A Comparative Study between GnRH Antagonist and Long Agonist Protocols in Patients with Polycystic Ovarian Syndrome (PCOS) Undergoing in vitro Fertilization

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Abstract

We compared the efficacy and safety of GnRH antagonist protocol and GnRH long agonist protocol in patients with PCOS undergoing IVF/ICSI. A total of 100 patients with PCOS candidate for IVF/ICSI were prospectively studied. Patients were randomly allocated to either antagonist or agonist groups. There was no significant difference between the two groups as regards the clinical pregnancy rate, ongoing pregnancy rate, miscarriage rate per clinical pregnancy and multiple pregnancy rates. However, there was a significantly lower dose and shorter duration of gonadotropin stimulation and lower incidence of severe ovarian hyperstimulation syndrome (OHSS) in the antagonist group (P = 0.001, 0.001 and 0.01 respectively). GnRH antagonist protocol may be the protocol of choice in PCOS patients undergoing IVF / ICSI.

Keywords: GnRH antagonist; GnRH agonist; Polycystic ovary syndrome; Ovarian hyperstimulation syndrome

Introduction

Polycystic ovary syndrome (PCOS) is a common endocrinological disorder affecting 6.6-8% of women of reproductive age [1]. It is associated with 75% of the causes of anovulatory infertility [2]. There has been much debate about the definition of PCOS. A refined definition was agreed at a recent joint European Society of Human Reproduction and Embryology/American Society for Reproductive Medicine (ESHRE/ASRM) consensus meeting [3]. The pathophysiology of PCOS is likely to be multifactorial and polygenic. There is a significant body of evidence suggesting that excess ovarian androgen production is central in the pathogenesis of PCOS [4].

One of the main problems facing patients with PCOS undergoing IVF / ICSI is developing ovarian hyperstimulation syndrome (OHSS); a serious iatrogenic complication of ovarian stimulation triggered by exogenous and/or endogenous hCG which varies from mild to severe and critical forms [5-7]. The long GnRH agonist protocol has been used for pituitary desensitization in patients with PCOS undergoing IVF / ICSI with the benefit of significant reduction in the incidence of premature LH surges and the frequency of cycle cancellation [8,9]. However, it has the disadvantages of long duration of GnRH agonist administration, increased dose and duration of gonadotropin stimulation with subsequent higher cost. Moreover, it does not reduce the incidence of OHSS [10].

GnRH antagonist down-regulation protocol in IVF / ICSI has gained much popularity over the last few years [11]. It acts by competitive inhibition of GnRH receptors in pituitary, and produce an immediate and rapid decrease in LH and FSH levels without GnRH receptor desensitization as well as flare-up effect. Previous studies have shown that GnRH antagonist protocols reduce the incidence of OHSS as well as the amount of gonadotropins used and the duration of stimulation as compared with GnRH agonist protocols in the general population [12-14]. In the last few years, there was more interest in using GnRH antagonist protocol in patients with PCOS undergoing IVF with the aim of reducing the incidence of OHSS in this vulnerable group of patients. Recent studies showed that GnRH antagonist protocol to be as effective as the GnRH agonist LP in PCOS patients with lower rates of OHSS [15-18]. This study was performed to evaluate the effectiveness and safety of GnRH antagonist protocol compared with the standard long agonist protocol in patients with PCOS undergoing IVF / ICSI.

Patients and Methods

This study was a prospective randomized controlled trial involving 100 patients with PCOS undergoing IVF / ICSI at Minia infertility research unit, Minia, Egypt in the period from June 2012 to May 2014. The Ethical approval for the study was obtained from the local ethical committee of Faculty of Medicine, Minia University, Egypt. All the patients signed written informed consents before inclusion in the study.

Inclusion criteria for the study were: a) age between 18 – 39 years, b) baseline FSH ≥ 10 c) diagnosis of PCOS based on the Rotterdam criteria, in which at least two of the following three criteria were met: (1) oligo or an ovulation, (2) clinical or biochemical hyper androgenaemia, (3) polycystic ovaries (> 12 follicles <10 mm and/or ovarian volume >10 ml per ovary by vaginal ultrasound). Hyperprolactinaemia, thyroid dysfunction, Cushing's syndrome, congenital adrenal hyperplasia, an adrenal or ovarian tumour were excluded before enrolment in the study. We excluded patients with: a) previous poor response to ovarian stimulation, b) endometriotic cyst c) uterine abnormality diagnosed with ultrason, hysterosalpingography (HSG) or hysteroscopy. d) any hormonal therapy taken within 3 cycles prior to the study. We performed intention to treat analysis.

