Clinical consequences of ovarian stimulation in assisted conception and in PCOS
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Chapter 9

Increasing the dose of human menopausal Gonadotrophins on day of GnRH antagonists administration: A randomized controlled trial

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Abstract

Objective: to investigate whether increasing dose of gonadotrophins on the day of antagonist administration in GnRH antagonist protocols would increase the pregnancy rate. The background behind this work is the reporting of a significantly lower pregnancy rates in GnRH antagonist protocol as compared to the long GnRH agonist protocol. The cause of this difference is not exactly known.

Design: an open labeled, single center, randomized controlled trial conducted in the Egyptian IVF-ET Centre, Maadi, Cairo and allocation was done using sealed envelopes.

Participants & Methods: One hundred and fifty one subfertile couples undergoing IVF/ICSI cycles were included in this study. Ovarian stimulation started on day 3 of the cycle by giving 150-300 I.U hMG / day depending on the age of the patient for five days then the dose was modified according to the ovarian response. From day 8 onward, daily vaginal ultrasound and daily urinary luteinizing hormone (LH) estimation were performed. If premature LH rise was detected the cycle was cancelled. The antagonist (0.25mg daily) was started when the leading follicle reached 15 mm in mean diameter and LH testing in urine was negative till and including the day of hCG injection. Patients were randomized into two groups: (group A : 72 with no increase in hMG dose) and group B (79 in whom the dose of hMG was increased by 75IU on the day of antagonist administration) and continued this increased dose until the day of hCG administration.

Results: Both groups showed similar patients characteristics. There was no statistically significant difference between both groups regarding number of oocytes retrieved, embryos obtained, implantation rate, clinical pregnancy rate, multiple pregnancy rate (Implantation rate 19.1% in group A and 17.2% in group B / Clinical pregnancy rate 34.0% vs 35.1% [O.R for PR (1.3 (95% C.I 0.63-2.6)] / multiple pregnancy rate (41.2% vs 38.9%).

Conclusion: there is no evidence of clinical value for increasing the dose of hMG on day of antagonist administration
Introduction
The introduction of GnRH antagonists in controlled ovarian hyperstimulation, namely Cetrorelix (Serono, Switzerland) and Ganirelix (Organon, Oss, The Netherlands) has set up a new concept in assisted reproduction techniques. GnRH antagonist resulted in a dramatic reduction in the treatment period and lower amounts of gonadotrophin requirement (1,2). Several large randomized multicenter trials compared the clinical pregnancy rate in antagonist versus agonist protocols (1,3,4). There was no statistically significant difference in the pregnancy rate between both arms. However, there was a consistent insignificant lower pregnancy rate in the antagonist arm.

A recent Cochrane systematic review (5) showed a significant lower pregnancy rate in the antagonist group. There was no clear explanation of this statistically significant difference. Several possibilities were raised, including the lower E2 level on the day of hCG and possible impact of the antagonist on the endometrium. With GnRH agonists the pituitary is down regulated and secretion of endogenous gonadotrophins is extremely low during stimulation and follicular growth will depend only on exogenous gonadotrophins whereas in antagonist cycles, follicular growth depends on both exogenous and endogenous FSH and LH. However, both endogenous FSH and LH secretion will fall when antagonist is started. Clinicians – in an attempt to enhance the response - may increase the dose of gonadotrophins. Whether this could bring better results in IVF/ICSI cycles is still unclear. The objective of the present work is to find out the possible effect of increasing the dose of gonadotrophins on the day of starting the antagonist on the pregnancy rate.
Materials and Methods

This is a prospective randomized single center study comparing patients who received an increased dose of hMG on the day of starting GnRH antagonist, versus no increase on the outcome of IVF and ICSI in patients using GnRH antagonist protocol.

Participants:
The study enrolled 151 subfertile couples undergoing IVF/ICSI cycles within four month period during the year 2002. The inclusion criteria were female age < 40 years old with different causes of infertility including tubal factor, endometriosis and unexplained infertility and male factor of infertility not necessitating surgically retrieved sperms. All patients signed an informed consent prior to study entry. Patients with a history of poor responses, general contraindications for pregnancy and the presence of a clinically significant systemic disease were excluded from the study. No patients with more than 3 failed cycles were included in the study.

