Profound LH suppression after GnRH antagonist administration is associated with a significantly higher ongoing pregnancy rate in IVF


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BACKGROUND: The significance of suppressed LH levels in GnRH antagonist cycles for IVF outcome is currently unknown. The purpose of this study was to evaluate prospectively the association between LH levels and ongoing pregnancy achievement after GnRH antagonist initiation in IVF cycles. METHODS: Ovarian stimulation with a fixed dose of 200 IU recombinant FSH and daily GnRH antagonist (ganirelix) 0.25 mg from day 6 of stimulation was initiated in 116 women. Patients were not pretreated with an oral contraceptive. Induction of final oocyte maturation was performed with HCG 10 000 IU as soon as three follicles of ≥ 17 mm were present in ultrasound, and was followed by oocyte pick-up, conventional IVF or ICSI, and embryo transfer. The luteal phase was supplemented with vaginal progesterone. RESULTS: A significant decrease of both ongoing pregnancy rate and implantation rate was present across groups of patients with increasing LH levels. The highest implantation rate and ongoing pregnancy rate was present in those patients with LH levels on day 8 of stimulation ≤ 0.5 IU/L. CONCLUSIONS: Profound suppression of LH on day 8 of stimulation is associated with a significantly higher chance of achieving an ongoing pregnancy. More studies are necessary to evaluate this phenomenon further.

Key words: GnRH antagonists/luteinizing hormone/ovarian stimulation/recombinant FSH

Introduction

The association between LH levels and achievement of pregnancy has attracted much attention both before and after introduction of GnRH analogues in assisted reproductive technologies (ART) (Stanger and Yovich, 1985; Howles et al., 1987; Fleming et al., 1998; 2000; Rekha et al., 1998). Deep suppression of LH by GnRH agonists has been associated with an adverse reproductive outcome (Westergaard et al., 2000; Esposito et al., 2001; Coppola et al., 2003). Although this association is not universally accepted (Lounaye et al., 1997; Balasch et al., 2001), the potential benefit from LH supplementation (in the form of recombinant LH or by using gonadotrophin preparations containing both LH and FSH) has remained in the focus of interest (Daya et al., 1995; Hull et al., 1995; Westergaard et al., 1996; Levy et al., 2000).

LH supplementation has in addition been considered as worth evaluating in GnRH antagonist cycles (Noyes et al., 2002; van Loenen et al., 2003; Cedrin Durnerin et al., 2003; Ludwig et al., 2002). Besides extrapolation from data available for GnRH agonists, this may also be attributed to the low pregnancy rates observed under very high antagonist doses, which result in very low LH levels (Ganirelix Dose-finding Study Group, 1998). It should be noted, however, that no information is available on the association between LH levels in the mid-follicular phase and IVF outcome, when the usual dose of GnRH antagonists is employed to inhibit premature LH surge.

Steady-state levels of ganirelix are reached after 2 days of treatment (Oberye et al., 1999). In a classical daily antagonist protocol in which antagonist is initiated on day 6 of stimulation, this means day 8 of stimulation. At that time, if profound suppression of LH is associated with a low pregnancy rate, there is still time to evaluate the concept of adding LH support in the form of urinary gonadotrophin or recombinant LH to improve the probability of pregnancy.

The purpose of this study was to evaluate prospectively the association between achievement of ongoing pregnancy and LH levels on day 8 of stimulation after GnRH antagonist initiation in patients treated by IVF.

Materials and methods

Patient population

One hundred and sixteen patients treated by IVF at the Centre for Reproductive Medicine of the Dutch-Speaking Brussels Free University from May 2002 until June 2003 were included in the study. Inclusion criteria were age < 39 years, body mass index...
Ohmic and estrogen (E2) levels were measured by means of the automated Elecsys Immunoanalyzer (Roche Diagnostics, Mannheim, Germany). Intra- and inter-assay coefficients of variation were <3% and <4% for LH, <3% and <6% for FSH, <5% and <7% for HCG, <5% and <10% for E2, and <3% and <5% for progesterone, respectively. The inter-assay coefficient of variation for LH at 0.4 IU/l is 6.6% and at 1.0 IU/l is 2.7%.

