Levonorgestrel-releasing intrauterine device can be used in oocyte donors during ovarian stimulation

V. Söderström-Anttila, A. Tiitinen and O. Hovatta

1 Department of Obstetrics and Gynaecology, University Central Hospital of Helsinki, Haartmaninkatu 2, FIN-00290 and 2 Infertility Clinic, The Family Federation of Finland, Helsinki, Finland

To whom correspondence should be addressed

Seven oocyte donors with a levonorgestrel-releasing intrauterine device (LNG–IUD) in situ (group A) underwent ovarian stimulation with human menopausal gonadotrophin (HMG) after goserelin down-regulation, in eight treatment cycles. The donors in a control group (group B, n = 16) were comparable in age, body mass index and parity characteristics. There were no statistically significant differences in response to ovarian hyperstimulation between the two groups. The number of oocytes recovered was 12.4 ± 5.1 (SD) following stimulation with 27.9 ± 9.3 ampoules of HMG over 11.2 ± 1.3 days in group A. Following stimulation with 26.2 ± 6.3 ampoules of HMG over 11.0 ± 1.0 days, the number of oocytes collected was 13.9 ± 10.4 in group B. The fertilization rate (2PN/cell) of cells in group A was 63% (62/99) and in group B, 53% (117/220, not significant). The cleavage rate of cells in group A was 63% (62/99) and in group B, 53% (117/220, not significant). On average, two embryos were transferred per cycle. In group A, the pregnancy rate per transfer was 40% (4/10) and in group B, 29% (6/21; not significant). In conclusion, LNG–IUD can be used as a contraceptive method during ovarian stimulation of volunteer oocyte donors.

Key words: contraception/fertilization/levonorgestrel-releasing IUD/oocyte donor/ovulation stimulation

Introduction

Oocyte donation has been carried out in Finland since the early 1990s. Mostly the oocytes are retrieved from young (aged < 35 years) fertile women unknown to the recipient couple. This treatment is associated with many ethical problems (Robertson, 1989; Abdalla, 1994), as well as complications (Sauer and Paulson, 1994). One of these is the occurrence of unintentional pregnancies, which has been reported to happen during the treatment cycle (Sauer and Paulson, 1994). Hence, these fertile women need an effective contraceptive during the treatment.

Whether or not a hormonal contraceptive, the levonorgestrel-releasing intrauterine device (LNG–IUD) (Levonova®; Leiras Pharmaceutical, Turku, Finland), disturbs follicular development in oocyte donors, or alters the capacity of the oocytes to be fertilized, is a question thus far unanswered. This device releases levonorgestrel (LNG) into the uterine cavity at a rate of 20 µg/24 h for at least 5 years (Luukkainen, 1991). Mean plasma LNG concentrations in LNG–IUD users have ranged between 100–200 pg/ml over a 6 year observation period (Luukkainen et al., 1990). Several mechanisms account for the contraceptive mode of action of the LNG–IUD. The main findings are prevention of endometrial proliferation (Silverberg et al., 1986), and thickening of the cervical mucus (Barbosa et al., 1990). Direct effects on sperm maturation and the process of fertilization cannot be ruled out (Luukkainen et al., 1990; Rybo et al., 1993). Suppression of ovarian function (55% anovulatory cycles) has been shown during the first year of use (Xiao et al., 1990). Later on, the majority of women have ovulatory cycles, according to their circulating progesterone concentrations (Nilsson et al., 1984; Scholten et al., 1989). However, despite ovulatory progesterone levels, a high frequency of abnormal follicular growth and rupture has been recognized (Barbosa et al., 1995). We therefore investigated whether exposure of oocytes to LNG, as occurs with a LNG–IUD in situ during donor cycles, affects the treatment outcome in comparison with that of a control group of oocyte donors.

Materials and methods

Donors

Between 1992 and 1995, seven oocyte donors (group A) who had a LNG–IUD in situ underwent ovarian stimulation in a total of eight treatment cycles, with the purpose of donating all oocytes. Five of these treatments were carried out anonymously at the Infertility Clinic of the Family Federation of Finland (Helsinki, Finland). Three cycles, in which the recipient was known, were carried out at the University Central Hospital of Helsinki (Helsinki, Finland). The characteristics of these donors are presented in Table I. Every donor had at least one child. The LNG–IUD had been inserted 2–36 (mean 15) months (Table V) before the treatment cycle and all donors had regular menstrual cycles (26–30 days).