Ovarian stimulation:
Started on day 3 of the cycle by giving 150-300 I.U hMG / day depending on the age and the weight of the patient for five days (Menogon, Ferring, the Netherlands) Patient below the age of 30 years had 2 ampoules, 30-35 years had 3 ampoules, above 35 years 4 ampoules. One extra ampoule was added to patients with BMI above 30, then the dose was modified according to the ovarian response.

From day 8 onward, daily vaginal ultrasound (using a 7-MHz transducer model 8538, ultrasound scanner model 1849 D, DK-2850; Bruel and Kjaer, Naerum, Denmark) and daily urinary luteinizing hormone (LH) estimation (Clearplan; Unipath Limited, Bedford, United Kingdom) were performed. If premature LH rise was detected the cycle was cancelled.

The antagonist was started when the leading follicle reached 15 mm in mean diameter and LH testing in urine was negative. Cetrorelix (Serono International S.A., Geneva, Switzerland). was administered daily in the form of 0.25 mg (S.C) till and including the day of hCG injection.

Participants were randomized into two groups (A & B). Randomization was done using sealed envelopes on the day of the start of GnRH antagonist. Participants in group A continued to receive the predetermined dose of hMG and those of Group B we increased the dose of hMG by 75IU daily until the day of hCG.
Ten thousand units of hCG (Pregnyl; Nile Co., Cairo, Egypt) were given I.M. when two or more follicles reached 18 mm in mean diameter. Oocyte retrieval using transvaginal ultrasound was scheduled 36 h after hCG injection.

All participants were enrolled in our IVF/ICSI program, which is described elsewhere (6). Embryo transfer was done on day 2 or 3 after OPU using the Wallace catheter (H.G.Wallace Ltd, West Sussex, UK) or a Cook catheter (Cook, Australia) if the Wallace catheter could not be inserted. Luteal phase support was given routinely in the form of a daily progesterone injection (100 mg, progesterone; Steris, Phoenix, AZ, USA). A serum B-hCG test was done to confirm pregnancy two weeks after embryo transfer. Clinical pregnancy was diagnosed 3 weeks after a positive test by the presence of a gestational sac with fetal echoes and pulsations on ultrasound.

Our primary outcome was clinical pregnancy rate / cycle started, while our secondary outcomes were number of hMG ampoules, fertilization rate, number of oocytes retrieved, number of embryos.

Power calculation showed that 350 patients will be required to achieve 5% difference in pregnancy rate between the two arms. The number was very large and we planned to stop at this phase and if there is a tendency towards improvement in pregnancy rate after increasing hMG dose, we would continue the study. Ethical approval from an internal ethical committee was obtained before the start of the trial.

**Statistical evaluation**

Data are presented as mean ± SD. Different outcome measures were compared using Student's t-test or Chi-Square test where appropriate. P values < 0.05 were considered to be significant. Statistics were done using Arcus Quickstat version I.
Results

The present study enrolled two groups (Table I): Group I (no increase in hMG dose) included 72 subjects while group II (increase hMG dose) included 79 subjects. Both groups showed similar patients characteristics. There was no statistically significant difference between both groups regarding number of oocytes retrieved, embryos obtained, implantation rate, clinical pregnancy rate, multiple pregnancy rate (Implantation rate 19.1% in group A and 17.2% in group B / Clinical pregnancy rate 36.2% vs 32.1% [O.R for PR (1.3 (95% C.I 0.63-2.6)] / multiple pregnancy rate (41.2% vs 38.9%).
Table I: characteristics of study groups

