Agonist versus antagonist in ICSI cycles: a randomized trial and cost effectiveness analysis

Amira Badrawi, M.Sc.*†
Hesham Al-Inany, M.D.†
Mahmoud Hussein, M.D.‡
Salah Zaki, M.D.*
Abdel Maguid Ramzy, M.D.†

Department of Obstetrics & Gynecology, Cairo University, and Nile Badrawi IVF unit, Cairo, Egypt

ABSTRACT

Objective: GnRH antagonists have been introduced into clinical practice as an attractive alternative to GnRH long protocol under the concept of a patient friendly medication. We wished to evaluate the cost effectiveness of a human menopausal gonadotropin (hMG) / GnRH antagonist flexible protocol versus a long GnRH agonist / hMG protocol.

Design: single center randomized controlled trial using sealed envelopes as a method for randomization.

Materials and methods: One hundred women undergoing ICSI were randomized to receive either hMG/GnRH agonist long protocol (group I) or hMG/GnRH antagonist when follicle reaches 15 mm (group II).

Results: Two cases had premature LH surge in group II. Fifteen cases (30%) got pregnant in the first group as compared to 12 cases (24%) in the second group. The difference was statistically non-significant. The mean cost of medications per cycle was estimated to be $608 (3740 Egyptian Pounds) in the hMG/antagonist group, while it was $680 (4180 E.P) in the long GnRH agonist protocol treated group. This difference was statistically. However, the total cost per pregnancy was $6531 (40166 EP) in the hMG/antagonist protocol and $5008 (30800 EP) in the GnRH-a/hMG protocol which is statistically significant.

Conclusion: the use of the hMG/antagonist protocol is not a cost effective strategy although it provides short and simple stimulation protocol.

Keywords: GnRH antagonist, Flexible, agonist, ovarian stimulation, ICSI

The use of gonadotrophin-releasing hormone (GnRH) agonists with gonadotropins has resulted in greater ease of planning the superovulation stimulation than was possible with the earlier use of clomiphene citrate (CC) with gonadotropins (1). The long GnRH- agonist protocol has been proven to be superior to other GnRH agonist protocols (2,3).

However, with the introduction of GnRH antagonists, reduction of treatment time, avoidance of estradiol withdrawal symptoms, and no ovarian cyst formation mean an important reduction of burden for the patients. However, GnRH antagonist-treated patients showed lower clinical pregnancy rates compared to GnRH agonist-treated patients (odds ratio 0.79, 95% CI 0.63-0.99) (4). It was suggested that a flexible regimen of GnRH antagonist, started when the lead follicle measures 15 mm, yields more oocytes than a fixed protocol (starting on day 6) (5).

The aim of this study is to compare in a randomized controlled trial a flexible regimen of GnRH-antagonist and hMG versus long protocol of GnRH-a and hMG as controlled ovarian stimulation in IVF/ICSI cycles.
**Table 1. Background characteristics of group I compared to group II**

<table>
<thead>
<tr>
<th></th>
<th>Group I (N = 50)</th>
<th>Group II (N = 50)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>30.28 ± 5.19</td>
<td>30.81 ± 4.8</td>
<td>P = 0.604</td>
</tr>
<tr>
<td>Infertility duration (years)</td>
<td>6.06 ± 3.12</td>
<td>5.46 ± 3.28</td>
<td>P = 0.356</td>
</tr>
<tr>
<td>Baseline FSH mIU/ml</td>
<td>5.94 ± 1.54</td>
<td>6.13 ± 1.89</td>
<td>P = 0.588</td>
</tr>
<tr>
<td>Day 3 LH mIU/ml</td>
<td>5.6 ± 4.76</td>
<td>7.1 ± 4.89</td>
<td>P = 0.043</td>
</tr>
<tr>
<td>Day 14 E2 pg/ml</td>
<td>40.92 ± 30.54</td>
<td>67.4 ± 51.4</td>
<td>P = 0.003 *</td>
</tr>
<tr>
<td>E2 pg/ml on day of HCG</td>
<td>2096.9 ± 578.58</td>
<td>1620.5 ± 442.28</td>
<td>P = &lt;0.001 *</td>
</tr>
</tbody>
</table>

