Induction of pre-ovulatory gonadotrophin surge with gonadotrophin-releasing hormone agonist compared to pre-ovulatory injection of human chorionic gonadotrophins for ovulation induction in intrauterine insemination treatment cycles

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The clinical outcome of intrauterine insemination (IUI) treatment cycles employing a gonadotrophin-releasing hormone agonist [GnRHa, triptorelin (Decapeptyl)] or human chorionic gonadotrophin (HCG) for ovulation induction was compared. A group of 48 patients presenting with amenorrhoea, oligomenorrhoea or unexplained infertility were all treated with human menopausal gonadotrophins (HMG) from day 5 of the cycle, on an individualized schedule. They were then randomly divided into two groups to receive either a single s.c. injection of 0.1 mg triptorelin or a single i.m. injection of 10 000 IU HCG after follicular maturation. IUI was performed ~ 24 and 48 h following the injection. A transitory increase in serum luteinizing hormone and follicle stimulating hormone concentrations was achieved following injection of GnRHa. A total of 24 patients received 72 treatment cycles with GnRHa, producing 11 conceptions (15.3%) and two abortions (18.2%), resulting in a term pregnancy rate of 13.6%. There were four cases of grade 3–4 ovarian hyperstimulation syndrome (OHSS), two of which were conception cycles. In all, 24 patients underwent 68 cycles treated with HCG, producing 18 conceptions (26.5%) and six abortions (33.3%), resulting in a term pregnancy rate of 19.0%. There were eight cycles of grade 3–4 OHSS, two of which were conception cycles. These results show that an s.c. injection of a relatively low dose of GnRHa can be as effective as HCG in producing pregnancy in IUI treatment cycles.

Key words: gonadotrophin-releasing hormone agonist/human chorionic gonadotrophin/intrauterine insemination/ovarian hyperstimulation syndrome/ovulation induction

Introduction
Human chorionic gonadotrophin (HCG) is routinely administered to trigger the final stages of follicular maturation in most ovulation induction cycles for infertility treatments because an endogenous luteinizing hormone (LH)/follicle stimulating hormone (FSH) surge is infrequent or attenuated in women treated with gonadotrophins (Itskovitz-Eldor et al., 1993). Although HCG is similar in action to LH, its administration does not induce the same physiological responses as the spontaneous LH surge. HCG has a much longer circulating half-life than LH (>24 h versus 1 h) and, therefore, a longer biological effect. In addition, HCG does not induce the FSH surge seen in spontaneous cycles (Moyle et al., 1975; Hoff et al., 1983).

Gonadotrophin-releasing hormone agonists (GnRHα) have been used successfully for triggering the LH/FSH surge in patients undergoing ovarian stimulation with gonadotrophins (Casper et al., 1980; Itskovitz et al., 1988; Gonen et al., 1990; Gerris et al., 1995). The use of a GnRHa may result in a more physiological response, similar to a spontaneous midcycle surge, with sustained release of both LH and FSH lasting for only several hours, depending on the dose administered (Itskovitz-Eldor et al., 1993). GnRHa has also been advocated for use in ovulation induction in women at risk for developing the ovarian hyperstimulation syndrome (OHSS) (Itskovitz et al., 1991; Shalev et al., 1994).

The purpose of this study was to compare hormonal responses, pregnancy and abortion rates and the occurrence of OHSS in patients treated by intrauterine insemination (IUI) who were randomized to receive either HCG or GnRHa during ovulation cycles stimulated by human menopausal gonadotrophin (HMG).