Ultrasound assessment

Ultrasound was performed on day 6 of stimulation and thereafter as necessary in order to ensure that HCG was injected on the first day that the patient had three or more follicles of ≥17 mm. For that purpose, a follicular growth of 2 mm per day was assumed to be present.

Outcome measures

Pregnancies progressing beyond the 12th week of gestation were considered to be ongoing. Ongoing implantation rate was calculated by dividing the number of gestational sacs with fetal heart beat present at 12 weeks of gestation by the number of embryos transferred.

Statistical analysis

Power analysis. No data were available in GnRH antagonist cycles to estimate accurately sample size for the present study, and the power analysis was based on the assumption that pregnancy rates would be higher (50%) in the middle LH group, and lower (20%) pregnancy rates would be observed in the low and high LH groups. Power analysis showed that a sample size of 102 patients achieves 80% power to detect an effect size W of 0.308 using a 2 degrees of freedom χ²-test with a significance level (α) of 0.05. Statistical tests. Groups of patients were defined by Tukey’s Hinges percentile analysis of LH levels on day 8 of stimulation. Normally distributed (Kolmogorov–Smirnov test with Lilliefors correction) metric variables were compared across groups of LH by one-way analysis of variance, while non-normally distributed metric variables were compared by Kruskal–Wallis analysis of variance. The association between achievement of pregnancy and LH levels on day 8 of stimulation was examined using the exact χ² for trend test. In addition, the effect of LH level on day 8 of stimulation on ongoing pregnancy achievement after oocyte retrieval was examined by robust logistic regression. Independent covariables were the age of the patient, the FSH level at initiation of stimulation and the number of previous ART trials.

All tests were two-tailed with a confidence level of 95% (P < 0.05). Values are expressed as mean ± standard error.

Results

Patient and stimulation characteristics

The mean age of the patients included in the study was 32.2 ± 0.3 years. Patients had performed a mean of 1.1 ± 0.2 previous IVF/ICSI trials, and the mean FSH at initiation of stimulation was 7.4 ± 0.2 IU/l. The majority of the couples were being treated for andrological infertility (64.7%), 12.1% for tubal infertility and 5.2% for combination of tubal and andrological infertility. In 18.1% of couples no reason for infertility could be identified (unexplained infertility).

The mean duration of FSH stimulation was 9.1 ± 0.1 days, and the mean total units of rFSH used was 1836 ± 31 IU. Of the 116 patients who reached oocyte retrieval, 11 did not have embryo transfer. In two patients this was due to the risk of developing ovarian hyperstimulation syndrome, and in the remaining patients was due to fertilization failure (n = 7), embryonic developmental arrest in culture (n = 1) or poor oocyte quality (n = 1). A mean of 12.1 ± 0.7 cumulus–oocyte complexes (COCs) were retrieved, and following fertilization a mean of 6.8 ± 0.4 2PN oocytes were available (fertilization rate 57.2 ± 2.3%). A mean of 1.9 ± 0.1 embryos were transferred per patient, resulting in...
a 25.5% ongoing implantation rate. Ongoing pregnancy rate per oocyte retrieval was 39.7%.

Association between LH levels on day 8 of stimulation and achievement of ongoing pregnancy after oocyte retrieval

The distribution of LH levels on day 8 is shown in Figure 1. LH levels of < 1 IU/l were present in 54% of the patients studied, while in 21.6% of patients LH levels were ≤ 0.5 IU/l. In Table I, baseline characteristics in three groups of patients defined according to Tukey’s Hinges percentile analysis of LH levels on day 8 of stimulation (group 1, 0–25th percentile; group 2, 25–75th percentile; and group 3, 75–100th percentile) are shown. No differences were present between the three groups of patients in terms of BMI, indication of treatment and female age. However, significant differences were observed between the three groups in baseline values of FSH and LH at initiation of stimulation. LH levels on day 1 and on day 8 of stimulation are shown in Figure 2 for each of the above groups of LH on day 8.

