of OHSS.

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