Early pregnancy

Does cessation of progesterone supplementation during early pregnancy in patients treated with recFSH/GnRH antagonist affect ongoing pregnancy rates? A randomized controlled trial


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Background: The aim of this study was to assess whether the cessation of progesterone (P) supplementation during early pregnancy after GnRH antagonist cycles is not inferior to its continuation in terms of pregnancy rates beyond 12 weeks of gestation.

Methods: There were 200 patients, with a positive β-hCG test (followed by a doubling in β-hCG levels 48 h later) after a fixed recombinant FSH (recFSH)/GnRH antagonist protocol for IVF/ICSI and a Day-3 fresh embryo transfer (ET), participated in this randomized controlled study. All patients received luteal support, with 200 mg vaginal P being administered three times daily for 14 days, beginning on the day of ET until the second β-hCG test, 16 days post-ET. In the control group (n = 100) the administration of P was continued until 7 weeks of gestation. In the study group (n = 100), vaginal P was discontinued on the 16th day post-ET.

Results: The ongoing pregnancy rate beyond 12 weeks, the primary outcome measure, did not differ between the study and control groups (82 versus 73%, P = 0.175; difference 9%, 95% CI: −2.6 to 20.3). There were also no significant differences observed between the study and control group in terms of abortion before or after 7 weeks of gestation [(9 versus 12%, P = 0.645) and (8 versus 10%, P = 0.806), respectively]. The same was true for bleeding episodes (14 versus 19%, P = 0.446).

Conclusions: After recFSH/GnRH antagonist cycles, the withdrawal of P supplementation in early pregnancy, with normally increasing β-hCG levels on the 16th day post-ET, had no significant clinical impact in terms of ongoing pregnancy rates beyond 12 weeks.

Key words: progesterone supplementation / GnRH antagonist / IVF / ICSI ongoing pregnancy rate

Introduction

Exogenous supplemental progesterone (P) is a common practice in IVF-stimulated cycles because of associated luteal phase defects (LPDs) (Kolibianakis et al., 2003). Although the benefit of P administration as luteal phase support has been well documented in IVF (Fatemi et al., 2007), the question regarding the optimal time for its discontinuation remains.

Following ovulation, P, produced by corpus luteum (CL), induces secretory transformations of the endometrium (Bourgain et al., 1990) and allows endometrial receptivity and embryo implantation (Kolibianakis and Devroey, 2002). In the case of conception, trophoblast production of hCG prevents regression of the CL and amplifies steroid secretion that consequently decidualizes the endometrial stroma and supports early embryonic development (Penzias, 2002).
Studies conducted more than three decades ago demonstrated that P secretion by the CL is absolutely essential for the success of early pregnancy. The excision of the CL (‘luteectomy’) before 7 weeks of gestation leads to a precipitate decrease in serum P concentrations, followed by pregnancy loss, while luteectomy at 8 weeks of gestation or later leads to a transient decrease in P levels without any negative impacts in pregnancy outcome (Csapo et al., 1972). However, external administration of P after early luteectomy (before 7 weeks of gestation) could prevent the inevitable miscarriage (Csapo et al., 1973). On the basis of the results of the above studies, it is obvious that the success of early pregnancy depends on the P produced by the CL before 7 eeks of gestation.

Although it is well accepted that P supplementation is crucial during the time between the disappearance of exogenous hCG administered for final oocyte maturation and the rise in endogenous hCG during early implantation (Andersen et al., 2002), the optimal duration of P supplementation in IVF cycles is still a matter of debate. In the existing literature, which concerned pituitary suppression with GnRH agonists, the duration of P supplementation was suggested to be limited to around the day of positive β-hCG (Mochtar et al., 1996; Schmidt et al., 2001; Andersen et al., 2002) up to the first ultrasound (6–7 weeks) (Aboulghar et al., 2008), up to 8 weeks (Polson et al., 1992; Miles et al., 1994) or, alternatively, up to 12 weeks of pregnancy (Smitz et al., 1988; Smitz et al., 1992; Van Steirteghem, 1998; Ludwig and Diedrich, 2001).

Currently, there is no data regarding the effect of prolongation of luteal support on early pregnancy in patients treated with a GnRH antagonist protocol. The purpose of this randomized controlled trial (RCT) was to assess whether the cessation of P supplementation during early pregnancy after GnRH antagonist cycles is not inferior to its continuation in terms of pregnancy rates beyond 12 weeks of gestation.

