Induction of the endogenous gonadotrophin surge for oocyte maturation with intra-nasal gonadotrophin-releasing hormone analogue (buserelin): effective minimal dose

W.M.Buckett1,4, B.Bentick2 and R.W.Shaw3
1Clinical Fellow, McGill University Reproductive Centre, Royal Victoria Hospital, 687 Avenue des Pins Ouest, Montreal, Quebec H3A 1A1, Canada, 2Consultant Obstetrician and Gynaecologist, Royal Shrewsbury Hospital and 3Professor in Obstetrics and Gynaecology, University of Wales, Cardiff, UK
4To whom correspondence should be addressed

From 1985–1987, a total of 34 couples undergoing superovulation for a single in-vitro fertilization (IVF) cycle with clomiphene citrate and purified follicle stimulating hormone (FSH) or human menopausal gonadotrophin (HMG) were randomly allocated doses of intra-nasal buserelin to induce an endogenous gonadotrophin surge, prior to oocyte collection. The doses ranged from a single 25 µg dose to 100 µg every 4 h for 20 h. In three cycles the treatment was abandoned because of a poor ovarian response. In the remaining 31 cycles buserelin was given to induce the endogenous gonadotrophin surge, but there was evidence of premature luteinization in eight cycles and a premature gonadotrophin surge in four cycles. Although a single dose as low as 40 µg induced a surge and resulted in a pregnancy, a single dose of 50 µg proved the most effective minimal dose consistently to induce a gonadotrophin surge and oocyte maturation. Recent reports using gonadotrophin-releasing hormone (GnRH) analogues to induce a gonadotrophin surge has prompted publication of this previously unpublished data.

Key words: gonadotrophin-releasing hormone/gonadotrophin surge/oocyte maturation

Introduction

Human chorionic gonadotrophin (HCG) is usually used to trigger ovulation after ovarian stimulation (Schwartz and Jewelewicz, 1981) and for oocyte maturation prior to oocyte retrieval following superovulation in in-vitro fertilization (IVF) cycles (Steptoe and Edwards, 1970). HCG is used because it possesses the same β subunit as luteinizing hormone (LH) although the half-life at over 4 h (Conburnous, 1989) is considerably longer. It is also associated with luteotropic effects and ovarian hyperstimulation syndrome (OHSS) (Rizk and Aboulghar, 1991).

To reduce the risk of severe ovarian OHSS, several authors have used a gonadotrophin-releasing hormone analogue (GnRHa) to induce an endogenous gonadotrophin surge for oocyte maturation and ovulation (Lanzone et al., 1989; Bentick et al., 1990; Gonen et al., 1990; Itskovitz et al., 1991a; Emperaire, 1991; Imoedemhe et al., 1991; van der Meer et al., 1993; Gerris et al., 1996).

All reports have used different GnRHa, different doses, and different routes of administration. Intra-nasal buserelin has been used successfully at doses of between 100 µg twice over 8 h (Imoedemhe et al., 1991) and three doses of 200 µg over 20 h (van der Meer et al., 1993).

The purpose of this study was to determine the minimal effective intra-nasal dose of buserelin needed to induce an endogenous gonadotrophin surge prior to successful oocyte retrieval for in-vitro fertilization and embryo transfer.

Materials and methods

A total of 34 couples undergoing superovulation for IVF was enrolled into the study. All women had at least a 2 year history of primary or secondary infertility and were under 40 years of age. The diagnoses were either tubal disease, unexplained infertility, or male factor infertility. Local ethical committee approval was granted.

Superovulation regimes used clomiphene 150 mg daily (Clomid; Nordic, UK) from days 2–6 of the menstrual cycle and daily HMG (Pergonal; Serono, UK) or follicle-stimulating hormone (FSH) (Metrodin; Serono) (150–300 IU) from day 2, 3 or 5 of the cycle. Treatment was monitored with daily transvaginal ultrasound examination, serum oestradiol, serum progesterone, and serum LH from day 9 of the cycle. When three or more mature follicles (mean diameter >15 mm and lead follicle mean diameter >17 mm) were achieved intra-nasal GnRHa was administered 34 h prior to the oocyte retrieval. The treatment cycle was cancelled if less than three mature follicles were obtained or if the follicular growth was arrested.