Randomization

Eligible patients who accepted to take part in the study were randomized into either study group (antagonist group, n = 50) or control group (GnRH agonist group, n = 50). Randomization was

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done simply using sealed envelopes. Neither patients nor doctors were blinded to the treatment assigned.

Ovarian stimulation

In the antagonist group, ovarian stimulation was commenced on day 2 of spontaneous or progesterone withdrawal bleeding. The starting dose was adjusted according to patient’s age, antral follicle count (AFC) and prior response to gonadotropin stimulation as per unit protocol. We used step up protocol of gonadotropin stimulation and the dose was adjusted every 3–4 days according to ovarian response. GnRH antagonist, ganirelix (Orgalutran, Organon, The Netherlands) 0.25 mg/day was started when a leading follicle reached 14 mm and continued till the day of HCG. In the agonist group, GnRH agonist, Lucraine (Abbott Cedex, Istanbul, Turkey) 0.1 mg/day was started on day 21 of the pretreatment cycle. WH pituitary desensitization was achieved, ovarian stimulation was started and the GnRH agonist was continued with the same dose till day of HCG. Ovarian stimulation was performed in the same way as in the antagonist group. The gonadotropin preparations used were highly purified FSH (Fostimone, IBSA, Switzerland) and highly purified hMG (Merional, IBSA, Switzerland).

Ovarian follicular response was monitored, using transvaginal ultrasound. Ultrasound scanning was started on stimulation day 7 then every other day. HCG injection was given (Choriomone 5,000 IU im, Choriomone, IBSA, Switzerland) when at least 3 follicles greater than 16 mm in diameter were detected on transvaginal ultrasound scan with the leading follicle reached 18-20 mm in diameter. Oocyte retrieval was performed under anaesthesia 36 hours after HCG administration. Fertilization was performed by standard IVF or ICSI.

Cleavage-stage embryo transfer (ET) was performed on day 2 or 3. Embryo transfer was performed under abdominal ultrasound guidance for proper embryo placement to the mid-uterine cavity. Two to five grade A or B embryos were transferred as per unit protocol. Embryo transfer was performed with a Wallace catheter (Smith Medical International Ltd, Hythe, Kent, UK). Progesterone support of luteal phase was commenced on the day of ET with 800 mg micronized progesterone vaginally till 12 weeks of pregnancy. A serum HCG pregnancy test was performed 14 days after ET. Clinical pregnancies were confirmed by at least one ultrasonographically confirmed viable fetus within the uterus 4 weeks after ET.

Outcome measures

The Primary outcome measure of the study was:

- Ongoing pregnancy, defined as a clinical pregnancy of 12 or more weeks of gestation, per allocated woman.

The secondary outcome measures of the study were:

- Clinical pregnancy rate; calculated as the number of patients with clinical pregnancy divided by the number of patients who had embryo transfer.

- Incidence of OHSS. We used the modified classification system suggested by Mathur et al., 2005 [19].

- Total dose and duration of gonadotropin stimulation.

- Miscarriage rate per clinical pregnancy; calculated as the number of patients who had miscarriage divided by the number of patients who had clinical pregnancies.

- Multiple gestations rate; calculated as the number of patients who had multiple gestation divided by the number of patients who had clinical pregnancies.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Antagonist group</th>
<th>Agonist group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>30.4 ± 5.3</td>
<td>29.6 ± 5.3</td>
<td>0.4</td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
<td>28.2 ± 3.1</td>
<td>27.9 ± 3.6</td>
<td>0.2</td>
</tr>
<tr>
<td>Duration of infertility (years)</td>
<td>7.5 ± 1.3</td>
<td>7.6 ± 0.7</td>
<td>0.9</td>
</tr>
<tr>
<td>Infertility type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary secondary</td>
<td>42 (84%)</td>
<td>38 (76%)</td>
<td>0.1</td>
</tr>
<tr>
<td>Basal FSH (IU/L)</td>
<td>5.9 ± 1.2</td>
<td>5.2 ± 1.3</td>
<td>0.6</td>
</tr>
<tr>
<td>Basal LH (IU/L)</td>
<td>7.2 ± 1.3</td>
<td>7.7 ± 1.5</td>
<td>0.4</td>
</tr>
<tr>
<td>Testosterone (ng/ml)</td>
<td>2.2 ± 0.4</td>
<td>1.7 ± 0.5</td>
<td>0.7</td>
</tr>
<tr>
<td>SHBG (ng/ml)</td>
<td>40.4 ± 5.6</td>
<td>37.9 ± 4.9</td>
<td>0.8</td>
</tr>
<tr>
<td>FAI</td>
<td>6.6 ± 2.2</td>
<td>6.3 ± 2.1</td>
<td>0.8</td>
</tr>
<tr>
<td>Prolactin (ng/ml)</td>
<td>8.9 ± 2.1</td>
<td>8.4 ± 2.8</td>
<td>0.3</td>
</tr>
<tr>
<td>AFC</td>
<td>27.3 ± 3.4</td>
<td>29.1 ± 3.1</td>
<td>0.5</td>
</tr>
<tr>
<td>Ovarian volume (ml)</td>
<td>12.3 ± 2.4</td>
<td>13.1 ± 2.2</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD or number (%)