To compare the results of the study group with those of our oocyte donation programme in general, a control group was chosen (group B, n = 16). For every group A donor, we took the occurrence of unintentional pregnancies, which has been reported to happen during the treatment cycle (Sauer and Paulson, 1994). Hence, these fertile women need an effective contraceptive during the treatment. For every group A donor, we took the immediately preceding and following donors on the clinic’s oocyte donation list. Of these donors, 10 had no contraceptive method or used condoms, four had recently discontinued contraceptive pills and two had a copper IUD. Counselling was provided on the need to use barrier contraceptive methods during the treatment. All control donors had regular menstrual cycles (26–32 days).

Treatment protocols were similar in both centres. All donors underwent pituitary down-regulation with a long-acting gonado-
Table I. Characteristics of oocyte donors. Values are means ± SD

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of donors</td>
<td>8</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>30.4 ± 5.1</td>
<td>29.8 ± 5.1</td>
<td>NS</td>
</tr>
<tr>
<td>Body mass index</td>
<td>21.7 ± 2.7</td>
<td>23.2 ± 3.9</td>
<td>NS</td>
</tr>
<tr>
<td>No. of deliveries</td>
<td>1.9 ± 0.6</td>
<td>1.6 ± 1.0</td>
<td>NS</td>
</tr>
<tr>
<td>No. of miscarriages</td>
<td>0.4 ± 0.5</td>
<td>0.5 ± 0.8</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS = not significant.

trophin-releasing hormone agonist (GnRHa), goserelin acetate (Zoladex®; Zeneca Pharma, Helsinki, Finland).

When suppression was achieved (no follicles >6mm and thin endometrium by ultrasound), follicular development was induced with human menopausal gonadotrophin (HMG, Pergonal®; Serono, Aubonne, Switzerland). In group A, the HMG dose for the first 6 days was 150 IU in six cycles and 225 IU in two cycles. In group B, the starting dose was 150 IU in 13 cycles and 225 IU in three cycles. Thereafter, the dose was adjusted according to follicular development as assessed by ultrasound scanning. When the leading follicle was 18 mm and there were at least three growing follicles, 5000–10 000 IU of human chorionic gonadotrophin (Profasi®; Serono or Pregnyl®; Organon, Oss, Netherlands) was given i.m. to induce ovulation. Oocyte retrieval was carried out under vaginal ultrasonic guidance and all follicles ≥8 mm were retrieved.

Recipients

The oocytes obtained from any one donor were allocated to one, two or three recipient couples. The mean age of the study group recipients (group A recipients; n = 12) was 33.9 ± 3.6 (SD) years and of control group recipients (group B recipients; n = 24) it was 31.7 ± 5.4 years (not significant). In both groups, 67% of the recipients had ovarian failure (8/12 in group A and 16/24 in group B) and 33% had functioning ovaries. Hormone replacement therapy was carried out as described earlier (Söderström-Anttila and Hovatta, 1995). The male partners in both groups had normal sperm counts, defined by >20×10⁶ spermatozoa/ml, progressive motility >40% and normal morphology >30%. The fertilization procedure was carried out as described earlier (Söderström-Anttila et al., 1996). Embryos were graded at the 2–4-cell stage according to the criteria set out by Scott et al. (1991).

Statistical analysis

Student’s t-test was used to compare the characteristics of the donors and the recipients in the two groups and to compare efficacy data concerning ovarian stimulation. The G-test (Sokal and Rohlf, 1995) was used to compare the fertilization and pregnancy rates and the proportion of embryos of different grades between the two groups. The level of significance was set at P <0.05.