Table II shows stimulation characteristics and embryological data in the three groups of LH on day 8 of stimulation. Significant differences were present in LH levels on the day of HCG administration, in the number of follicles of 15–16 mm on the day of HCG, and in the number of COCs retrieved and 2PN oocytes available. No differences were observed between groups of patients defined according to LH levels on day 8 of stimulation in terms of fertilization rates, the number and quality of the embryos transferred, the quality of the embryos cryopreserved, or the type of embryo transfer performed.

A significant decrease of both ongoing pregnancy rate and implantation rate was seen across groups of patients with increasing LH levels, defined according to Tukey’s Hinges percentile analysis of LH values on day 8 of stimulation (Table III). The highest implantation rate and ongoing pregnancy rate was present in those patients with LH levels on day 8 of stimulation between 0.1 and 0.5 IU/l.

Robust logistic regression with dependent variable being the achievement of ongoing pregnancy after oocyte retrieval and independent variables being the age of the patient, the level of FSH at initiation of stimulation, the number of previous ART trials and LH levels on day 8 of stimulation, is shown in Table IV. A significant effect on the achievement of ongoing pregnancy after oocyte retrieval was observed for LH levels on day 8 of stimulation (odds ratio 0.61). The higher the levels of LH on day 8 of stimulation, the lower the probability of achieving an ongoing pregnancy after oocyte retrieval.

Discussion

The question the present study aimed to answer was whether the LH levels on day 8 are associated with ongoing pregnancy achievement. If a negative association was present between LH levels 2 days after antagonist administration and ongoing pregnancy, then a threshold of LH could be defined. This could make feasible the selection of patients in a future study to evaluate the concept of LH supplementation in GnRH antagonist cycles.

Table I. Baseline characteristics of the patients analysed across different groups of LH on day 8 of stimulation

<table>
<thead>
<tr>
<th>LH group²</th>
<th>0–25th (n = 25)</th>
<th>25–75th (n = 25)</th>
<th>75–100th (n = 25)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline parameters</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female age (years)</td>
<td>31.8 ± 0.6</td>
<td>32.1 ± 0.4</td>
<td>32.7 ± 0.7</td>
<td>0.65</td>
</tr>
<tr>
<td>FSH on day 1 of stimulation (IU/l)</td>
<td>6.1 ± 0.4</td>
<td>7.9 ± 0.4</td>
<td>8.9 ± 0.4</td>
<td>0.001</td>
</tr>
<tr>
<td>LH on day 1 of stimulation (IU/l)</td>
<td>3.6 ± 0.4</td>
<td>5.1 ± 0.3</td>
<td>6.0 ± 0.4</td>
<td>0.001</td>
</tr>
<tr>
<td>Number of previous trials</td>
<td>1.0 ± 0.3</td>
<td>1.0 ± 0.3</td>
<td>1.2 ± 0.3</td>
<td>0.83</td>
</tr>
<tr>
<td>Indication for treatment [n (%)]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Andrological</td>
<td>17 (68.0)</td>
<td>39 (62.9)</td>
<td>19 (65.5)</td>
<td></td>
</tr>
<tr>
<td>Idiopathic</td>
<td>3 (12.0)</td>
<td>15 (24.2)</td>
<td>3 (10.3)</td>
<td></td>
</tr>
<tr>
<td>Tubal</td>
<td>5 (20.0)</td>
<td>5 (8.1)</td>
<td>4 (13.8)</td>
<td></td>
</tr>
<tr>
<td>Andrological and tubal</td>
<td>5 (0.0)</td>
<td>3 (4.8)</td>
<td>3 (10.3)</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.1 ± 0.6</td>
<td>23.1 ± 0.4</td>
<td>23.6 ± 0.6</td>
<td>0.68</td>
</tr>
</tbody>
</table>

²Values are mean ± standard error, except where indicated.
The present study has shown that LH levels following GnRH antagonist initiation are negatively associated with the achievement of ongoing pregnancy in IVF cycles. A significant trend towards higher pregnancy rates is observed with decreasing LH levels.