*Statistically significant results

**MATERIALS AND METHODS**

One hundred subfertile couples were recruited from IVF unit Nile Badrawi Hospital. All participants were primary infertility patients, 18-39 years old, with regular menstrual cycle and FSH levels < 10 IU/L done at cycle day 3 and ultrasonography showed normal uterus. Women with severe endometriosis (American Fertility Society stage III and IV), and azoospermic males were excluded from the study. The Ethical committee approved the trial and consent was obtained from all participants.

Patients were recruited and randomized into two groups using sealed envelopes: Group 1: Included fifty patients who received Gonadotrophin releasing hormone agonist (GnRH-a) Suprefact (Hoechst Marion Russel) "long luteal protocol" / human menopausal Gonadotrophin (hMG Menogon, Ferring Germany). Group 2: Included fifty patients who received Gonadotrophin releasing hormone (GnRH) antagonist Ganirelix 0.25 mg (the active Ingredient of Orgalutran(R) and Antagon, Org 37462; NV Organon OSS, The Netherland) / human menopausal Gonadotrophin (hMG Menogon, Ferring Germany).

In Group I, GnRH-a (Suprefact, Hoechst, UK) was administered as nasal spray 600 (g/day divided into 6 daily doses, starting in the mid luteal phase of the cycle preceding the treatment cycle and continued until the day of Human chorionic gonadotropin (HCG) administration. Estradiol was done 14 days later to confirm downregulation and then human menopausal gonadotropin (HMG) was administered (225 IU) (hMG Menogon, Ferring Germany).

In Group II, hMG was first administered on the second day of the cycle, 3 ampoules (225 IU Menogon) daily and Ganirelix 0.25 mg(Organon OSS, The Netherland) was administered S.C. daily, starting when the lead follicle measures 14 mm up to and including the day of hCG administration.

HCG 10,000 IU (Chorimon IBSA, Suisse) was administered deeply IM when the leading follicle reached 20mm in mean diameter with at least three follicles >18 mm. The endometrial thickness was 6mm or more and estradiol level was >1200 pg/ml.

Thirty-four to thirty-six hours later after hCG administration, transvaginal ultrasound-directed oocyte recovery was performed in the operating theater under full aseptic technique using Double-lumen needle (Rocket UK) aspiration needle for OPU. Follicular aspirate was examined immediately after recovery in tissue culture quality dish (Falcon, Decton Dickinson, UK) using a stereomicroscope (Nikon, SMZ-2T, Japan). The whole set up is put inside a horizontal laminar flow hood (Forma Scientific, USA) to help maintain sterile conditions.

As soon as the oocyte is identified, it is transferred with sterile Pasteur pipette to the outer well of the oocyte and embryo culture dish (Falcon, Decon Dickinson, UK). In this outer well the oocyte cumulus complex is rinsed in the clean medium by few passages in and out the tip of the glass Pasteur pipettes. Finally, the oocyte is transferred to the culture well, which contains 1ml of ready-made culture medium (Medicult, Denmark). The dish was then promptly
Table 2. Different clinical outcomes of group I compared to group II