Materials and methods
Patients
A total of 48 infertile women were enrolled in the study. All of them were treated with ovulation induction because of amenorrhoea, oligomenorrhoea or unexplained infertility. All couples had previously undergone an infertility evaluation which included hormonal profiles, mechanical evaluation (hysterosalpingography, laparoscopy, or a combination of laparoscopy and hysteroscopy), semen analysis and post-coital tests. All inseminations used spermatozoa donated by the husband and were normozoospermic according to World Health Organization criteria (1992). All women were consulted concerning the possibility of multiple pregnancy due to ovulation induction protocols (in Israel, this is rarely a chief concern). Women at high risk of developing severe OHSS (>20 mature pre-ovulatory follicles and oestradiol concentrations >4000 pg/ml) were excluded from this protocol and referred for other treatments, e.g. cancellation of cycle, in-vitro fertilization (IVF), albumin treatment (Shalev et al., 1994).

Protocols
HMG (Pergonal: Teva, Israel) containing 75 IU FSH and 75 IU LH was used for ovarian stimulation. An individualized daily regimen was instituted starting on the fifth day of the cycle, after evaluation by transvaginal ultrasound to rule out ovarian cysts and serum samples for oestradiol, FSH, LH, thyroid-stimulating hormone (TSH), free thyroxine (FT4), prolactin and testosterone concentrations to rule out abnormalities. The follicular phase was monitored by daily
transvaginal ultrasound (Elscint 2000, Elscint, Israel) scanning of the ovaries starting on day 9, and measurements of serum oestradiol and progesterone concentrations.

A single s.c. injection of 0.1 mg triptorelin (Decapeptyl: Ferring, Sweden) or a single i.m. injection of 10 000 IU HCG (Chorigon: Teva, Israel) was administered when at least one follicle attained a diameter of 16 mm. IUI was performed 24 and 48 h after the injection. The spermatozoa were prepared by discontinuous Percoll gradient followed by washing the sperm pellet twice. A volume of 0.3–0.5 ml of the sperm suspension was placed high in the uterine cavity using a 2 ml syringe attached to a Tefcat catheter (Cook Ltd., Australia). The average number of motile spermatozoa inseminated on each day was 19×10^6/ml.

In GnRHa treated patients, the serum concentrations of FSH and LH were measured 12 h after the GnRHa was injected.

Early luteinization was ascertained by transvaginal ultrasound and high progesterone concentrations coupled with descending oestradiol concentrations prior to HCG or triptorelin administration. The luteal phase duration was measured in both groups by determining the number of days from 36–40 h after GnRHa or HCC administration until the next menses.

Patients were closely monitored for the symptoms of OHSS and these were graded according to the criteria of Schenker and Weinstein (1978).

Clinical pregnancy was determined by the presence of a gestational sac in the uterus by transvaginal ultrasound. A preclinical pregnancy was defined by the absence of a gestational sac following detection of a BHCG concentration >100 IU/l.

**Hormonal assays**

All serum hormone measurements were determined using commercially available radioimmunoassay kits: oestradiol and progesterone (Coat-A-Count: Diagnostic Products Corp., Los Angeles, CA, USA); LH and FSH (Amerlex M: Amersham International, Amersham, UK). The progesterone assay kit did not yield exact values above concentrations of 20 ng/ml.

**Statistical analysis**

All data were tested by χ² test applying the Yates correction and Fisher's exact test. The level of significance was set at P < 0.05.

**Results**

There were no significant differences between the treatment groups with regard to the number of primary or secondary infertility cases, the infertility diagnoses, the serum oestradiol concentration prior to ovulation induction, the number of pre-ovulatory follicles/cycle or the pregnancy outcome.

All patients who developed OHSS presented with more than eight pre-ovulatory follicles.

A total of 24 patients were treated with GnRHa for 72 cycles (Table I). Six treatment cycles were cancelled because of early luteinization. The progesterone concentration on day 9 following the injection of GnRHa was >10 ng/ml and the average luteal phase duration was 12.8 days (range 11–16 days).

All patients (66 cycles) showed a pituitary response detectable 12 h after injection of GnRHa. The mean LH concentration was 82 IU/l (range 64–118) and the mean FSH concentration was 32 IU/l (range 22–61).