The validity of the assessment of the role of LH in the achievement of ongoing pregnancy in the present study is supported by several reasons. All patients were stimulated with the same gonadotropin, which did not contain LH, and received the same number of units per day, while the dose remained constant during stimulation until the criteria for HCG were met. Criteria for HCG were independent from E2 response and thus from LH levels (Adonakis et al., 1998). Moreover, they were strict, as the signal for inducing final oocyte maturation and luteinization was administered as soon as three or more follicles of ≥17 mm were present on ultrasound. Prolongation of the follicular phase has been shown to be associated with a lower chance of achieving an ongoing pregnancy (Kolibianakis et al., 2004). Finally, the association between different LH level groups and achievement of an ongoing pregnancy was analysed according to groups defined by Tukey’s Hinges percentile analysis, and thus was not based on the use of arbitrary thresholds of LH levels.

Embryo transfer was performed on day 3 or day 5 of in-vitro culture. This is unlikely to be a source of bias in the present study, as a similar proportion of patients in the LH level groups on day 8 had embryo transfer on day 3 and day 5 (Table II). Moreover, the hypothesis that blastocysts result in a higher probability of pregnancy compared with day 3 transfer is not supported by randomized controlled trials (Kolibianakis and Devroey, 2002; Blake et al., 2004).

No data have been published to date on GnRH antagonist cycles regarding the association of LH levels following GnRH antagonist administration and the probability of achieving an ongoing pregnancy.

A comparison of the results of the current study with those available so far in GnRH agonist cycles or non-down-regulated cycles is probably not appropriate. Such a comparison, focused on the predictive ability of LH for achievement of pregnancy, would ignore the entirely different setting under which the establishment of a predictive model is performed. Differences in the endocrine environment present in the luteal phase of the cycle preceding stimulation and the obvious hormonal differences in the follicular phase between cycles stimulated with agonist or antagonists, or those not using down-regulation, might render such a comparison invalid.

Recognizing the above limitations, the data obtained in the present study are in line with observations performed in GnRH agonist down-regulated cycles (Stanger and Yovich, 1985; Macnamme et al., 1987), which provide indications that increased LH levels during ovarian stimulation are associated with a decreased chance of pregnancy. In the same direction are data which indicate that LH levels in the early follicular phase of GnRH antagonist cycles are negatively associated with the chance of achieving an ongoing pregnancy (Kolibianakis et al., 2003).

The data in the current study are also in line with those provided by Humaidan et al. (2002) in GnRH agonist down-regulated cycles, who showed that the highest implantation rate was achieved in patients with the lowest LH levels on stimulation day 8 (≤0.5 IU/l). In addition, no adverse role of low LH levels on pregnancy rates was reported by Esposito et al. (2001), Balasch et al. (2001) and Loumaye et al. (1997) in GnRH agonist down-regulated cycles.
The study by Westergaard et al. (1996) is frequently cited to support an adverse role of deep LH suppression during ovarian stimulation. However, although Westergaard et al. showed that there is an increased risk of early pregnancy loss associated with profound suppression of LH, they could not demonstrate a significant association between profound LH suppression and the probability of delivery per patient. It therefore appears that no study currently exists to suggest that suppressed LH levels are associated with a lower probability of pregnancy during ovarian stimulation for IVF using GnRH analogues.

The current study shows that low LH levels on day 8 of stimulation not only should not be considered as an adverse prognostic factor during ovarian stimulation with rFSH and GnRH antagonists starting on day 6 of stimulation, but they are associated with a higher probability of ongoing pregnancy. Moreover, the present study does not support the need to evaluate the addition of LH under the above setting, when low LH levels are present following down-regulation with GnRH antagonists. Nevertheless, such studies have already been initiated and, not surprisingly, preliminary results do

### Table II. Stimulation characteristics and embryological data in three groups of patients categorized according to Tukey’s Hinges percentile analysis of LH levels on day 8 of stimulation