<table>
<thead>
<tr>
<th></th>
<th>Group I (N = 50)</th>
<th></th>
<th>Group II (N = 47)</th>
<th></th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
<td></td>
</tr>
<tr>
<td>HMG Ampoule</td>
<td>36.88</td>
<td>7.77</td>
<td>34.09</td>
<td>3.35</td>
<td>P= 0.025</td>
</tr>
<tr>
<td>Stimulation duration</td>
<td>11.42</td>
<td>2.31</td>
<td>10.32</td>
<td>1.38</td>
<td>P= 0.005*</td>
</tr>
<tr>
<td>Number of follicles</td>
<td>16.34</td>
<td>7.77</td>
<td>11.83</td>
<td>5.59</td>
<td>P= 0.001*</td>
</tr>
<tr>
<td>Size of follicles (mm)</td>
<td>17.6</td>
<td>1.54</td>
<td>18</td>
<td>1.05</td>
<td>P= 0.135</td>
</tr>
<tr>
<td>Endometrial thickness</td>
<td>11.08</td>
<td>1.16</td>
<td>10.87</td>
<td>1.48</td>
<td>P= 0.443</td>
</tr>
<tr>
<td>Number of Oocytes</td>
<td>12.6</td>
<td>6.15</td>
<td>9.68</td>
<td>5.28</td>
<td>P= 0.014*</td>
</tr>
<tr>
<td>Number of MII Oocytes</td>
<td>10.46</td>
<td>5.25</td>
<td>8.26</td>
<td>4.96</td>
<td>P= 0.036*</td>
</tr>
<tr>
<td>Number of Oocytes Fertilized</td>
<td>7.88</td>
<td>4.15</td>
<td>6.38</td>
<td>3.05</td>
<td>P= 0.047*</td>
</tr>
<tr>
<td>Fertilization rate</td>
<td>77.7%</td>
<td></td>
<td>82.5%</td>
<td></td>
<td>P=0.179</td>
</tr>
<tr>
<td>Embryos</td>
<td>7.78</td>
<td>4.2</td>
<td>6.11</td>
<td>3.1</td>
<td>P=0.029*</td>
</tr>
<tr>
<td>No of transferred embryos</td>
<td>2.68</td>
<td>0.81</td>
<td>2.4</td>
<td>1.01</td>
<td>P= 0.015*</td>
</tr>
<tr>
<td>Pregnancy Rate/ET</td>
<td>15/35</td>
<td>30%</td>
<td>12/35</td>
<td>25.5%</td>
<td>P= 0.657</td>
</tr>
<tr>
<td>Abortion Rate</td>
<td>2</td>
<td>13.3%</td>
<td>1</td>
<td>8.3%</td>
<td>P= 0.84</td>
</tr>
<tr>
<td>OHSS</td>
<td>2</td>
<td>4</td>
<td>2</td>
<td>4.3</td>
<td>P= 0.668</td>
</tr>
</tbody>
</table>

*Statistically significant results

transferred to the carbon dioxide incubator (Forma Scientific, USA) and the oocyte grade was recorded.

The husband produces a semen sample 2 hours later to the procedure (Around 38 hours following hCG injection) by masturbation in a sterile container (Elkay, UK). The sample is assessed 30 minutes after production. Then standard ICSI procedure was done using an inverted microscope (Nikon Diaphot 300, JAPAN) equipped with micromanipulators and microinjectors (Narishige, JAPAN) Magnification of X 200 and X 400.

The procedure was carried out in a plastic microinjection culture dish (Falcon, U.K.) containing a number of 10(l droplets of HEPES-buffered medium (MILIEU BM1, France) covered with mineral oil (Mineral Oil, Sigma M-8410). Each micro droplet contains one mature oocyte which was denuded from the surrounding cumulus and corona cells using enzymatic (Hyaluronidase enzyme Sigma, H-4272).

In the injection pipette, a single living morphologically normal-looking spermatozoon was aspirated. After immobilization, the spermatozoon was aspirated. The oocyte was held in the correct position and sperm was injected. Then, they were incubated at 37°C in an atmosphere of 5% CO₂ (Forma Scientific Incubator, USA). The injected oocytes were examined for fertilization at about 16-18 hours after ICSI.

After another 24 hours of culture, the cleaving embryos were scored according to equality of size of the blastomeres and proportion of anucleate fragments. Embryo transfer was performed 2-3 days after OPU. The patient remained resting with a slight head-down tilt to her bed for 2h before being allowed home.

