Human chorionic gonadotrophin luteal support overcomes luteal phase inadequacy after gonadotrophin-releasing hormone agonist-induced ovulation in gonadotrophin-stimulated cycles

Joana Peñarrubia1, Juan Balasch1,3, Francisco Fábregues1, Montserrat Creus1, Roser Casamitjana2, José L. Ballescà1, Bienvenido Puerto1 and Juan A. Vanrell1

1Department of Obstetrics and Gynecology, and
2Hormonal Laboratory, Faculty of Medicine–University of Barcelona, Hospital Clinic i Provincial–Institut d’Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain
3To whom correspondence should be addressed at: Department of Obstetrics and Gynecology, Hospital Clinic i Provincial, C/Casanova 143, 08036-Barcelona, Spain

Gonadotrophin-releasing hormone agonist (GnRHa)-induced ovulation after gonadotrophin ovarian stimulation is used to prevent ovarian hyperstimulation syndrome and multiple pregnancy in polyfollicular cycles. However, one of the major problems to be resolved is corpus luteum function after follicular maturation and ovulation by mid-cycle GnRHa administration. The present report investigated the luteal phase in non-conceptual polyfollicular cycles in 26 patients (group 1) receiving a single dose of 0.5 mg leuprolide acetate to induce ovulation and in a control group of patients (n = 26) (group 2) who were given human chorionic gonadotrophin (HCG) (10 000 IU i.m.) for ovulation induction. All of them were normal ovulatory women undergoing gonadotrophin ovarian stimulation because of unexplained infertility or male factor. In both groups of patients two doses of 2500 IU HCG i.m. were given 6 and 10 days after the ovulatory dose of HCG or GnRHa to support the luteal phase. All cycles were ovulatory as shown by mid-luteal serum progesterone concentrations >10 ng/ml. Mean serum progesterone concentrations were 62% higher in group 2 than in group 1, but this difference was not statistically significant. The mean length of the luteal phase was similar in groups 1 and 2. It is concluded that HCG luteal support is a useful tool to overcome the luteal phase inadequacy that characterizes GnRHa-triggered cycles after gonadotrophin stimulation.

Key words: GnRH agonists/HCG/luteal phase deficiency/ovulation induction/plasma progesterone

Introduction

Recently, different studies have suggested the use of gonadotrophin-releasing hormone agonists (GnRHAs) instead of human chorionic gonadotrophin (HCG) as an ovulation trigger in polyfollicular gonadotrophin-stimulated cycles in order to prevent ovarian hyperstimulation syndrome and multiple pregnancy both in in-vitro fertilization (IVF) and non-IVF patients. The subject, however, is still a matter of debate (Ben-Arie et al., 1996; Casper, 1996; Kol et al., 1996).

As recently stressed, one of the major concerns still seeking a solution is corpus luteum function after follicular maturation and ovulation by mid-cycle GnRHa administration (Ben-Arie et al., 1996). Thus, we and others have reported short luteal phases in as many as 16–42% of cycles treated by GnRHa (Emperaire and Ruffie, 1991; Itskovitz et al., 1991; Segal and Casper, 1992; Corson et al., 1993; Balasch et al., 1994a, 1995; Lanzone et al., 1994; Scott et al., 1994). Corson et al. (1993) and Lanzone et al. (1994) concluded that ovulation induction with GnRHa after gonadotrophin priming produces unacceptable luteal phase cycles in the absence of hormonal support while others have stressed the need for further research in order to study the luteal phase in ovarian-stimulated patients in whom ovulation induction was induced by GnRHa (Segal and Casper, 1992; Itskovitz et al., 1993).

In a previous study (Balasch et al., 1995) we showed that the luteal phase following GnRHa injection for triggering ovulation in gonadotrophin-stimulated cycles is characterized by prompt and adequate luteinization of the follicles but in most patients this is followed by an inadequate production of progesterone in quantity and/or duration. Furthermore, this luteal phase inadequacy was not prevented by luteal support with micronized vaginal progesterone. The present report shows that luteal phase support with HCG is a useful tool to overcome this deficiency.