Buserelin (d-Ser6-Ethylmide10-GnRH) 100 µg nasal spray (Suprefact®; Hoechst UK Ltd, Hounslow, UK) was diluted 1 in 4 and 1 in 10, so each actuation contained 25 µg and 10 µg buserelin respectively. Prior to superovulation, the women were randomly allocated to receive single intra-nasal dose of 25 µg (n = 5), 30 µg (n = 6), 40 µg (n = 5), 50 µg (n = 6), 100 µg (n = 7), or five doses of 100 µg 4 hourly over 20 h (n = 5).

Prior to oocyte retrieval three cycles were abandoned due to poor ovarian response. Retrospectively, in a further eight cycles there was evidence of premature luteinization as indicated by poor follicular growth by ultrason examination and rising serum progesterone (Hamori et al., 1987) and in four cycles there was an undiagnosed spontaneous premature gonadotrophin surge. Without using pituitary desensitization, 15 out of the initial 34 patients failed to go on to oocyte retrieval. A total of 19 patients with an adequate ovarian response and no evidence of premature gonadotrophin surge or premature luteinization underwent buserelin administration to obtain oocyte maturation prior to oocyte retrieval. Of these, two patients received a single 25 µg dose, three patients received a single 30 µg dose, four patients received a single 40 µg dose, three patients received a single 50 µg dose, five patients received a single 100 µg...
Table I. Mean age, serum oestradiol, serum progesterone, serum luteinizing hormone (LH), and serum follicle-stimulating hormone (FSH) before administration of the different doses of buserelin in the different groups

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Mean age (years)</th>
<th>Mean serum oestradiol (pmol/ml)</th>
<th>Mean serum progesterone (nmol/l)</th>
<th>Mean serum LH (IU/l)</th>
<th>Mean serum FSH (IU/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A (25 µg, n = 2)</td>
<td>32</td>
<td>3670</td>
<td>1.9</td>
<td>8.5</td>
<td>2.9</td>
</tr>
<tr>
<td>Group B (30 µg, n = 3)</td>
<td>35</td>
<td>292</td>
<td>0.9</td>
<td>8.4</td>
<td>6.3</td>
</tr>
<tr>
<td>Group C (40 µg, n = 4)</td>
<td>32</td>
<td>3414</td>
<td>1.0</td>
<td>4.0</td>
<td>4.3</td>
</tr>
<tr>
<td>Group D (50 µg, n = 3)</td>
<td>35</td>
<td>3607</td>
<td>1.4</td>
<td>5.7</td>
<td>6.5</td>
</tr>
<tr>
<td>Group E (100 µg, n = 5)</td>
<td>35</td>
<td>3437</td>
<td>1.8</td>
<td>6.2</td>
<td>4.3</td>
</tr>
<tr>
<td>Group F (100 µg × 5, n = 2)</td>
<td>33</td>
<td>3766</td>
<td>1.2</td>
<td>8.7</td>
<td>2.6</td>
</tr>
</tbody>
</table>

Blood was obtained and stored for subsequent serum LH and FSH assays immediately before administration of buserelin and 4 h, 8 h and 12 h thereafter. Serum LH, FSH, oestradiol and progesterone were also measured immediately prior to oocyte retrieval (34 h after buserelin administration).

Oocyte retrieval, embryo transfer, and laboratory procedures were as previously described (Shaw et al., 1987). Luteal phase support was with progesterone pessaries (Cyclogest®; Hoechst UK) 200 mg twice daily.

Statistical analysis

The pre-GnRHa hormone profiles (oestradiol, progesterone, LH, and FSH) were compared using the Kruskal–Wallis test for the comparison of multiple non-parametric continuous variables. Student’s unpaired t-test was used to compare LH and FSH levels within each group at pre-GnRHa, and at 4 and 8 h after administration.

Results

Patient characteristics

Of the 19 patients without a premature gonadotrophin surge and without premature luteinization who received GnRHa, the mean female age was 34 years (range 24–39 years). The diagnoses were tubal disease (n = 8), unexplained infertility (n = 6), and male factor infertility (n = 5). There were no significant differences between the six treatment groups and the superovulation protocols were not significantly different either. Pre-GnRHa levels of oestradiol, progesterone, LH, and FSH (Table I) were similar in all treatment groups (Kruskal–Wallis: T = 0.57, P = 0.98).

