Short communication

Clinical outcome following stimulation with HMG versus highly purified HMG in patients undergoing ICSI

Ismail Aboul Foutouh¹,³, Sherif Khattab¹, Iman Abdel Mohsen¹, Mohamed Moaz², Hesham Al-Inany¹
¹Department of Obstetrics and Gynecology, Cairo University; ²The Egyptian International Fertility Center, Cairo, Egypt; ³Correspondence: Misr International Hospital, 40 Abdel Rehim Sabry St, Dokki, Cairo, Egypt; e-mail: kaainih@link.net

Abstract

Current purification processes allow the production of highly purified human menopausal gonadotrophin (HP-HMG), with human chorionic gonadotrophin (HCG) constituting most of its LH-like activity. This retrospective study aimed to compare the effectiveness of HP-HMG to the widely used traditional human menopausal gonadotrophin (HMG) preparation. A total of 174 women undergoing intracytoplasmic sperm injection cycles were allocated to either HMG or HP-HMG for ovarian stimulation. The number of mature oocytes was significantly higher in the HP-HMG group (14.72 ± 7.81) than in the HMG group (12.15 ± 11.07) (P < 0.05). However, the number of good quality embryos was not significantly different between both groups (HMG: 1.65 ± 1.54; HP-HMG: 1.78 ± 1.41). Similarly, there was no statistically significant difference in number of embryos transferred per woman (HMG: 3.95 ± 1.87; HP-HMG: 4.27 ± 1.60). The pregnancy rate per woman was 38.39% versus 51.79% in the HMG- and HP-HMG-treated groups respectively. These findings suggest that HP-HMG produces more mature oocytes than ordinary HMG, but similar pregnancy rates.

Keywords: HMG, HP-HMG, ICSI, oocytes, ovarian stimulation, pregnancy

Introduction

Human menopausal gonadotrophin (HMG) has been used for ovulation stimulation in assisted conception for many years with proven efficacy and safety (Al-Inany et al., 2005). However, it contains many impurities, hence cannot be self-administered subcutaneously. Recently, highly purified HMG (HP-HMG) has been introduced into the market (European and Israel Study Group, 2002) demonstrating a different mechanism of ovarian stimulation (Platteau et al., 2006).

However, there is substantial evidence in the medical literature that HP-HMG is not the same composition as the usual HMG. Although all HMG preparations contain human chorionic gonadotrophin (HCG), HP-HMG contains more HCG than traditional HMG and less LH. The HCG component in HP-HMG provides most of the LH-like activity in HP-HMG (Wolfenson et al., 2005). This was shown to induce a different follicular development profile (Filicori et al., 2001).

While the role of LH activity in ovarian stimulation was the subject of intense debate, the additional LH-like activity of HCG was recently demonstrated to influence embryo quality in IVM, as demonstrated by the MERIT study (Andersen et al., 2006). Although, it would be logical to move from urinary HMG to HP-HMG, which can be given subcutaneously, a direct comparison between both products is warranted before such a step is made. The preparation Merional was chosen as the study HP-HMG, because Menopur is not available in Egypt yet, and its effectiveness was compared to that of the commonly used HMG, Menogon. This situation is not peculiar to Egypt and occurs in many other countries.

Materials and methods

This was a retrospective controlled study including women undergoing intracytoplasmic sperm injection (ICSI) from August 2004 to August 2006 at The Egyptian International Infertility Centre (EIFC). The study protocol was approved by the local ethical committee. Inclusion criteria were women between 18–40 years old who decided to have IVF for the first time with no ovarian stimulation in the previous cycle. All cases had HMG concentrations greater than 10 IU/l at cycle day 3 and ultrasound examination showed a normal uterus. Different causes of infertility were included except those with severe endometriosis. Women with endocrine abnormalities such as hyperprolactinaemia were also excluded.

As multifollicular growth is a direct action of gonadotrophin administration in assisted reproduction, the number of oocytes was chosen as the primary outcome in this study. In both groups, ovarian stimulation was performed according to long standard protocol gonadotrophin-releasing hormone analogue (GnRHa) Triptorelin (Decapeptyl 0.1 mg, Ferring, Denmark) for down-regulation, starting in the mid-luteal phase of the
cycle preceding the treatment cycle and continued until the
day of HCG administration. Serum oestradiol assay was
carried out 14 days later to confirm down-regulation, then
women were allocated into two groups: Group A received
HP-HMG (Merional 75 IU, IBSA, Italy); Group B received
traditional HMG (Menogon, Ferring).

Monitoring was by ultrasound in all cases, and also by
oestradiol assay in those with a large number of follicles,
until the three leading follicles reached a mean diameter of
18 mm. Then 10,000 IU HCG (Chorimon IBSA, Suisse) was
administered deeply i.m. when the leading follicle reached 20
mm in diameter, with at least three follicles >18 mm. Oocyte
retrieval and ICSI were performed 34 to 36 hours later, as
previously described (Khattab et al., 2006).

Embryo transfer was performed 2–3 days later. Luteal
phase support was given to all patients (Cyclogest 400 mg,
Alpharma, USA) as vaginal pessaries, 400 mg twice a day
continued for 2 weeks followed by a β-HCG test.

Data are presented as mean ± standard deviation. Different
outcome measures were compared using Student’s t test
or Fisher’s exact test where appropriate. P-values < 0.05
were considered to be significant. Statistical analyses were
performed using Arcus Quickstat version I.

Results

A total of 174 women were enrolled in this study. There were
no differences regarding their background characteristics. The
response to ovarian stimulation was similar in both groups.
However, there were significantly fewer ampoules used in the
HP-HMG group (P = 0.001) (Table 1).