Results

There were no statistically significant differences in the main efficacy parameters of the donors’ treatment cycles (Table II). No cycle was cancelled in either group. One donor in group A developed moderate hyperstimulation syndrome (OHSS) and two group B donors had symptoms of mild OHSS. Tables III and IV show the outcome of in-vitro fertilization (IVF). There was no clear difference in fertilization rate of the oocytes from individual donors with varying length of use of LNG–IUD (Table V). The recipient couples were allocated a mean of 8.2 oocytes each (range 4–15) in group A and a mean of 9.2 oocytes (range 3–31) in group B. On average, two embryos were transferred per recipient, in both groups. Because of insufficient endometrial preparation, all embryos were cryopreserved for later transfer in two cycles, in both groups. In group B recipients, no fertilization occurred in one cycle. Of 10 embryo transfers in group A recipients, four clinical pregnancies started (one pair of twins and three singletons). Four healthy infants have been born and one pregnancy had to be interrupted because of brain malformation in the fetus. Six clinical pregnancies (one triplet and five singletons) started in the control group following 21 embryo transfers. Of these, seven healthy children have been born and one ended in spontaneous abortion.

Discussion

In this study, we investigated whether or not a LNG–IUD disturbs follicular maturation in oocyte donors during long GnRH–HMG ovarian stimulation. Our two donor groups were comparable in age, body mass index and parity characteristics. As regards contraceptive methods in the control group, four donors had recently discontinued using contraceptive pills, but thereafter had spontaneous ovulatory cycles. Two control donors with a copper-IUD were not excluded, as this IUD has been shown to be free from systemic steroidal effects (Sivin and Stern, 1994). In recent years there has been a tendency towards simplification of
Levonorgestrel-releasing IUD in oocyte donors

Table IV. In-vitro fertilization outcome in recipients obtaining oocytes from women using a levonorgestrel-releasing intrauterine device (group A recipients) and controls (group B recipients). Values are means ± SD

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of recipients</td>
<td>12</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Oocytes per recipient</td>
<td>8.2 ± 3.7</td>
<td>9.2 ± 5.8</td>
<td>NS</td>
</tr>
<tr>
<td>Fertilized cells (2PN) per recipient</td>
<td>5.2 ± 2.6</td>
<td>4.9 ± 4.8</td>
<td>NS</td>
</tr>
<tr>
<td>Cleaved cells per recipient</td>
<td>4.9 ± 2.6</td>
<td>4.3 ± 4.2</td>
<td>NS</td>
</tr>
<tr>
<td>No. of transferred embryos per recipient</td>
<td>2.0 ± 0.7</td>
<td>2.0 ± 0.5</td>
<td>NS</td>
</tr>
<tr>
<td>Pregnancy rate per embryo transfer (%)</td>
<td>2.2 ± 7.6</td>
<td>2.4 ± 4.1</td>
<td>NS</td>
</tr>
<tr>
<td>Pregnancy rate per started cycle (%)</td>
<td>33 (4/12)</td>
<td>25 (6/24)</td>
<td>NS</td>
</tr>
<tr>
<td>Implantation rate (%)</td>
<td>25 (5/20)</td>
<td>20 (8/41)</td>
<td></td>
</tr>
</tbody>
</table>

2 PN = two pronuclear; NS = not significant.

Table V. Data on the individual donors with levonorgestrel-releasing intrauterine device (LNG–IUD)

<table>
<thead>
<tr>
<th>Donor no.</th>
<th>Age (years)</th>
<th>Length of time (months) the LNG–IUD had been in use</th>
<th>Fertilization rate (2PN/cell)</th>
<th>No. of recipients for embryo transfer</th>
<th>No. of pregnancies</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>24</td>
<td>2</td>
<td>65 (13/20)</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>II</td>
<td>23</td>
<td>3</td>
<td>60 (9/15)</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>III</td>
<td>28</td>
<td>6</td>
<td>63 (5/8)</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>IV</td>
<td>31</td>
<td>16</td>
<td>43 (3/7)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>V</td>
<td>33</td>
<td>18</td>
<td>86 (12/14)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>VIa</td>
<td>33</td>
<td>15</td>
<td>40 (6/15)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>VIb</td>
<td>33</td>
<td>22</td>
<td>73 (11/15)</td>
<td>0b</td>
<td>0</td>
</tr>
<tr>
<td>VII</td>
<td>38</td>
<td>36</td>
<td>60 (3/5)</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

a Donor VI was stimulated twice.
b No fresh transfer because of insufficient endometrial preparation.

the performance of the IVF procedure (Wikland et al., 1994). In our oocyte programme, we have reduced visits to the clinic to a minimum and serum oestradiol measurement has been carried out only when regarded as necessary. Thus, we were unable to compare circulating oestradiol and progesterone concentrations in our two groups.