Materials and methods

A total of 52 infertile women (26 cases and 26 controls) were included in this prospective non-randomized study. All of them were normally ovulating women who were treated with ovulation induction alone or in combination with intrauterine insemination because of unexplained infertility or male factor which were defined as previously reported (Balasch et al., 1994b).

Patients were treated with 150 IU s.c./day of highly-purified follicle stimulating hormone (FSH; Neo-Fertinorm®; Serono, Madrid, Spain) from cycle day 3 until follicular maturation was reached. The follicular phase was monitored by daily transvaginal ultrasound scanning and measurements of serum oestradiol concentrations starting on day 6. Ovulation was induced once follicular maturation was completed (leading follicular diameter >17 mm). In 26 consecutive patients (group 1) the ovulation injection of HCG was withheld because >4 mature follicles (>14 mm in diameter) were present irrespective of oestradiol serum concentrations. These women received a single dose of 0.5 mg leuprolide acetate s.c. (Procrin®; Abbot Laboratories, Madrid, Spain) instead of HCG to induce ovulation. As a control group (n = 26) (group 2) the nearest gonadotrophin-induced cycle in normal ovulatory women having <4 follicles >14 mm on the day.
of ovulation induction with HCG (10 000 IU i.m.; Profasi®; Serono) after each GnRHa-induced cycle (i.e., the closest subsequent cycle in temporal relationship to the index cycle) was used. In both groups of patients two doses of 2500 IU HCG i.m. were given 6 and 10 days after the ovulatory dose of HCG or GnRHa to support the luteal phase.

For the specific purpose of this study oestradiol and progesterone serum concentrations were measured in all patients 8 days after the GnRHa or HCG ovulatory injection. Ovulation was considered to have occurred when circulating progesterone concentrations exceeded 10 ng/ml in the mid-luteal phase. The luteal phase duration was measured in both groups by determining the number of days from 48 h after GnRHa or HCG administration up to and including the day before the onset of menstruation. A short luteal cycle was defined as one lasting <11 days (Jones, 1975; Lenton et al., 1984). Only non-conceptual cycles were analysed.

Oestradiol and progesterone concentrations in serum were estimated by direct radioimmunoassay (BioMérieux, Marcy l’Etoile, France for oestradiol; Immunotech International, Mârseilles, France for progesterone). Intra-assay and interassay coefficients of variation were <4 and <5.5% respectively for oestradiol, and <6.5% and <8% respectively for progesterone. Ultrasonic scans were performed using a 5 MHz vaginal transducer attached to an Aloka sector scanner (Model SSD-620; Aloka Ltd, Tokyo, Japan).

Data were analysed by SPSS version 6.1.3 statistical software (SSPS Inc., Chicago, IL, USA) using the Mann–Whitney U-test. Results are expressed as means with standard error (SE). The level of significance was set at \( P < 0.05 \).

### Results

Clinical characteristics of the patients, follicular response to gonadotrophin treatment, and luteal phase parameters in the two groups studied are presented in Table I. There were no differences between groups regarding age, duration of infertility, and total quantity of FSH required to obtain ovarian response to gonadotrophin treatment. Multifollicular development, as shown by ultrasonography, was present in all patients at the time of leuprolide acetate or HCG administration. As expected, the mean number of mature follicles on the day of ovulation induction with GnRHa or HCG was higher in group 1. Accordingly, oestradiol serum concentrations on this day were also higher in the latter group although the difference was not statistically significant. Seven patients in group 1 had serum oestradiol values >1000 pg/ml (mean 1594 pg/ml, range 1080–2912) on the day of GnRHa injection. Two patients in group 2 had oestradiol serum concentrations >1000 pg/ml (1572 and 1754 pg/ml, respectively) on the day of HCG ovulatory injection.

All cycles showed mid-luteal serum progesterone concentrations >10 ng/ml, thus indicating the presence of luteal tissue responsive to HCG. Mean serum progesterone concentrations in the mid-luteal phase were 62% higher in group 2 than in group 1, but the difference was not statistically significant. Mean mid-luteal phase serum oestradiol concentrations were significantly higher in patients receiving HCG (group 2) for ovulation induction as compared with those treated with GnRHa (group 1). The mean length of the luteal phase was similar in groups 1 and 2. There were two short luteal phases (10 and 11 days, respectively) in group 1, and one (10 days) in group 2. Mid-luteal serum progesterone values in these three patients were 37.8 ng/ml, 53 ng/ml, and 67.8 ng/ml, respectively. No patient developed ovarian hyperstimulation syndrome.