(BMI = body mass index, FSH = follicle stimulating hormone, LH = luteinizing hormone, SHBG = sex hormone binding globulin, FAI = free androgen index, AFC = antral follicle count)

Table 1: Characteristics of the study population.

- Total number of retrieved oocytes and mature oocytes.

- Total number of embryos and grade A embryos.

Embryos were classified according to Veeck’s grading [20] as follow:

- Grade 1: preembryos with blastomeres of equal size and no cytoplasmic fragmentations;

- Grade 2: preembryos with blastomeres of equal size with cytoplasmic fragmentations equal to 15% of the total embryo volume;

- Grade 3: uneven blastomeres with no fragmentations;

- Grade 4: uneven blastomeres with gross fragmentation (≥ 20% fragments).

Statistical methodology

Statistical analysis was performed using the Statistical Package for Social Science (SPSS Inc, Chicago) version 17 for Microsoft Windows. Data were described in terms of mean ± SEM (standard deviation) for continuous variables and frequencies (number of cases) and percentages for categorical data. Independent Student’s t-test was used to compare quantitative variables and Chi square test was used to compare categorical data. A P value <0.05% was considered significant.

Results

There was no significant difference in the demographic, hormonal or sonographic features between the two groups. Characteristics of the study population are summarized in Table 1.

Fifty cycles were initiated in each group. In the agonist group, 3 cycles were cancelled after oocyte retrieval due to high risk of OHSS. Frozen embryos were transferred later in non stimulated cycles. No cycles were cancelled in the antagonist group. This difference in the cycle cancellation rate was statistically significant (P = 0.01). The dose and duration of gonadotropin stimulation were significantly lower in the antagonist group as compared with the agonist group (P = 0.001). There were no significant differences between the two groups regarding the total number of retrieved oocytes, mature oocytes, total number of embryos, grade A embryos, fertilization and cleavage rates. The characteristics of ovarian stimulation in both groups are summarized in Table 2.
Table 2: Characteristics of ovarian stimulation in both groups.

<table>
<thead>
<tr>
<th>Antagonist group (n = 50)</th>
<th>Agonist group (n = 50)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cycles initiated</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>No. of ET cycles</td>
<td>50</td>
<td>47</td>
</tr>
<tr>
<td>Cancellation rate</td>
<td>0%</td>
<td>6%</td>
</tr>
<tr>
<td>Total HMG dose (IU)</td>
<td>2049.5 ± 396.2</td>
<td>2702.2 ± 618.9</td>
</tr>
<tr>
<td>Duration of stimulation (days)</td>
<td>11 ± 1.5</td>
<td>20.1 ± 1.6</td>
</tr>
<tr>
<td>Pre-ovulatory follicle (n)</td>
<td>13.1 ± 2.6</td>
<td>13.3 ± 2.5</td>
</tr>
<tr>
<td>Retrieved oocytes (n)</td>
<td>12.6 ± 5.3</td>
<td>10.9 ± 5.1</td>
</tr>
<tr>
<td>Mature oocytes (n)</td>
<td>7.3 ± 3.3</td>
<td>6.5 ± 2.6</td>
</tr>
<tr>
<td>Total no. of embryos</td>
<td>4.2 ± 2.4</td>
<td>4.4 ± 1.8</td>
</tr>
<tr>
<td>Embryo transferred (n)</td>
<td>3.3 ± 1.3</td>
<td>3.3 ± 0.9</td>
</tr>
<tr>
<td>Grade A embryo transferred (n)</td>
<td>2.3 ± 0.8</td>
<td>2.4 ± 0.7</td>
</tr>
<tr>
<td>Fertilization rate (%)</td>
<td>64.4 ± 9.2</td>
<td>68.1 ± 9.3</td>
</tr>
<tr>
<td>Cleavage rate (%)</td>
<td>94.5±0.6</td>
<td>94.7±0.5</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD or number (%)  
*Statistically significant difference

Table 3: The outcome measures in both groups.

