The efficacy of modified luteal phase support with intramuscular progesterone in IVF/ICSI cycles: a retrospective observational study

A. CONFORTI1, I. STRINA1, A. MOLLO1, R. AMOROSO1, V. MARRONE1, C. ALVIGGI1, R. MARCI2, G. DE PLACIDO1

1Department of Neuroscience, Reproductive Science and Odontostomatology, University of Naples Federico II, Naples, Italy
2Department of Morphology Surgery and Experimental Medicine, University of Ferrara, Ferrara, Italy

Abstract. – OBJECTIVE: The use of gonadotropin-releasing hormone agonist for ovulation triggering has become an intriguing topic in the last few years. As long as adequate luteal phase support is provided, it may be a valuable alternative to standard hCG triggering, associated with a significant reduction in OHSS incidence. Several luteal phase support options have been proposed, but few studies have addressed the issue of the appropriate route for progesterone administration to women triggered with GnRHa.

The aim of the study was to evaluate the effect of GnRHa triggering on IVF/ICSI outcomes, using modified luteal phase support with intramuscular progesterone.

PATIENTS AND METHODS: A retrospective study was carried out between January 2014 and December 2015, comparing the reproductive outcome in GnRHa triggered women given modified luteal phase support with intramuscular progesterone (Group A) with the outcome in women triggered with standard hCG (Group B) in IVF/ICSI cycles.

RESULTS: 200 (Group A n = 100; Group B n = 100) consecutive normoresponder women were included. No differences with respect to Age, BMI, basal FSH, basal Estradiol and infertility diagnosis were observed between groups. Increased numbers of retrieved oocytes (8.1 ± 3.3 versus 6.8 ± 3.5, p = 0.009) and mature oocytes (5.8 ± 2.6 versus 5.1 ± 2.7, p = 0.03) were detected in Group A compared with Group B. Implantation, biochemical pregnancy and ongoing pregnancy rates were similar.

CONCLUSIONS: Our findings confirmed that the GnRHa triggering strategy is associated with increased number of oocytes retrieved and of mature oocytes even in normoresponder women. Moreover, in these patients, the use of intramuscular progesterone during luteal phase support achieved satisfactory IVF outcomes.

Key Words:
GnRH agonist, Ovarian triggering, hCG, IVF.

Introduction

The use of gonadotropin-releasing hormone agonist (GnRHa) for ovulation triggering is an intriguing strategy in the reproductive field1,2. The main advantage consists in a significant reduction in ovarian hyperstimulation syndrome (OHSS), which is a common complication of human chorionic gonadotropin (hCG) administration. GnRHa has a shorter half-life and, at the same time, is able to induce oocyte maturation through the “flare up” effect. GnRHa is also able to induce a more physiological ovulation by increasing both FSH and LH levels4, and fewer patients experience discomfort, reduced ovarian volume, ascites and abdominal pain5,6.

On the other hand, a recent meta-analysis7 concluded that this kind of strategy may be associated with lower pregnancy rates, live birth rates and higher incidence of miscarriage. These negative effects are not observed in donor-recipient cycles7.

The negative impact on IVF has raised many doubts regarding the use of GnRHa for ovulation triggering in assisted reproductive technology (ART). The abnormal luteal phase induced by GnRHa is believed to be the most important physiopathological reason for impaired ovarian response. Specifically, GnRHa is able to induce a LH surge that lasts only 24-36h8 – not adequate for appropriate luteal support6.

In order to ameliorate luteal phase support, several strategies have been proposed9 with satisfactory results even in women not at risk of developing OHSS9. Nonetheless, there is no consensus on the optimal luteal phase support protocol9. For instance, some authors9,10 have suggested that progesterone route could be of importance in women triggered with intramuscular progesterone.
GnRHa to adequately sustain corpus luteum activity. However, few trials have addressed this issue.

A retrospective observational study was carried out with the aim of evaluating the effect of luteal phase support with intramuscular progesterone in normoresponder women triggered with GnRHa.

**Patients and Methods**

From January 2014 to December 2015 we retrospectively analyzed only normogonadotropic normoresponder Caucasian women. The following inclusion criteria were adopted: age between 21-44 years, body mass index (BMI) 18-40 kg/m², FSH < 10 UI/L. We excluded patients with endocrine inflammatory disorders, immune disorders and uterine malformations.

All patients underwent GnRH antagonist cycle with exogenous gonadotropin, using individualized starting dosages according to BMI, age and baseline hormonal characteristics. The ovarian response was monitored by ultrasound examination and the dose was adjusted on the basis of response.

Ovarian maturation was induced with GnRHa in the study group (Ferring S.P.A., Milan, Italy) and with hCG in the control group (Gonasi HP; IBSA Farmaceutici Italia Srl, Lodi, Italy) when at least three follicles reached a mean diameter of 17 mm at the dosage of 10,000 IU and 0.2 mg. Oocytes were retrieved 35 h after ovulation induction.