Luteal phase support is given to all patients who have been on analog protocols. Cyclogest (Shire Pharmaceuticals Ltd., Andover, UK) vaginal pessaries, 400mg twice a day continued for 2 weeks. B-HCG was done 2 weeks following embryo transfer and if negative Cyclogest is stopped. If, however, pregnancy test (B-HCG) was positive, Cyclogyst is continued until 12 weeks gestation.

**Statistical evaluation**

No power calculation was done because it would require a large number of participants to detect such difference. Al-Inany and Aboulghar (4) found that there is a significant difference only in their meta-analysis while other RCTs failed to show such statistical difference.

Data are presented as mean ± SD. Different outcome measures were compared using Student's
Table 3. Cost-effective analysis of the hMG/antagonist protocol as compared to the long agonist protocol

<table>
<thead>
<tr>
<th></th>
<th>Cost of drugs / cycle</th>
<th>PR (%)</th>
<th>Cost / pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>hMG/antagonist (Group II)</td>
<td>4140</td>
<td>24</td>
<td>40166</td>
</tr>
<tr>
<td>hMG/GnRHa (Group I)</td>
<td>3740</td>
<td>30</td>
<td>30800</td>
</tr>
<tr>
<td>Difference</td>
<td>400</td>
<td>6</td>
<td>9366</td>
</tr>
</tbody>
</table>

*Cost is in Egyptian pounds

Cost of medications (GnRH a) = 2065 (hMG/GnRHa) + 275 [1% (hidden cost) 25 x 11 (days of stimulation)] + 1400 cost of luteal phase support (cyclogest 100 x 14 days)
Total: - 3740 EP
Cycle cost: 5500 EP
Total Cost per cycle 9240 EP

Cost of Medications (antagonist) 2490 (hMG/antagonist) + 250 [1% (hidden cost) 25 x 10 (days of stimulation)] + 1400 cost of luteal phase support (cyclogest 100 x 14 days)
Total: - 4140 EP
Cycle cost: 5500 EP
Total Cost per cycle 9640 EP

hMG 45 EP / ampoule (see results)
GnRHa 200 EP / nasal spray (average 2)
Antagonist 160 EP / injection (average 6)

t-test or Fisher's exact test where appropriate. P values <0.05 were considered to be significant. Statistics were done using Arcus Quickstat version I.

RESULTS

There was no statistically significant difference between both groups regarding their background characteristics (Table 1). Three cases in group II discontinued due to poor response. Different clinical outcomes are illustrated in table 2. There were 15 conception cycles in group I (30%) including two miscarriages (13.3%) at mean of 5.5 weeks gestation, resulting in 13 deliveries of healthy children. In group II there were 12 (25.5%) conception cycles with one miscarriage (8.3%) at 5 weeks duration resulting in 12 healthy children born (one twin pregnancy). These data were not statistically different (P= 0.657). The pregnancy rate per attempt was 30% in Group I & 24% in group II which was not significantly different (P=0.652).

The mean cost of medications per cycle was estimated to be 3740 E.P in the hMG/agonist group (group I), while it was 4140 E.P in the antagonist (group II) protocol treated group. This difference was statistically significant. However, the total cost per pregnancy was 40166 EP in the hMG/antagonist protocol and 30800 EP in the GnRH-a/hMG protocol, which is statistically significant (P<0.05) Table 3.

DISCUSSION

The application of GnRH antagonists has been used in ovarian stimulation regimens aiming to prevent premature LH surge. In the presented work we have found that the duration of stimulation and number of HMG ampoules used were both significantly lower in the antagonist (group II). These findings correspond with the findings of other clinical trials (4, 6-8). A likely explanation is that the agonist suppresses the natural cycle follicular recruitment initiated by inter cycle FSH rise so that longer treatment with gonadotropins is required which allows more follicles to enter the growing phase.