Materials and Methods

Patient population

Between September 2008 and April 2010, 200 patients, with a positive β-hCG test (>75 IU/l), absence of vaginal bleeding and a normal doubling of β-hCG levels (Daya, 1987) 48 h after the first measurement (16 days post ET), were randomized. Allocations were concealed in opaque, sealed envelopes, opened once written informed consent was obtained. Randomization was performed by the attending physician according to a computer-generated concealed randomization list (ratio 1:1) using random permuted blocks with a fixed block size of two. The control group continued to receive P until 7 weeks of gestation. The study group discontinued the P administration 16 days post-ET.

All patients were asked to mention any vaginal bleeding during the first 3 weeks between randomization and ultrasonography. Three weeks later, an ultrasound scan was performed and the presence of an intrauterine gestational sac confirmed a clinical pregnancy. A second ultrasound was performed at 12 weeks to exclude a missed abortion and to confirm a normally developing pregnancy.

The primary outcome measure was ongoing pregnancy rate beyond 12 weeks per randomized patient. Secondary outcomes included abortion (biochemical, ectopic pregnancies) before or after 7 weeks of gestation, bleeding episodes and ongoing pregnancies at 7 weeks. A biochemical pregnancy was defined as a pregnancy that, although detectable by assays of serum β-hCG, failed to develop a physiological increase in β-hCG levels and, therefore, could not be confirmed clinically. An ongoing pregnancy was defined as one developing beyond 12 weeks, while early pregnancy loss was defined as a clinical pregnancy that failed to develop to 12 weeks of gestation. In cases of biochemical pregnancy, ectopic pregnancy or missed abortion, the P supplementation of the control group was discontinued.

The research project was approved by our Institutional Review Board and was registered in the ClinicalTrials.gov as NCT01147770, in June 2010 after patient recruitment was completed.

Statistical analysis

The original sample size calculations were based on the findings of an earlier study with GnRH agonist down-regulation (Andersen et al., 2002). In that study, 85% of all patients with a positive hCG had an ongoing pregnancy. Using 80% power and a difference of −7%, a sample size of 320 patients is needed in each group with a = 0.025 (one-sided test, equivalent to α = −0.05 two-sided test). Such a sample size is not feasible for a single centre study. Thus, embarking on the current study, the aim was to provide data on the influence of prolongation of luteal support on the ongoing pregnancy rate beyond 12 weeks in recFSH/GnRH antagonist cycles on a relatively large patient population, which could be included in a future meta-analysis on this issue. An arbitrary choice was made to perform an analysis when 100 patients had been included in each arm.

Normally distributed metric variables were analysed using the independent sample t-test, while not normally distributed variables were analysed using the Mann–Whitney U-test. Nominal variables were analysed in the form of frequency tables using the Fisher’s exact test. All tests were two-tailed with a significance level of 5%.

Results

The mean age of the patients included in the study was 31.4 ± 4.3 years. Patients had performed a mean of 1.8 ± 0.9 previous IVF/
ICSI cycles, while the mean FSH level at the initiation of stimulation was 7.5 ± 2.2 IU/l. Andrological infertility was present in 51% of the couples, tubal factor infertility in 9% and dysovulation in 7%, while in 33%, idiopathic infertility with failed IUI was identified.

Characteristics of patients and stimulation data for the two groups are shown in Table I. No significant differences were observed between the two groups.

between the two groups. Similarly, hCG levels were not significantly different on Days 14 and 16 between the study and control groups.

The pregnancy outcomes are described in Table II. No significant differences were observed between the two groups in terms of abortion rates before or after 7 weeks of gestation [(9 versus 12%, \( P = 0.645 \)) and (8 versus 10%, \( P = 0.806 \)), respectively], or bleeding episodes (14 versus 19%, \( P = 0.446 \)) or ongoing pregnancy rates beyond 12 weeks (82 versus 73%, \( P = 0.175 \); difference 9%, 95% CI: 2.6–20.3).

### Discussion

According to previous findings the prolongation of P supplementation in early pregnancy has no influence on pregnancy outcomes in GnRH agonist cycles (Schmidt et al., 2001; Andersen et al., 2002). The present study confirms these findings in GnRH antagonist IVF cycles as well. Interruption of P supplementation after 4 weeks and 2 days of gestation did not decrease the probability of ongoing pregnancy beyond 12 weeks (73% control versus 82% study group). Additionally, bleeding episodes following P discontinuation were similar between the groups (14 versus 19%).