In LNG–IUD users, plasma concentrations of LNG (100–200 pg/ml) have been shown to have only occasional and weak effects on ovarian function; after the first year of use, 85% of all menstrual cycles are ovulatory, as reflected in circulating progesterone concentrations (Nilsson et al., 1984; Scholten et al., 1989). However, despite ovulatory progesterone concentrations, Barbosa et al. (1995) detected a great number of disturbances of follicular maturation in LNG–IUD users. In addition, this contraceptive method is associated with an increased incidence of functional ovarian cysts (Robinson et al., 1989; Sivin and Stern, 1994), which may reflect a disturbing effect on ovarian function. Furthermore, elevated circulating progesterone concentrations in the early follicular phase have been suggested to impair follicular recruitment (Sims et al., 1994). On the other hand, in women under continuous low-dose progesterone administration, the duration of the functional life-span of the anovulatory follicle did not differ from that of a normal follicle/corpus luteum unit (Fauth et al., 1996). We found that following HMG stimulation, and in connection with goserelin, the number of developing follicles and retrieved oocytes was the same in women with a LNG–IUD as in the control group. The numbers also compared well with our earlier results (Söderström-Anttila et al., 1996). Neither were there more empty follicles or functional cysts in the study group than in the control group. It has been shown that plasma concentrations of LNG are highest during the first year after IUD insertion and decline thereafter (Luukkainen et al., 1996). Neither were there more empty follicles or functional cysts in the study group than in the control group. It has been shown that plasma concentrations of LNG are highest during the first year after IUD insertion and decline thereafter (Luukkainen et al., 1996). Neither were there more empty follicles or functional cysts in the study group than in the control group. It has been shown that plasma concentrations of LNG are highest during the first year after IUD insertion and decline thereafter (Luukkainen et al., 1996). Neither were there more empty follicles or functional cysts in the study group than in the control group. It has been shown that plasma concentrations of LNG are highest during the first year after IUD insertion and decline thereafter (Luukkainen et al., 1996). Neither were there more empty follicles or functional cysts in the study group than in the control group. It has been shown that plasma concentrations of LNG are highest during the first year after IUD insertion and decline thereafter (Luukkainen et al., 1996). Neither were there more empty follicles or functional cysts in the study group than in the control group. It has been shown that plasma concentrations of LNG are highest during the first year after IUD insertion and decline thereafter (Luukkainen et al., 1996). Neither were there more empty follicles or functional cysts in the study group than in the control group. It has been shown that plasma concentrations of LNG are highest during the first year after IUD insertion and decline thereafter (Luukkainen et al., 1996). Neither were there more empty follicles or functional cysts in the study group than in the control group. It has been shown that plasma concentrations of LNG are highest during the first year after IUD insertion and decline thereafter (Luukkainen et al., 1996). Neither were there more empty follicles or functional cysts in the study group than in the control group. It has been shown that plasma concentrations of LNG are highest during the first year after IUD insertion and decline thereafter (Luukkainen et al., 1996). Neither were there more empty follicles or functional cysts in the study group than in the control group. It has been shown that plasma concentrations of LNG are highest during the first year after IUD insertion and decline thereafter (Luukkainen et al., 1996). Neither were there more empty follicles or functional cysts in the study group than in the control group. It has been shown that plasma concentrations of LNG are highest during the first year after IUD insertion and decline thereafter (Luukkainen et al., 1996). Neither were there more empty follicles or functional cysts in the study group than in the control group. It has been shown that plasma concentrations of LNG are highest during the first year after IUD insertion and decline thereafter (Luukkainen et al., 1996). Neither were there more empty follicles or functional cysts in the study group than in the control group. It has been shown that plasma concentrations of LNG are highest during the first year after IUD insertion and decline thereafter (Luukkainen et al., 1996). Neither were there more empty follicles or functional cysts in the study group than in the control group. It has been shown that plasma concentrations of LNG are highest during the first year after IUD insertion and decline thereafter (Luukkainen et al., 1996). Neither were there more empty follicles or functional cysts in the study group than in the control group. It has been shown that plasma concentrations of LNG are highest during the first year after IUD insertion and decline thereafter (Luukkainen et al., 1996). Neither were there more empty follicles or functional cysts in the study group than in the control group. It has been shown that plasma concentrations of LNG are highest during the first year after IUD insertion and decline thereafter (Luukkainen et al., 1996). Neither were there more empty follicles or functional cysts in the study group than in the control group. It has been shown that plasma concentrations of LNG are highest during the first year after IUD insertion and decline thereafter (Luukkainen et al., 1996). Neither were there more empty follicles or functional cysts in the study group than in the control group. It has been shown that plasma concentrations of LNG are highest during the first year after IUD insertion and decline thereafter (Luukkainen et al., 1996). Neither were there more empty follicles or functional cysts in the study group than in the control group. It has been shown that plasma concentrations of LNG are highest during the first year after IUD insertion and decline thereafter (Luukkainen et al., 1996). Neither were there more empty follicles or functional cysts in the study group than in the control group. It has been shown that plasma concentrations of LNG are highest during the first year after IUD insertion and decline thereafter (Luukkainen et al., 1996). Neither were there more empty follicles or functional cysts in the study group than in the control group. It has been shown that plasma concentrations of LNG are highest during the first year after IUD insertion and decline thereafter (Luukkainen et al., 1996).
control group. An explanation for this increased cleaving capacity is difficult to give. Unfortunately, no serum LNG measurements had been carried out during the treatment cycles. However, results of experiments with animals bearing subdermal implants of LNG are consistent with our results. When mice were subjected to injections of gonadotrophins to stimulate ovulation, LNG exposure had no adverse effect on fertilization or embryonic development; in some cases it actually increased the proportion of fertilized oocytes (Shirley and Bundren, 1995). As regards the effect of high endogenous progesterone on the fertilization rate, the literature is conflicting. Some investigators have reported reduced fertilization rates in association with a subtle rise in progesterone concentrations before HCG administration (Mio et al., 1992; Yovel et al., 1995). In several studies, no relationship between a premature increase in serum progesterone and fertilization has been found (Hofmann et al., 1993; Check et al., 1994; Silverberg et al., 1994; Bustillo et al., 1995), which is in accordance with our experience with LNG. Elevated progesterone concentrations have also been associated with polyspermic fertilization (Edwards, 1985). In our study group of patients, there was no increase in the incidence of polyspermy.