When GnRHa was adopted for ovarian triggering, modified luteal phase support was provided with hCG 1500 IU i.m. at the time of oocyte retrieval plus estradiol valerate (Progonova Bayer S.p.A. Milan, Italy) 4 mg per day and intramuscular injection of progesterone 50 mg per day (IBSA Farmaceutici Italia S.r.l., Lodi, Italy). In the hCG group, luteal phase support was provided vaginally in the form of 400 mg micronized progesterone (Prometrium; Rottapharm S.p.A., Milan, Italy).

Signed written informed consent was obtained from all participants, who also consented to the anonymous processing of their personal data.

A biochemical pregnancy was defined as a positive βhCG concentration test and ongoing pregnancy by direct visualization of gestation sac by ultrasound.

The primary outcome of this study was the ongoing pregnancy rate. The secondary outcomes were: the number of oocytes retrieved, the number of mature oocytes, the implantation rate and the ongoing pregnancy rate.

**Statistical Analysis**

Results were analyzed using the statistical package SPSS 22 for Windows (SPSS IBM, USA).

Student’s t-test was used to compare continuous variables while the χ²-test was adopted to compare categorical data. Continuous data were expressed as mean ± standard deviation. Categorical data were expressed as percentages. A p-value < 0.05 was considered statistically significant.

**Results**

A total of 200 consecutive women were included: Group A consisted of 100 patients who underwent GnRHa at the time of triggering; Group B of 100 women served as the control group, in which hCG was adopted for follicle maturation (n = 100). No difference with respect to age, BMI, FSH and estradiol baseline levels and infertility diagnosis were observed between groups (Table I). The duration of ovarian stimulation, the total amount of exogenous FSH and the stimulation duration were all comparable between groups (Table II). The number of follicles observed at the time of triggering did not differ between groups (Table II).

An increased number of retrieved oocytes (8.1 ± 3.3 versus 6.8 ± 3.5, p = 0.009) and mature oocytes (5.8 ± 2.6 versus 5.1 ± 2.7, p = 0.03) was detected in Group A compared with Group B. Nonetheless, the implantation rate, biochemical pregnancy rate and ongoing pregnancy rate were similar in the two groups (Table I).

**Discussion**

Our study has provided further evidence showing that ovulation maturation induced by GnRHa triggering has a positive effect in terms of number of oocytes retrieved and mature oocytes. Moreover, satisfactory pregnancy, implantation and ongoing pregnancy rates were observed in the study group (Table II). The hypothesis that GnRHa triggering may improve the number of mature oocytes has been advocated since 2005; however, conflicting results have been reported. The phenomenon was attributed to the release of a more physiological surge of gonadotropins, containing not only LH as hCG, but also FSH. Particularly the FSH surge seems to have an effect on oocyte maturation processes.
The efficacy of modified luteal phase support with intramuscular progesterone in IVF/ICSI cycles

In a study including 122 women randomized to receive 10000 IU hCG or 0.5 mg of buserelin, the GnRHa group developed a higher number of mature oocytes, but had a lower pregnancy rate\(^1\). A significant impact on oocyte maturation was also reported by Reddy et al\(^{15}\) and Otkay et al\(^{16}\) in patients with breast cancer undergoing COS for fertility preservation with an aromatase inhibitor. In line with our results are findings from Lin et al\(^{17}\), who adopted a dual trigger with 250 mg of recombinant hCG plus 0.2 mg of triptorelin. Specifically, the authors observed significantly higher pregnancy and live birth rates in the “dual trigger” group compared with the standard hCG trigger.

Our findings are consistent with Lin et al\(^{17}\) in terms of number of oocytes retrieved and of mature oocytes. However, we did not detect any difference with respect to implantation rate and ongoing pregnancy rate. Although GnRHa may ameliorate the quality of oocytes, the impaired luteal phase support associated with this approach should be avoided. Specifically, in our study, we adopted modified luteal phase support according to Humaidan et al\(^{18}\) with a low adjuvant dose of hCG at the time of oocyte retrieval. Instead of vaginal administration, we used intramuscular injections of progesterone. Although the route of progesterone administration does not seem to influence reproductive outcome in standard IVF, the effect may be different in patients triggered with GnRHa.