<table>
<thead>
<tr>
<th>LH groupa</th>
<th>0–25th (n = 25)</th>
<th>25–75th (n = 62)</th>
<th>75–100th (n = 29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days of HCG administration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days of stimulation</td>
<td>9.3 ± 0.3</td>
<td>9.4 ± 0.2</td>
<td>8.6 ± 0.3</td>
</tr>
<tr>
<td>Days of antagonist administration</td>
<td>5.3 ± 0.3</td>
<td>5.4 ± 0.2</td>
<td>4.6 ± 0.3</td>
</tr>
<tr>
<td>Total units of rFSH used (IU)</td>
<td>1864 ± 56</td>
<td>1880 ± 47</td>
<td>1717 ± 53</td>
</tr>
<tr>
<td>Follicles of ≥17 mm</td>
<td>4.4 ± 0.6</td>
<td>4.0 ± 0.3</td>
<td>3.9 ± 0.3</td>
</tr>
<tr>
<td>Follicles of 15–16 mm</td>
<td>3.2 ± 0.5</td>
<td>3.4 ± 0.4</td>
<td>1.7 ± 0.3</td>
</tr>
<tr>
<td>Follicles of 11–14 mm</td>
<td>6.9 ± 1.1</td>
<td>5.6 ± 0.7</td>
<td>3.8 ± 0.6</td>
</tr>
<tr>
<td>Endometrium thickness (mm)</td>
<td>7.5 ± 0.6</td>
<td>7.6 ± 0.2</td>
<td>8.2 ± 0.4</td>
</tr>
<tr>
<td>LH (IU/l)</td>
<td>0.7 ± 0.2</td>
<td>1.5 ± 0.3</td>
<td>3.4 ± 0.4</td>
</tr>
<tr>
<td>E2 (pg/ml)</td>
<td>1704 ± 182</td>
<td>1834 ± 119</td>
<td>1649 ± 142</td>
</tr>
<tr>
<td>Progesterone (ng/ml)</td>
<td>1.3 ± 0.1</td>
<td>1.3 ± 0.1</td>
<td>1.1 ± 0.1</td>
</tr>
</tbody>
</table>

Embryological data

- COCs | 15.5 ± 2.3 | 12.1 ± 1.0 | 9.3 ± 1.0 |
- 2PN oocytes | 8.6 ± 1.0 | 6.7 ± 0.6 | 5.3 ± 0.4 |
- Fertilization rate (%) | 59.9 ± 4.5 | 54.9 ± 3.0 | 59.6 ± 5.4 |
- Embryos transferred | 1.8 ± 0.2 | 2.0 ± 0.1 | 1.8 ± 0.2 |
- Quality score of embryos transferred | 2.0 ± 0.1 | 1.8 ± 0.1 | 2.1 ± 0.1 |
- Quality score of embryos cryopreservedb | 1.7 ± 0.1 | 1.7 ± 0.1 | 1.7 ± 0.2 |
- Type of embryo transfer [n (%)] | | | |
- Day 3 | 15 (60.0) | 40 (64.5) | 18 (62.1) |
- Day 5 | 10 (40.0) | 22 (35.5) | 11 (37.9) |

aValues are mean ± standard error, except where indicated.
bFor patients who had cryopreserved embryos.

### Table III. Ongoing pregnancy rate and ongoing implantation rate across groups of patients with increasing LH levels according to percentile analysis

<table>
<thead>
<tr>
<th>LH level on day 8</th>
<th>Ongoing pregnancy rate per OPU [% (n)]</th>
<th>Ongoing implantation rate [% (n)]</th>
<th>Pregnancy loss after HCG detection before 12 weeks [% (n)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentile</td>
<td>Mean</td>
<td>Min</td>
<td>Max</td>
</tr>
<tr>
<td>0–25th</td>
<td>0.3</td>
<td>0.1</td>
<td>0.5</td>
</tr>
<tr>
<td>25–75th</td>
<td>1.0</td>
<td>0.6</td>
<td>1.9</td>
</tr>
<tr>
<td>75–100th</td>
<td>3.3</td>
<td>1.9</td>
<td>8.4</td>
</tr>
</tbody>
</table>

P < 0.010a

P < 0.018a

P < 0.71a

aExact χ² for trend.