The present study is the first attempt to assess the need for P administration up to 7 weeks of gestation in GnRH antagonist cycles. The withdrawal of vaginal P 2 days after a positive pregnancy test, when a normal hCG rise was confirmed, does not have any influence on the miscarriage rate, and thus no effect on ongoing pregnancy rate beyond 12 weeks. The present study is the first RCT to test the safety of the withdrawal of vaginal P 2 days after a positive pregnancy test, when a normal hCG rise was confirmed, does not have any influence on the miscarriage rate, and thus no effect on ongoing pregnancy rate beyond 12 weeks. The present study is the first RCT to test the safety

### Table I Baseline and embryological data in the study (no P support after 4 weeks and 2 days of gestation) and control (P until 7 weeks of gestation) groups.

<table>
<thead>
<tr>
<th></th>
<th>Study group (n = 100)</th>
<th>Control group (n = 100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female age (years)</td>
<td>31.1 ± 4.2</td>
<td>31.5 ± 4.5</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.9 ± 3.6</td>
<td>23.4 ± 3.6</td>
</tr>
<tr>
<td>No. of trials</td>
<td>1.8 ± 0.9</td>
<td>1.9 ± 0.9</td>
</tr>
<tr>
<td>Indication for treatment (%)</td>
<td>Andrological 51</td>
<td>51</td>
</tr>
<tr>
<td>Fertilization procedure (%)</td>
<td>IVF 15</td>
<td>8</td>
</tr>
<tr>
<td>FSH on Day 1 of stimulation (IU/l)</td>
<td>7.5 ± 2.2</td>
<td>7.1 ± 2.4</td>
</tr>
<tr>
<td>Total units of FSH (IU)</td>
<td>1656.1 ± 571.5</td>
<td>1884.1 ± 689.4</td>
</tr>
<tr>
<td>Duration of stimulation (days)</td>
<td>8.8 ± 2.3</td>
<td>8.8 ± 1.9</td>
</tr>
<tr>
<td>E2 on the day of hCG administration (pg/ml)</td>
<td>1860.8 ± 1176.1</td>
<td>1708.9 ± 942.1</td>
</tr>
<tr>
<td>P on the day of hCG administration (ng/ml)</td>
<td>1.1 ± 1.0</td>
<td>1.0 ± 0.5</td>
</tr>
<tr>
<td>Number of cumulus-oocyte complexes</td>
<td>11.6 ± 6.2</td>
<td>11.7 ± 6.2</td>
</tr>
<tr>
<td>2PN embryos</td>
<td>7.1 ± 4.4</td>
<td>6.9 ± 3.6</td>
</tr>
<tr>
<td>No. of embryos transferred</td>
<td>1.5 ± 0.6</td>
<td>1.5 ± 0.6</td>
</tr>
<tr>
<td>Quality score of transferred embryos</td>
<td>1.3 ± 0.6</td>
<td>1.3 ± 0.5</td>
</tr>
<tr>
<td>No. of cryopreserved embryos</td>
<td>2.3 ± 2.8</td>
<td>2.1 ± 2.3</td>
</tr>
<tr>
<td>hCG levels on 14th day post-ET (IU/l)</td>
<td>412.7 ± 238.6</td>
<td>383.4 ± 247.5</td>
</tr>
<tr>
<td>hCG levels on 16th day post-ET (IU/l)</td>
<td>1438.0 ± 1444.5</td>
<td>2067.7 ± 2020.1</td>
</tr>
<tr>
<td>P on 14th day post-ET (ng/ml)</td>
<td>56.6 ± 30.6</td>
<td>52.3 ± 21.2</td>
</tr>
<tr>
<td>P on 16th day post-ET (ng/ml)</td>
<td>60.7 ± 38.5</td>
<td>65.6 ± 24.5</td>
</tr>
</tbody>
</table>

Values are mean (SD) unless otherwise indicated. No significant differences were observed between the two groups.

### Table II Reproductive outcomes for the study (no P support after 4 weeks and 2 days of gestation) and control (P until 7 weeks of gestation) groups.

<table>
<thead>
<tr>
<th></th>
<th>Study group (n = 100)</th>
<th>Control group (n = 100)</th>
<th>% Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biochemical pregnancies</td>
<td>0 1 10 (−5.4, 2.8)</td>
<td></td>
<td></td>
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<tr>
<td>Ectopic pregnancies</td>
<td>1 4 −3.0 (−8.9, 2.1)</td>
<td></td>
<td></td>
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<tr>
<td>Abortion ≤ 7 weeks (%)</td>
<td>9 12 −3.0 (−11.9, 5.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleeding episodes</td>
<td>14 19 −5.0 (−15.3, 5.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ongoing pregnancies at 7 weeks</td>
<td>90 83 7.0 (−2.6, 16.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abortion &gt; 7 weeks (%)</td>
<td>8 10 −2.0 (−10.4, 6.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ongoing pregnancies beyond 12 weeks</td>
<td>82 73 9.0 (−2.6, 20.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>73 66 7.0 (−5.7, 19.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Twin</td>
<td>8 6 2.0 (−5.6, 9.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triple</td>
<td>1 1 0.0 (−4.5, 4.5)</td>
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</table>

No significant differences were observed between the groups compared.
of discontinuing P, further studies to test the same intervention are therefore needed. A limitation of this trial is that it was conducted with ‘ideal’ patients (<39 years old with normal hormonal profile). Older patients and those with endometriosis, in which P resistance has been reported, might need longer P support (Bulun et al., 2006).