### Discussion

The use of GnRHa in the context of triggering ovulation has been suggested several years ago (Itskovitz et al., 1988). The nearly physiological luteinizing hormone (LH) and FSH surges induced by a single GnRHa injection are followed by timely ovulation (Kol et al., 1996). The FSH stimulation that accompanies the GnRHa-induced endogenous surge is the first and most obvious advantage of triggering ovulation with GnRHa rather than HCG. Although an FSH surge is not absolutely essential, it may facilitate several processes such as the expansion of the cumulus and others that may impact on the efficiency of actual ovulation (Zelinski-Wooten et al., 1991; Scott et al., 1994). In fact, this method was found effective in the induction of follicular maturation and ovulation with pregnancy rates comparable to HCG administration, in both IVF and other ovulation induction programmes (Ben-Arie et al., 1996). In the study by Imoedemhe et al. (1991) an even
higher rate of mature oocytes and replaceable embryos was obtained with GnRHa use.

A second potential advantage for the use of GnRHa instead of HCG stems from the short (34 h) duration of the LH surge induced by GnRHa, which provides a more physiological ovulatory stimulus than the extended surge (approximately 6 days) associated with HCG (Casper, 1996). This time-limited stimulus can trigger the ovulation of fewer follicles (compared with HCG under similar conditions) and thus a lower frequency of multiple pregnancies could be expected in patients undergoing ovulation induction (Itskovitz et al., 1993; Kol et al., 1996). This may also explain why GnRHa therapy has been found to be effective for prevention of ovarian hyperstimulation syndrome in patients thought to be at risk of having the syndrome (Itskovitz et al., 1991; Balasch et al., 1994a; Shalev et al., 1994, 1995a,b; Ben-Arie et al., 1996; Kol et al., 1996). However, others disagree and emphasize that the reduction in severe ovarian hyperstimulation syndrome in the GnRHa-triggered cycles reported to date may be partially a result of using progesterone, in place of HCG, for support of the luteal phase (Casper, 1996).

In this respect it is notable that previous work by our group (Balasch et al., 1995) has shown that as many as 70% of patients undergoing GnRHa-induced ovulation in exogenous gonadotrophin-stimulated cycles had mid-luteal serum progesterone concentration <2 SD below the mean value observed in control fertile women during spontaneous ovulatory cycles, and 40% of patients had short luteal phases. This was true irrespective of whether one or two doses of leuprolide acetate were used and despite the use of luteal phase support with progesterone in all stimulated cycles. This may be explained by the shorter duration of LH activity following GnRHa compared with HCG administration which may indeed reduce the stimulation of the luteal ovary. In addition, a period of down-regulation of GnRH receptors in the pituitary occurs even after a single mid-cycle injection of GnRHa (Casper, 1996). This will further reduce endogenous LH stimulation of the corpora lutea. As the young corpora lutea lack the necessary gonadotrophin support, their demise is reflected in a fall in progesterone concentrations (Kol et al., 1996). Therefore, the need for further research in order to study the luteal phase in ovarian-stimulated patients in whom ovulation induction was induced by GnRHa has been pointed out by several authors (Segal and Casper, 1992; Itskovitz et al., 1993; Ben-Arie et al., 1996). The present report provides further data on the subject.

Luteal phase evaluation rather than possible prevention of ovarian hyperstimulation syndrome was the goal of our study. Only 27% of patients with GnRHa-triggered cycles were at high risk for developing this complication according to oestradiol serum concentrations (Kol et al., 1994). The present report provides further data on the subject. A second potential advantage for the use of GnRHa instead of HCG stems from the short (34 h) duration of the LH surge induced by GnRHa, which provides a more physiological ovulatory stimulus than the extended surge (approximately 6 days) associated with HCG (Casper, 1996). This time-limited stimulus can trigger the ovulation of fewer follicles (compared with HCG under similar conditions) and thus a lower frequency of multiple pregnancies could be expected in patients undergoing ovulation induction (Itskovitz et al., 1993; Kol et al., 1996). This may also explain why GnRHa therapy has been found to be effective for prevention of ovarian hyperstimulation syndrome in patients thought to be at risk of having the syndrome (Itskovitz et al., 1991; Balasch et al., 1994a; Shalev et al., 1994, 1995a,b; Ben-Arie et al., 1996; Kol et al., 1996). However, others disagree and emphasize that the reduction in severe ovarian hyperstimulation syndrome in the GnRHa-triggered cycles reported to date may be partially a result of using progesterone, in place of HCG, for support of the luteal phase (Casper, 1996).