### Table IV. Robust logistic regression on achievement of ongoing pregnancy after oocyte retrieval (dependent variable: achievement of ongoing pregnancy)

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>P</th>
<th>Odds ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>LH level on day 8</td>
<td>0.02</td>
<td>0.61</td>
<td>0.40</td>
</tr>
<tr>
<td>Number of previous ART trials</td>
<td>0.19</td>
<td>0.86</td>
<td>0.68</td>
</tr>
<tr>
<td>Age at initiation of stimulation</td>
<td>0.61</td>
<td>1.03</td>
<td>0.91</td>
</tr>
<tr>
<td>FSH level on day 1 of stimulation</td>
<td>0.90</td>
<td>0.99</td>
<td>0.83</td>
</tr>
</tbody>
</table>

Model, P = 0.049; Hosmer and Lemeshow test, P = 0.29. CI = confidence interval.

The study by Westergaard et al. (1996) is frequently cited to support an adverse role of deep LH suppression during ovarian stimulation. However, although Westergaard et al. showed that there is an increased risk of early pregnancy loss associated with profound suppression of LH, they could not demonstrate a significant association between profound LH suppression and the probability of delivery per patient. It therefore appears that no study currently exists to suggest that suppressed LH levels are associated with a lower probability of pregnancy during ovarian stimulation for IVF using GnRH analogues.

The current study shows that low LH levels on day 8 of stimulation not only should not be considered as an adverse prognostic factor during ovarian stimulation with rFSH and GnRH antagonists starting on day 6 of stimulation, but they are associated with a higher probability of ongoing pregnancy. Moreover, the present study does not support the need to evaluate the addition of LH under the above setting, when low LH levels are present following down-regulation with GnRH antagonists. Nevertheless, such studies have already been initiated and, not surprisingly, preliminary results do
not appear to support a beneficial role of LH supplementation (Cedrin Durnerin et al., 2003; Ludwig et al., 2003; Noyes et al., 2002; van Loenen et al., 2002).

Patients with very low LH levels on day 8 had more COCs, and in turn more 2PN oocytes available, compared with those with high LH levels. This appears to be in line with an adverse role of high LH levels during ovarian stimulation on follicular development, the ceiling hypothesis proposed by Hillier (1993). Alternatively, it might also be attributed to the significantly lower FSH present at initiation of stimulation in the group of patients with lower LH levels on day 8, which is an indication of a better ovarian reserve.

However, regardless of the number of COCs retrieved and the number of 2PN oocytes available, similar fertilization rates were observed across groups of LH on day 8 of stimulation. Moreover, no difference was present in the number of embryos transferred or in their quality. This is probably due to the fact that patients who participated in the present study produced a sufficient number of 2PN oocytes to allow transfer of one or two embryos of equal morphological quality.

Therefore, although it cannot be excluded that higher LH levels on day 8 might be associated with a worse ovarian reserve in patients treated with rFSH and daily GnRH antagonist, this is not likely to be the explanation for the negative association present between LH levels on day 8 and ongoing pregnancy achievement.

Multivariate analysis supported the above hypothesis, as when controlling for the effect of age, FSH on day 1 and the number of previous trials, the association of LH with the probability of pregnancy was still present.

As shown in Table III, the patients with low LH levels on day 8 of stimulation also had significantly lower LH levels on day 1 of stimulation. Lower LH levels on day 1 of stimulation have been associated with less advanced endometrial histology, while endometrial advancement has been negatively associated with the chance of ongoing pregnancy (Kolibianakis et al., 2002). Although no endometrial histological data are available in this study to support a direct or indirect role of LH on endometrium quality, it is likely that the differences observed in pregnancy and implantation rates between LH level groups might not be due to an oocyte/embryonic factor.

In conclusion, the present study shows that a positive association exists between very low mid-follicular LH levels and the chance of achieving an ongoing pregnancy in patients stimulated with rFSH and GnRH antagonists.

Acknowledgements

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