In this study, all LNG–IUD donors had regular menstrual cycles. In general, 11% of LNG–IUD users develop amenorrhea as a result of strong suppression of the endometrium (Nilsson et al., 1982). The menstrual bleeding pattern in LNG–IUD users does not, however, predict the level of ovarian function. In amenorrheic women the mean mid-luteal progesterone and oestradiol concentrations are mostly at ovulatory volumes (Nilsson et al., 1984). In copper IUD users, the circulating concentration of placental protein 14 has been shown to be substantially lower than in controls (Sellem et al., 1996). Whether in LNG–IUD users the strong suppression of the functional endometrium, with alterations in secretion of various growth factors, has an impact at the follicle or oocyte level, is unclear.

Young fertile oocyte donors should be counselled as regards the increased risk of becoming pregnant during the ovulation stimulation. Although we have no information on unintentional pregnancies among our oocyte donors, many of them have been concerned about this risk. In summary, oocyte donors with LNG–IUD responded similarly to Scott, R.T., Hofmann, G.E., Veeck, L.L. and Nick Bolton for revising the text. The study was supported by grants from Finska Läkaresällskapet and Svenska Kulturfonden in Finland.

Acknowledgements

We would like to thank Helena Korpelainen for statistical assistance and Nick Bolton for revising the text. The study was supported by grants from Finska Läkaresällskapet and Svenska Kulturfonden in Finland.

References


Levonorgestrel-releasing IUD in oocyte donors


*Received on July 19, 1996; accepted on December 18, 1996*