Pregnancy resulted from 11 treatment cycles (15.3%), of which two were twin pregnancies. Two spontaneous abortions occurred early and nine babies were delivered at term (Table II). The term pregnancy rate was 13.6% (9/66 excluding cancelled cycles).

Two patients developed a grade 3-4 OHSS, each twice in two different treatment cycles (Table III). Their symptoms included abdominal swelling, pain, nausea, weight gain and severely enlarged ovaries (>10 cm in diameter). In no case did severe ascites, hypovolaemia or electrolyte imbalance occur. Two of the four OHSS cycles were conception cycles, and one of them was a twin pregnancy. Only the twin pregnancy proceeded to delivery.

In all, 24 patients received 68 treatment cycles using HCG for ovulation induction. Five cycles were cancelled due to early luteinization. The progesterone concentration on day 9 following the injection of HCG was >10 ng/ml and the average luteal phase duration was 13.1 days (range 11–16 days).

A total of 18 treatment cycles resulted in pregnancy (26.5%). Two of the pregnancies were preclinical only and another four ended early, spontaneous abortion, leaving 12 pregnancies which proceeded to term (19.0%; 12/63 excluding cancelled cycles; Table II).

Six women developed a grade 3–4 OHSS in eight treatment cycles. Two of the OHSS cycles resulted in pregnancy, of which one aborted and the second reached term (Table III).

**Discussion**

The results of this study demonstrate that a single s.c. injection of a relatively low dose of GnRHa can be as effective as HCG in inducing ovulation resulting in pregnancies after IUI treatment. Term pregnancy rates were 13.6% (GnRHa) and 19.0% (HCG) respectively, which was not significantly different.

The spontaneous, endogenous midcycle LH surge is delineated by a rapidly ascending phase (14 h), a plateau phase (14 h) and a long descending phase (20 h) (Hoff et al., 1983). Itskovitz et al. (1991) showed that 0.25 or 0.50 mg of buserelin induces an LH surge similar in magnitude to the natural LH surge, but defined by a short ascending phase (>4 h) and a
long descending phase (32 h). The same study showed that the GnRHa-induced FSH surge is similar in pattern and duration to that observed in the natural cycle. Our study shows that a single s.c. injection of 0.1 mg of triptorelin is also capable of inducing a transient increase in LH and FSH concentrations, although it is probable that we missed measuring the peak concentrations which would be expected to occur within 12 h of injection (Itskovitz et al., 1991). Another study which also induced ovulation with triptorelin used three interspersed injections of 0.1 mg each (Emperaire and Ruffie, 1991). The minimum effective dose of GnRHa is yet to be established (Itskovitz-Eldor et al., 1993).

Somewhat lower concentrations of progesterone in the luteal phase have been reported after ovulation induction with buserelin (Itskovitz et al., 1991; Andersen et al., 1993) or leuprolide acetate (Scott et al., 1994) compared to HCG. Our data show similarly high progesterone concentrations 9 days after induction and similar luteal phase duration, whether induction was produced by either HCG or triptorelin. Two other studies employing buserelin (Imoedemhe et al., 1991) and leuprolide acetate (Gonen et al., 1990) support this view. This discrepancy may be related to the use of different GnRH agonists and/or different dosages.

The adequacy of the luteal phase following the use of GnRHa for ovulation induction is debatable. Our data revealed no difference in pregnancy rate between the GnRHa and HCG groups. Several groups have reported the use of luteal phase support (Imoedemhe et al., 1991; Itskovitz et al., 1991; Segal and Casper, 1992) while others have not (Gonen et al., 1990; Tulchinsky et al., 1991; Corson et al., 1993; Scott et al., 1994). Even though progesterone concentrations after GnRHa may be reduced compared to those in HCG induced cycles, the clinical significance is questionable, since all the groups reported ongoing or term pregnancies following ovulation induction with either GnRHa or HCG.