In this respect it is notable that previous work by our group (Balasch et al., 1995) has shown that as many as 70% of patients undergoing GnRHa-induced ovulation in exogenous gonadotrophin-stimulated cycles had mid-luteal serum progesterone concentration <2 SD below the mean value observed in control fertile women during spontaneous ovulatory cycles, and 40% of patients had short luteal phases. This was true irrespective of whether one or two doses of leuprolide acetate were used and despite the use of luteal phase support with progesterone in all stimulated cycles. This may be explained by the shorter duration of LH activity following GnRHa compared with HCG administration which may indeed reduce the stimulation of the luteal ovary. In addition, a period of down-regulation of GnRH receptors in the pituitary occurs even after a single mid-cycle injection of GnRHa (Casper, 1996). This will further reduce endogenous LH stimulation of the corpora lutea. As the young corpora lutea lack the necessary gonadotrophin support, their demise is reflected in a fall in progesterone concentrations (Kol et al., 1996). Therefore, the need for further research in order to study the luteal phase in ovarian-stimulated patients in whom ovulation induction was induced by GnRHa has been pointed out by several authors (Segal and Casper, 1992; Itskovitz et al., 1993; Ben-Arie et al., 1996). The present report provides further data on the subject.

Luteal phase evaluation rather than possible prevention of ovarian hyperstimulation syndrome was the goal of our study. Only 27% of patients with GnRHa-triggered cycles were at high risk for developing this complication according to oestradiol serum concentrations >1000 pg/ml. However, all of them had four or more mature follicles which is generally accepted as an indication to withhold HCG ovulatory injection irrespective of oestradiol serum concentrations (Lightman et al., 1988; Rivlin, 1990; Franks and Hamilton-Fairley, 1996). Our study indicates that HCG luteal support can be a useful tool to overcome the luteal phase inadequacy that characterizes GnRHa-triggered cycles after gonadotrophin stimulation. This is supported by the following facts. First, mid-luteal serum progesterone concentrations were not significantly different in groups 1 and 2. The higher non-significant mean value for progesterone and the significantly higher mid-luteal oestradiol serum concentrations in group 2 in spite of a low number of follicles, can be explained by the more intense and prolonged biological action of HCG in comparison with the GnRHa-induced LH release as discussed above. Second, the duration of the luteal phase was similar in both treatment groups. In our previous reports on GnRHa-triggered cycles with no luteal support, luteal phases ≤11 days were found in as many as 40% of patients, and luteal phase durations as short as 6 days were seen (Balasch et al., 1994a, 1995). In the present study only two patients (7.6%) in the GnRHa-treated group had short luteal phases (10 and 11 days, respectively) for an incidence similar to that found in group 2 (3.8%; one patient had a luteal phase duration of 10 days).

In conclusion, the present study shows that the luteal phase inadequacies reported previously by us and others following ovulation induction by GnRHa in gonadotrophin-stimulated cycles can be overcome by luteal support injections of HCG. It should be noted, however, that non-ovulated follicles after GnRHa injection may continue to grow and contribute to a multiple pregnancy if a patient is ovulating at the time of luteal HCG administration; 6 and 10 days after the GnRHa injection seems to be the appropriate time to give HCG doses to avoid additional luteal ovulations. Nevertheless, the exogenous HCG administered in the late luteal phase should be taken into account when early pregnancy diagnosis by means of urinary or serum HCG concentrations is considered. Therefore, further studies are necessary in order to establish whether this type of luteal support is better than vaginal progesterone in terms of adequate endometrial maturation, pregnancy rates and also the incidence of ovarian hyperstimulation syndrome.

References


J. Peñarrubia et al.


Received on April 21, 1998; accepted on September 11, 1998.