Some authors\(^9\) have claimed that the use of intramuscular progesterone may be important for a successful intensive luteal phase in this subgroup

### Table I. Basal characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Group A (n = 100)</th>
<th>Group B (n = 100)</th>
<th>(p)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>32.8 ± 4.9</td>
<td>33.9 ± 4.3</td>
<td>NS</td>
</tr>
<tr>
<td>BMI kg/m(^2)</td>
<td>24.2 ± 6.2</td>
<td>24.7 ± 6.2</td>
<td>NS</td>
</tr>
<tr>
<td>FSH (UI/L)</td>
<td>5.9 ± 2.4</td>
<td>6.4 ± 2.4</td>
<td>NS</td>
</tr>
<tr>
<td>Basal estradiol (pg/ml)</td>
<td>70.9 ± 80.3</td>
<td>74.3 ± 106.2</td>
<td>NS</td>
</tr>
<tr>
<td>Ovulation disorders</td>
<td>16%</td>
<td>15%</td>
<td>NS</td>
</tr>
<tr>
<td>Male</td>
<td>37%</td>
<td>48%</td>
<td>NS</td>
</tr>
<tr>
<td>Tubal</td>
<td>9%</td>
<td>10%</td>
<td>NS</td>
</tr>
<tr>
<td>Unexplained</td>
<td>23%</td>
<td>17%</td>
<td>NS</td>
</tr>
<tr>
<td>Others</td>
<td>15%</td>
<td>10%</td>
<td>NS</td>
</tr>
</tbody>
</table>

Continuous data are expressed in mean ± standard deviation; Categorical data are expressed in percentage %. BMI: body mass index; FSH: follicle stimulating hormone; NS: no statistical significance.

### Table II. Ovarian stimulation outcome.

<table>
<thead>
<tr>
<th></th>
<th>Group A (n = 100)</th>
<th>Group B (n = 100)</th>
<th>(p)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total FSH dosage</td>
<td>1126.6 ± 744.9</td>
<td>1268.7 ± 958.7</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of stimulation (n. day)</td>
<td>9.1 ± 2.5</td>
<td>9.2 ± 1.7</td>
<td>NS</td>
</tr>
<tr>
<td>N. follicles day of triggering &lt;15 mm</td>
<td>9.1 ± 3.1</td>
<td>8.5 ± 3.8</td>
<td>NS</td>
</tr>
<tr>
<td>Estradiol day 5 (pg/ml)</td>
<td>464.8 ± 368.9</td>
<td>427.6 ± 275.7</td>
<td>NS</td>
</tr>
<tr>
<td>Estradiol day 8 (pg/ml)</td>
<td>1068.2 ± 692.6</td>
<td>907.5 ± 492.1</td>
<td>NS</td>
</tr>
<tr>
<td>Estradiol peak (pg/ml)</td>
<td>1630.7 ± 862.7</td>
<td>1385.4 ± 997.1</td>
<td>NS</td>
</tr>
<tr>
<td>N. oocytes retrieved</td>
<td>8.1 ± 3.3</td>
<td>6.8 ± 3.5</td>
<td>0.009</td>
</tr>
<tr>
<td>N. mature oocytes</td>
<td>5.8 ± 2.6</td>
<td>5.1 ± 2.7</td>
<td>0.03</td>
</tr>
<tr>
<td>N. embryo transferred</td>
<td>2.04 ± 0.57</td>
<td>2.13 ± 0.59</td>
<td>NS</td>
</tr>
<tr>
<td>Implantation rate</td>
<td>20.9%</td>
<td>15.3%</td>
<td>NS</td>
</tr>
<tr>
<td>Biochemical pregnancy</td>
<td>39%</td>
<td>35%</td>
<td>NS</td>
</tr>
<tr>
<td>Ongoing pregnancy rate</td>
<td>27%</td>
<td>23%</td>
<td>NS</td>
</tr>
</tbody>
</table>

Continuous data are expressed in mean ± standard deviation; Categorical data are expressed in percentage %. FSH: follicle stimulating hormone; NS: no statistical significance.
of women. To date, we still do not know which progesterone route is preferable. The use of intramuscular progesterone for luteal phase support has already been adopted in women at high risk of OHSS syndrome\textsuperscript{11,19,20}. To our knowledge, this is the first study where the use of intramuscular progesterone was adopted in normal responder women triggered with GnRHa with a positive trend regarding the ongoing pregnancy rate and implantation rate in the GnRHa triggered group. The trend did not reach statistical significance (Table II).

Nonetheless, larger randomized trials are required to clarify whether the route of progesterone administration is of importance in this group of patients. Optimal luteal phase support in GnRHa triggered women is still a matter of debate and there is no clear consensus on dosage and timing.

Hopefully, a specific model will be designed with the aim of providing tailored luteal phase support based on individual profiles\textsuperscript{6}. For instance, the administration of hCG might not be indicated, when the ovarian response is excessive in terms of number of follicles or estradiol peak.

Conclusions

According to our findings, the GnRHa triggering strategy may be a valuable alternative even in women not at risk of developing OHSS, as long as adequate luteal phase support is provided. Furthermore, luteal phase support using intramuscular progesterone is associated with higher pregnancy and ongoing pregnancy rates than standard hCG triggering.

Conflict of interest

The authors declare no conflicts of interest.

References


13) Engmann L, DeLugli A, Schmidt D, Nulsen J, Maijer D, Benadiva C. The use of gonadotropin-releasing hormone (GnRH) agonist to induce oocyte maturation after cotreatment with GnRH antagonist in