The number of mature oocytes was significantly higher
in HP-HMG group (14.72 ± 7.81) than in the HMG group
(12.15 ± 11.07) (P = 0.01) However, the number of good
quality embryos was not significantly different between both
groups (HMG: 1.65 ± 1.54; HP-HMG: 1.78 ± 1.41). Similarly,
there was no statistically significant difference in number of
embryos transferred per woman (HMG group: 3.95 ± 1.87;
HP-HMG group: 4.27 ± 1.60). The pregnancy rate per woman
was 38.39% versus 51.79% in the HMG and HP-HMG treated
groups, respectively (Table 1).

Discussion

The potential benefit from LH has remained the focus of
interest (Levy et al., 2000; Kolibianakis et al., 2004). In the
present study, although both drugs are urinary gonadotrophins,
the HCG content of HP-HMG is much higher (10–11 IU/vial)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HMG</th>
<th>HP-HMG</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cycles</td>
<td>118</td>
<td>56</td>
<td>–</td>
</tr>
<tr>
<td>Age of patient (years)</td>
<td>29.23 ± 3.90</td>
<td>28.25 ± 4.55</td>
<td>NS</td>
</tr>
<tr>
<td>No. of days of stimulation</td>
<td>10.59 ± 1.27</td>
<td>10.39 ± 1.43</td>
<td>NS</td>
</tr>
<tr>
<td>No. of ampoules used</td>
<td>40.28 ± 12.85</td>
<td>25.14 ± 20.81</td>
<td>0.001</td>
</tr>
<tr>
<td>Cumulus</td>
<td>14.54 ± 8.97</td>
<td>18.33 ± 9.77</td>
<td>0.01</td>
</tr>
<tr>
<td>Metaphase II</td>
<td>12.15 ± 11.07</td>
<td>14.72 ± 7.81</td>
<td>0.01</td>
</tr>
<tr>
<td>Metaphase I</td>
<td>1.18 ± 2.28</td>
<td>1.85 ± 1.98</td>
<td>0.09</td>
</tr>
<tr>
<td>2 pronuclei</td>
<td>5.62 ± 4.40</td>
<td>6.38 ± 3.99</td>
<td>NS</td>
</tr>
<tr>
<td>No. of transferred embryos</td>
<td>3.95 ± 1.87</td>
<td>4.27 ± 1.60</td>
<td>NS</td>
</tr>
<tr>
<td>No. of cryopreserved embryos</td>
<td>0.85 ± 2.79</td>
<td>0.77 ± 2.39</td>
<td>NS</td>
</tr>
<tr>
<td>Total embryos</td>
<td>4.19 ± 1.53</td>
<td>4.38 ± 1.38</td>
<td>NS</td>
</tr>
<tr>
<td>Good quality</td>
<td>1.65 ± 1.54</td>
<td>1.78 ± 1.41</td>
<td>NS</td>
</tr>
<tr>
<td>Fair quality</td>
<td>1.77 ± 1.33</td>
<td>2.05 ± 1.54</td>
<td>NS</td>
</tr>
<tr>
<td>Poor quality</td>
<td>0.85 ± 1.20</td>
<td>0.76 ± 1.27</td>
<td>NS</td>
</tr>
<tr>
<td>Pregnancy rate (%)</td>
<td>38.39</td>
<td>51.79</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are mean ± standard deviation unless otherwise stated; NS = not statistically significant; OR = odds
ratio; CI = confidence interval.
than the LH content, demonstrating that the LH-like activity of the product is due to the HCG content (Giudice et al., 2001). Whether this has higher value than HMG itself is still unclear. Studies published so far on HP-HMG have compared it to recombinant FSH (Andersen et al., 2006; Platteau et al., 2006).

Although it is reasonable to believe that HCG may provide a different stimulation profile when compared with LH (other than what is related to different potency), there is no published evidence of it. The present study is the first to assess the efficacy of using highly purified HMG as compared with traditional HMG. Use of HP-HMG resulted in a higher number of mature oocytes with a lower number of ampoules administered. This is likely to be related to the LH-like activity of HCG which synergizes with HMG once larger ovarian follicles begin to express granulosa cell LH receptors, a hypothesis which matches with previously published studies (Kilani et al., 2003).

Long luteal protocol for down-regulation was used as it is the gold standard in ovarian stimulation in ICSI programmes. Depot GnRH agonist was not used for down-regulation as it is known to result in profound pituitary suppression, which might artificially contribute to the advantages of excess LH-like activity.

In this study, ICSI was chosen as the sole assisted reproduction technique in order to document unequivocally oocyte maturity on the day of oocyte retrieval and to eliminate the occurrence of fertilization failures dependent on factors unrelated to the quality of the ovarian stimulation.

There was no significant difference in the number of embryos replaced and clinical pregnancy rate was not statistically different between the two groups. There was no statistically significant difference in the incidence of ovarian hyperstimulation syndrome in the two groups and no recorded serious local reaction following either HP-HMG or HMG treatment.

Another point to be considered is that amount of HCG in the HP-HMG administered was negligible in comparison to the amount administered at the end of the stimulation (10,000 IU). No negative effect on the triggering of ovulation due to this amount of HCG was observed.

Although this study is retrospective with a limited sample size, the findings suggest that highly purified HMG produces more mature oocytes with fewer ampoules, but a similar pregnancy rate, compared with ordinary HMG.

References


Khattab S, Mohsen IA, Foutouh IA et al. 2006 Metformin reduces abortion in pregnant women with polycystic ovary syndrome. Gynecological Endocrinology 22, 680–684.


Received 13 November 2006; reffered 4 December 2006; accepted 8 December 2006.