The longer half-life of HCG can promote a sustained lutetrophic effect, with multiple corpora luteae and excessively high concentrations of oestradiol during the luteal phase. Certain patients with exaggerated sensitivity to gonadotrophin stimulation may be susceptible to OHSS, while excessive concentrations of serum oestradiol may be related to increased rates of implantation failure and early embryonic loss in stimulated cycles (Gidley-Baird et al., 1986; Forman et al., 1988; Itskovitz et al., 1991). Although our study showed a higher percentage of OHSS cases in the HCG stimulated group, this difference was not statistically significant. As might be expected, a positive correlation between the grade of OHSS and the number of mature preovulatory follicles and preovulatory oestradiol concentrations in both groups was detected. The clinical benefits of GnRHa in ovulation induction for women at risk of developing OHSS are well documented (Emperaire and Ruffie, 1991; Itskovitz et al., 1991; Shalev et al., 1994).

Most of the current studies employing GnRHa for ovulation induction were performed in IVF cycles. Four small non-IVF studies used 0.6 mg of buserelin (Lanzone et al., 1989); 1.0 mg (Tulchinsky et al., 1991) or 2.0 mg (Scott et al., 1994) of leuprolide acetate; or 0.5 mg of triptorelin (Shalev et al., 1994), all of which were effective in producing ovulation and pregnancy. This larger, prospective work attests to the efficacy of a single s.c. dose of 0.1 mg of triptorelin for ovulation induction in IUI treatment cycles. A low dose of GnRHa, similar to that used in this study, may not alter the pulsatile pattern of pituitary LH secretion during the luteal phase which is important for the proper formation of the corpus luteum (Hutchison et al., 1986).

Although this study and others support the potential for using GnRHa in place of HCG for ovulation induction, it should be noted that GnRHa will not be applicable in every situation, such as in pituitary failure or following the prior use of GnRHa for hormonal down-regulation (Tulchinsky et al., 1991). Further large scale studies will help determine the proper dosage and overall clinical effectiveness of GnRHa for ovulation induction.

### Table II. Clinical results of intrauterine insemination treatment in relation to ovulation induction by gonadotrophin-releasing hormone agonist (GnRHa, triptorelin) or human chorionic gonadotrophin (HCG)

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>No. of patients</th>
<th>No. of cycles</th>
<th>No. of cycles cancelled</th>
<th>Total no. of pregnancies</th>
<th>No. of abortions (%)</th>
<th>Pregnancy rate/cycle (%)</th>
<th>Pregnancy rate/completed cycle (%)</th>
<th>Term pregnancy rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GnRHa</td>
<td>24</td>
<td>72</td>
<td>6</td>
<td>11^a</td>
<td>2 (18.2)</td>
<td>15.3</td>
<td>16.7</td>
<td>13.6</td>
</tr>
<tr>
<td>HCG</td>
<td>24</td>
<td>68</td>
<td>5</td>
<td>18</td>
<td>6 (33.3)</td>
<td>26.5</td>
<td>28.6</td>
<td>19</td>
</tr>
</tbody>
</table>

^aTwo of the 11 pregnancies were twin pregnancies.

^bNo significant differences between treatment groups.

### Table III. Occurrence of ovarian hyperstimulation syndrome (OHSS) in relation to ovulation induction by a gonadotrophin-releasing hormone agonist (GnRHa, triptorelin) or human chorionic gonadotrophin (HCG)

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>No. of cycles</th>
<th>Grade 3-4 OHSS</th>
<th>No. of patients</th>
<th>No. of cycles</th>
<th>No. of pregnancies</th>
<th>No. of abortions</th>
</tr>
</thead>
<tbody>
<tr>
<td>GnRHa (triptorelin)</td>
<td>72</td>
<td>2</td>
<td>4 (5.6)^a</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>HCG</td>
<td>68</td>
<td>6</td>
<td>8 (11.8)^a</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

^aNot significantly different.


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