Endocrinology

An endogenous FSH (data not shown) and LH (Figure 1) surge was induced in all patients receiving a single dose of
50 µg intra-nasal buserelin (Group D, \( n = 3 \)), a single dose of 100 µg intra-nasal buserelin (Group E, \( n = 5 \)), and five doses of 100 µg intra-nasal buserelin over 20 h (every 4 h) (Group F, \( n = 2 \)). There was a positive correlation between the buserelin dose and the mean LH peak value, although this was not significant \((P > 0.05)\). There was also a rise in the serum progesterone (data not shown) in all patients in these treatment groups.

An endogenous FSH (data not shown) and LH (Figure 2) surge was induced in one patient receiving a single 25 µg dose (Group A) but not in the second. Similarly, only one patient out of three in the single 30 µg group (Group B) and two patients out of four in the single 40 µg group (Group C) had a gonadotrophin surge. The upper limit for detection of both the LH and the FSH assay was 100 IU/l. The FSH surge mimicked the LH surge and was smaller in all cases.

**Oocyte retrieval and embryo transfer**

From the treatment groups in which an endogenous gonadotrophin surge did not always occur, no oocytes were retrieved in four of the nine patients. Although oocytes were retrieved and fertilized in one patient on the lowest dose of GnRHa who had no apparent induced gonadotrophin surge, this may have been an unmonitored spontaneous surge. A maximum of three embryos were transferred.

Overall, three pregnancies were achieved, two in Group D (50 µg)(one live birth of twins, one biochemical pregnancy) and one in a patient in Group C (40 µg) who had an endogenous gonadotrophin surge.

**Discussion**

While we recognize that the number of individuals in each group is very small, our results suggest that a minimum dose of a single 50 µg intra-nasal actuation of buserelin may be able to induce an endogenous gonadotrophin surge following superovulation for in-vitro fertilization. Smaller doses only occasionally induced such surges, which may have been secondary to a spontaneous surge triggered by the rising serum oestradiol (Messinis and Templeton, 1986; Kreiner et al., 1988).

Following the first reports of the use of GnRHa for follicular maturation in IVF (Gonen et al., 1990) and to trigger ovulation (Lanzone et al., 1989) it was hoped that by substituting HCG with GnRHa, it would be possible to avoid the development of severe OHSS in patients at risk of this complication (Imoedemhe et al., 1991a). However, subsequent reports showed that substitution of HCG with GnRHa did not completely prevent OHSS (Bentick et al., 1990; van der Meer et al., 1993) although the severity may be less in non-HCG triggered cycles (Gerris et al., 1995).

The use of GnRHa, rather than HCG, to trigger ovulation in ovulation induction cycles or in association with the ovarian stimulation and intrauterine insemination is still a useful alternative in cases at risk of OHSS. In these patients doses as low as a single dose of 50 µg intra-nasal buserelin should be used. Initial attempts using GnRHa to trigger ovulation in non-IVF treatments have used higher doses of GnRHa (Lanzone et al., 1989; Tulchinsky et al., 1991; Shalev et al., 1994; Scott et al., 1994), but our results support the subsequent findings that with other GnRHa lower doses can trigger ovulation (Shalev et al., 1995). Although there may be less impairment of luteal function using a smaller dose it would still be prudent to use luteal progestosterone support (Gerris et al., 1996).

Obviously, the use of this method in IVF cycles at risk of severe OHSS is only relevant where there has not been previous desensitization with GnRHa (Porter et al., 1984; Smitz et al., 1987) which would render follicular maturation impossible. Although a comparison of GnRHa versus HCG has suggested higher oocyte yield and quality (Imoedemhe et al., 1991b), most centres offering IVF–embryo transfer now use GnRHa to desensitize the pituitary prior to ovarian stimulation. While assessment of pituitary desensitization was not one of the primary outcomes of this study, the data confirm that where pituitary desensitization is not used a high number do not go on to oocyte retrieval (15 out of the initial 34 women in this study). Nevertheless, the data regarding the minimal effective dose in this study remains of importance in non-IVF–embryo transfer ovulation induction.

In patients who have had pituitary suppression with GnRHa prior to superovulation regimens, and in whom it would not be possible to induce an endogenous surge of gonadotrophins, recombinant LH (Emperaire, 1994) rather than HCG could be used to avoid severe OHSS and possibly improve oocyte yield, although findings from comparative studies are awaited.

**References**


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W.M.Buckett et al.

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