On the day of HCG administration we have found that in the antagonist group there were significantly fewer follicles, and lower E2 levels. This corresponds to the findings of other clinical trials (4, 7, 8). This may be partly explained by the shorter mean duration of treatment and lower total dose of HMG administration in subjects treated...
with ganirelex (antagonist). We have also noticed that E2 done on day of ET was significantly lower in the antagonist group. Day 3 LH levels assessment showed a statistically significant difference between both groups which could be a major reason for the non significant differences found in pregnancy rate in both groups.

At oocyte retrieval the number of oocytes retrieved was significantly lower in the antagonist group. More over the number of MII and cleaved oocytes (embryos) were significantly lower in that group. This data was consistent with the findings of other clinical trials (4,7).

As regards the fertilization rate and quality of embryos in the two groups we have found no significant difference. These findings are in agreement with those of previous controlled studies with GnRh antagonist (6,7).

The cost of ovulation induction drugs is one of the main limiting factors in assisted reproduction. Costs and effectiveness can be brought together to aid the judgment about whether one drug should be preferred to a comparator.

For any drug the optimum position of an experimental treatment would be both to save costs and have greater effectiveness relative to a comparator. In a recently published guidelines for the management of infertility (The British National Formulary, 2004) (8), the cost of antagonists for a five-day treatment schedule is around £120 and the cost of agonists for a much longer schedule (24 to 31 days) is £111. However, the cost of agonists increases with longer schedules of treatment (from around £88 for a shorter schedule to around £111 for a longer schedule). This could be an underestimate if a woman requires a few more doses of agonists, which may only be available in 30-dose or 60-dose units.

The cost of gonadotrophins is the same for both treatments since it typically involves around ten days of treatment. The total cost of gonadotrophins (using The British National Formulary prices) is around £544 for a low dose schedule for women who are expected to respond well to ovulation induction and around £1,050 for a high dose schedule. The overall cost of a schedule of ovulation induction with antagonists is between £645 and £1,170 per cycle of treatment. The cost of agonists is between £623 and £1,138 per cycle of treatment. In practice, the cost of the antagonist schedule is likely to be toward the lower end of the cost range as the patient uses fewer doses of gonadotropins. The agonist schedule of treatment is likely to cost toward the higher end of the range since women tend to use the agonist for longer periods of time before starting gonadotrophins. Therefore, The British National Formulary (2004) concluded that it is likely that the agonist schedule is less costly than antagonist schedule.

In the present study, all patients were treated for only one cycle and both treatment protocols were found to be effective in producing a satisfactory ovulation rate. However, the pregnancy rate was insignificantly less in the hMG/antagonist treated group (groupII) compared to the other one. The mean cost of medications per cycle was estimated to be 4,140 E.P in the hMG/antagonist group, while it was 3,740 E.P in the long GnRH agonist protocol treated group. This difference was statistically significant. However, the total cost per pregnancy was 40,166 EP in the hMG/antagonist protocol and 30,800 EP in the GnRH-a/hMG protocol which is also statistically significant.

It is true that IVF procedures are costly, as the intensive use of human resources must be covered and the rapid technological advances in the laboratory and in pharmaceutical product development must be recapitalized. These issues lead to tremendous pressures, both economic and no economic, to maximize success. Against this backdrop, therefore, it is critical to consider any monetary savings that can accrue from the decreased use of less effective therapies (e.g., tubal surgery) while moving patients rapidly into therapeutic algorithms that offer an improved likelihood of success. The rapid achievement of pregnancy may also produce a significant monetary and societal cost saving due to a lower incidence of infertility-related depression resulting from untreated or unsuccessfully treated infertility. In addition to discouraging the use of less effective therapies, it is also incumbent on us as a specialty to realize any potential cost savings associated with effective therapies. Although the use of GnRH agonists may not lower the cost of an individual IVF cycle, the observation that its use requires fewer cycles to achieve a pregnancy suggests that the total cost of treating a population of patients...
will be significantly reduced.

In summary the use of GnRH antagonists results in shorter duration of stimulation, and reduction of HMG use. However, GnRH agonist is more cost effective.

REFERENCES


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