Regarding prior similar studies, it is interesting to note that, in GnRH antagonist cycles, Andersen et al. (2002) reported an insignificant trend towards more patients with vaginal bleeding, higher miscarriage rates and lower delivery rates in the group in which P was discontinued. However, in contrast to the above results, in GnRH antagonist cycles, the reverse trend was observed. This might be explained by the fact that there is a rapid recovery of the pituitary following a GnRH antagonist cycle (Dal Prato and Borini, 2005). On the other hand, using down-regulation with GnRH agonist, LH secretion may not have completely recovered during the luteal phase (Smitz et al., 1998), as suppression of pituitary LH secretion for as long as 10 days after the last dose of GnRH agonist has been reported. Without this LH signal, the CL may be dysfunctional (Pritts and Atwood, 2002).

The introduction of GnRH antagonists in IVF raised speculations that a rapid recovery of pituitary function (Albano et al., 1996) would obviate the need for luteal-phase supplementation (Elter and Nelson, 2001). However, various studies of GnRH antagonist co-treatment in IVF have since found different results. Luteolysis is also initiated prematurely in antagonist-co-treated IVF cycles, causing a significant reduction in the luteal-phase length and compromising the chances of pregnancy (Albano et al., 1998; Beckers et al., 2003). Despite the rapid recovery of pituitary function in GnRH antagonist protocols (Dal Prato and Borini, 2005), luteal-phase supplementation remains mandatory (Tarlatzis et al., 2006). Moreover, Friedler et al. (2006) demonstrated that the luteal phase characteristics and dynamics of IVF cycles using GnRH agonist or antagonist cycles are similar. Further to the above findings, it now appears that prolonged P supplementation in GnRH antagonist as well as in agonist cycles has no clinical benefit in terms of ongoing pregnancy beyond 12 weeks.

The main cause of LPD observed in stimulated IVF cycles is not related to the GnRH analogue (agonist or antagonist) but to the multifollicular development achieved during ovarian stimulation, which completely alters the hormonal environment. It can be postulated that one of the main causes of the LPD in stimulated IVF cycles is supra-physiological levels of steroids secreted by a high number of corpora lutea during the early luteal phase, which directly inhibits LH release via negative feedback actions at the level of the hypothalamic–pituitary axis (Fauser and Devroey, 2003).

P supplementation is mandatory in the first 2 weeks after embryo transfer (Smits et al., 1998; Soliman et al., 1994). However, once the trophoblast commences the production of hCG, all the corpora lutea are stimulated to produce steroids, which are necessary for the survival of the pregnancy. The hCG administered for final oocyte maturation covers the luteal phase for a maximum of eight days (Fatemi et al., 2007). Under normal circumstances, further LH secretion would stimulate the corpora lutea but, due to the suppressed LH levels in IVF cycles, there is no stimulus for the corpora lutea. The LH levels measured during the luteal phase of stimulated cycles are below the detection limit (Fauser and Devroey, 2003).

The increase in endogenous hCG levels during early pregnancy makes up for any possible lack of endogenous LH that has been caused by stimulated IVF cycles. First-trimester P supplementation in IVF may support early pregnancy in the first 7 weeks by delaying a miscarriage, but it does not improve live birth rates (Proctor et al., 2006). Due to the fact that P supplementation during early pregnancy is a widespread practice, it was difficult to convince the patients to be enrolled in this study even though the drug is costly and inconvenient to use. However, based on our findings, P supplementation in GnRH antagonist cycles may be safely withdrawn during early pregnancy without any obvious negative effect on pregnancy rates beyond 12 weeks of gestation. A modified policy regarding the duration of luteal phase support in GnRH antagonist cycles should be recommended.

Authors’ roles

D.K. played a role in conception, study design, data collection, analysis and interpretation, and drafting the manuscript; H.M.F. was involved in conception, study design, data interpretation, drafting and revising the manuscript; L.Z. was responsible for drafting and revising the manuscript; A.R. collected the data; E.G.P. was involved in revising the manuscript; B.C.T. and P.D. played a role in final approval.

Conflict of interest: none declared.

References