<table>
<thead>
<tr>
<th></th>
<th>Increase (no=79)</th>
<th>No increase (no=72)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>32.8 ± 5.1</td>
<td>31.9 ± 6.1</td>
<td>NS (p=0.17)</td>
</tr>
<tr>
<td>Infertility duration</td>
<td>9.3 ± 5.5</td>
<td>9.2 ± 5.9</td>
<td>NS (P= 0.46)</td>
</tr>
<tr>
<td>HMG ampoules</td>
<td>44.3 ± 14.6</td>
<td>34.4 ± 10.5</td>
<td>S (P&lt;0.001)</td>
</tr>
<tr>
<td>Oocytes</td>
<td>9.2 ± 2.1</td>
<td>10.1 ± 3.8</td>
<td>NS</td>
</tr>
<tr>
<td>2 PN oocytes</td>
<td>4.3 ± 3.7</td>
<td>5.8 ± 3.3</td>
<td>NS</td>
</tr>
<tr>
<td>Embryos transferred</td>
<td>2.8 ± 0.9</td>
<td>2.9 ± 0.7</td>
<td>NS</td>
</tr>
<tr>
<td>Clinical P.R</td>
<td>36.2%</td>
<td>32.1%</td>
<td>N.S</td>
</tr>
<tr>
<td>Implantation rate</td>
<td>19.1%</td>
<td>17.2%</td>
<td>N.S</td>
</tr>
</tbody>
</table>
Discussion

The ideal protocol for antagonist use during ovarian stimulation has not been achieved as yet. The antagonist must be started early enough in the course of stimulation to prevent premature LH rise, but late enough so as to not increase gonadotrophin requirements by excessive suppression of endogenous gonadotrophins.

Although the large randomized controlled trials (3,4) used the multiple daily protocol with lowest possible dose (0.25mg) with a maximum of 1.5mg antagonist administered. Yet, the pregnancy rate was lower in the antagonist compared to the agonist. A significant lower pregnancy rate in the antagonist arm was demonstrated in a Cochrane review (OR 95% C.I., 0.62-0.97) (5). The potential direct effects of GnRH antagonists on ovarian function, endometrium and embryo quality are not known (7).

The cause of increased pregnancy rate in the long GnRH agonist protocol over the antagonist protocol is unknown. It has been proposed that there may be a negative effect of the antagonist on endometrial receptivity (8) The learning curve could be another possible explanation (9).

One of the advantages of the antagonist protocol is the lower dose of FSH used (1). This may be because the hypothalamo-pituitary axis was not down regulated and subsequently endogenous FSH together with the exogenous FSH stimulates the growing follicles while in the long GnRH protocol stimulation depends only on exogenous FSH.

We hypothesized that on the day of starting GnRH antagonist, the endogenous FSH will suddenly stop and this will reduce the total FSH available for the growing follicles until the day of hCG. In an attempt to test this hypothesis, we randomized patients to an arm which will continue the same dose and an arm with an increased dose with the idea of compensating for the endogenous FSH.

Some doctors may have tended to increase the dose of gonadotrophins in the 3 mg Cetrotide tailored protocol because they were afraid of estradiol drop as a potential detrimental outcome. However, if such an estradiol drop occurs, it does not appear to harm follicular growth on pregnancy rates in 3 mg Cetrotide protocol (9). In our center, we do not measure E2 during our routine cycles except in poor responders and very high responders threatened to develop OHSS. We decided to follow our protocol during the study.
There were many modifications on the original multiple dose GnRH antagonist protocol, as flexible GnRH protocol (10), adjusting dose to body weight (11) were all introduced hoping to improve the pregnancy rate. Unfortunately, there was no improvement in the pregnancy rate following the modified antagonist protocol. The possible profound suppression of endogenous LH activity after administration of GnRH antagonists could not be responsible for the lower pregnancy rate in the antagonist protocol (12).

If there is any question of profound LH suppression, it is anticipated that FSH preparation containing LH will be favored, and subsequently it is not expected that recombinant FSH would be better. In a recent meta-analysis (13) urinary gonadotrophins were compared to recombinant FSH and there was no significant difference in the pregnancy rate between the two arms of the analysis.

All the multicenter clinical studies used the fixed dose of antagonist from day 6 of the cycle, however, it was found that delaying the starting day of the antagonist will reduce the dose required with a minimal risk of premature LH rise (9-10). In fixed protocols, ultrasound examination starts day 6 of the cycle, however, in flexible protocols the ultrasound is delayed to day 8 because it is not expected that follicles will reach size of 15mm before that. In conclusion, there is no evidence of clinical value for increasing the dose of hMG on day of antagonist administration. The cost of increasing the dose of hMG should discourage such policy. Although in this study, we are reporting negative results, we believe that publishing these data will save time and efforts of other gynecologists who may try to test the same hypothesis. Reporting our results also helps avoiding more costs. This will ultimately result in better patient care.