<table>
<thead>
<tr>
<th></th>
<th>Antagonist group (n = 50)</th>
<th>Agonist group (n = 50)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical pregnancy rate (%)</td>
<td>24/50 (48%)</td>
<td>22/50 (44%)</td>
<td>0.8</td>
</tr>
<tr>
<td>Ongoing pregnancy rate (%)</td>
<td>20/50 (40%)</td>
<td>19/50 (38%)</td>
<td>0.9</td>
</tr>
<tr>
<td>Miscarriage rate (%)</td>
<td>4/24 (16.7%)</td>
<td>3/22 (13.6%)</td>
<td>0.7</td>
</tr>
<tr>
<td>Multiple pregnancy rate (%)</td>
<td>2/24 (8.3%)</td>
<td>4/22 (18.2%)</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Results obtained from a recent meta-analysis done by lin et al. (2014) including 1142 patients from nine studies that showed no difference between the use of GnRH antagonist protocol compared with the standard long protocol with respect to clinical pregnancy rate (CPR) and ongoing pregnancy rate (OPR) in patients with PCOS undergoing IVF while significantly reducing the rate of severe OHSS. That meta-analysis highlights the need for further RCTs to allow more solid conclusion [23].

The difference in the occurrence of OHSS observed in the current study does not appear to be associated with the number of retrieved oocytes as there was no significant difference between the two groups. However that may be related to the number of small follicles which were not retrieved and might be associated with the total dose and duration of gonadotropin stimulation which were significantly lower in the antagonist group.

One of the main advantages of the GnRH antagonist protocol that it is more patient friendly as the dose gonadotropin stimulation may be low and the duration of treatment is short by at least 14 days. If we take into consideration the cost of treatment per pregnancy including the working hours lost due to prolonged treatment and inconvenience of multiple injections for more days with the traditional long agonist protocol as well as the cost of hospitalization due to OHSS, the final cost may be considerably lower with the antagonist protocol. This economic comparison needs to be evaluated in further studies.

In conclusion, GnRH antagonist protocol can achieve a similar clinical pregnancy and ongoing pregnancy rates in patients with PCOS undergoing IVF / ICSI as compared with the traditional GnRH agonist long protocol with lower dose and shorter duration of gonadotropin stimulation and less risk of severe OHSS. GnRH antagonist protocol may be the protocol of choice in PCOS patients undergoing IVF / ICSI.

Discussion

Over the past few years, GnRH antagonist protocols have been more frequently used in IVF / ICSI in a wide range of patients including patients with expected high response. This last group includes PCOS patients who are at higher risk of developing OHSS during ovarian stimulation. Theoretically, GnRH antagonist protocols can reduce the OHSS rate. There is limited number of published studies evaluating the use of GnRH protocol in PCOS patients undergoing IVF / ICSI.

In this study, we evaluated the efficacy, safety of GnRH antagonist protocol in PCOS patients undergoing IVF / ICSI as compared with the traditional GnRH agonist long protocol. We used the ongoing pregnancy rate as the primary outcome. Incidence of OHSS, clinical pregnancy rate, total dose and duration of gonadotropin stimulation, miscarriage rate per clinical pregnancy and multiple pregnancy rate were used as the secondary outcome for the study.

In agreement with the results of the present study, Griesinger et al. (2006) in a meta-analysis including 305 patients from four studies found no significant difference in pregnancy rates in the agonist and antagonist groups, but a significantly higher incidence of severe OHSS in the agonist group [21]. Another meta analysis was done by Xio et al. (2013) including 1332 PCOS patients from 12 studies showed that GnRH antagonist protocol as compared to GnRH agonist protocols, is associated with fewer oocytes retrieved, lower E2 levels, and thinner endometrium whereas the clinical pregnancy and cycle cancellation rates are similar [22].

Acknowledgment

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