ART

Mild stimulation in assisted reproduction

PEDRO N. BARRI, ROSA TUR, FRANCISCA MARTINEZ, & BUENAVENTURA COROLEU

Department of Gynecology, Obstetrics and Reproductive Medicine, Institut Universitari Dexeus, Gran Via de Carlos III, Barcelona, Spain

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Abstract
The conventional ovarian stimulation protocols currently applied have several drawbacks arising from the intense ovarian stimulation and from the high financial cost. Recently, new concepts such as mild stimulation and friendly in vitro fertilisation have rapidly acquired great popularity among infertile patients although the medical world is still reluctant to apply these protocols generally. We have observed that although with soft stimulation fewer oocytes are retrieved, pregnancy rates are not affected if more than five oocytes are obtained in the follicular aspiration. Another important issue is the additional value of the embryo cryopreservation programmes that will result in cumulative pregnancy rates no different from those obtained with conventional protocols. The benefits of combining these mild stimulation protocols with a selective reduction of the number of embryos to replace have helped us in reducing the incidence of multiple pregnancies and the global cost of the treatment.

Keywords: Assisted reproduction, IVF, ovarian simulation protocols, mild stimulation, friendly IVF

Introduction
Although the birth of Louise Brown, the first human being to be conceived following the application of in vitro fertilisation (IVF) techniques, was the result of a spontaneous cycle [1], nowadays, almost all of the IVF cycles that are carried out in the world are accompanied by several ovarian stimulation protocols that enhance multiple follicular development with the aim of achieving a larger number of oocytes and of embryos, thus increasing the chances of achieving a pregnancy [2].

Most of the protocols that are applied now combine the pituitary suppression achieved with administration of a GnRH analogue with ovarian stimulation through administration of exogenous gonadotrophins. However, these treatments have a number of drawbacks arising from the intense ovarian stimulation, such as physical and mental distress for the patient, the risk of developing an ovarian hyperstimulation syndrome, the excessive incidence of multiple pregnancies and the high financial cost [3].

Recently, mild stimulation protocols have been applied, in which low doses of exogenous gonadotrophins are administered during the second half of the follicular phase together with GnRH antagonists [4]. Although these protocols can involve a certain reduction in the efficacy of the IVF cycles, it is clear that they help to make the treatment more bearable for the patients. New concepts are arising such as minimal stimulation and friendly IVF, which have rapidly acquired great popularity among patients though there is a reluctance in the medical world to apply these protocols generally [5,6].

In this friendly environment, there is one more element, the selective reduction of the number of embryos to transfer. In this way, the mild stimulation, which is beneficial for the patient's comfort, is combined with the potential reduction in the risk of multiple pregnancy; this is obviously useful in view of the growing epidemic of multiple pregnancies that are produced by application of assisted reproduction techniques (ART) [7,8]. Recently, a prospective randomised study has been published that clearly shows a significant reduction in the percentage of embryonic aneuploidies in the group of patients that underwent a mild stimulation protocol in comparison with the group of IVF patients who underwent a conventional stimulation protocol [9]. There is also a further aspect to consider, the cost-benefit analysis that must be performed to assess the possibility of a general application of these strategies [10].
Material and methods

To decide on the right ovarian response parameters to stimulation for IVF with the aim of achieving a pregnancy, we assessed the results obtained after 5476 IVF cycles depending on the consumption of gonadotrophins and the number of oocytes retrieved.

After applying a multivariate logistical regression analysis to the data obtained in these cycles, and after adjustment for the patients’ age and basal FSH levels, we were able to establish three dichotomous categories. We saw that below five oocytes retrieved the chances of achieving pregnancy were significantly reduced. The ideal number is between six and eight oocytes; if the number of oocytes obtained was nine or more, the pregnancy rate did not increase significantly (Table I). We found a similar distribution on studying the implantation rate as a function of the number of oocytes obtained. Below five oocytes, the implantation rate fell significantly in relation to what was reached when the number of retrieved oocytes was between 5 and 15. Above that the implantation rate no longer increased significantly.

As for gonadotrophin consumption, we observed an inverse relationship between the total dose of gonadotrophins that was used and the possibility of achieving a pregnancy. We found that at a total dose of more than 3225 IU the possibilities of pregnancy fell significantly and this finding was valid for all age groups (Table II and Figure 1). We also found that in the cycles in which the total gonadotrophin consumption was less than 1500 IU, more oocytes were obtained, and it was possible to freeze more embryos than when the consumption of gonadotrophins was higher (4.6 vs. 2.1, \( p < 0.001 \)). On analysing the accumulated pregnancy rate after the transfer in the fresh cycle plus that of the cryo-transfer cycle, we found that the rate was higher when the gonado-

Troponin consumption had been below 1500 IU, 63.3% against 43.5% in the cycles with greater consumption (\( p < 0.002 \)) and when the number of oocytes retrieved in the initial fresh cycle was greater (Table III and Figure 2).

With regard to the rates for aneuploidies found in the embryos that were submitted to embryo biopsy for preimplantational genetic diagnosis (PGD) as a function of the consumption of gonadotrophins, we studied the results obtained from analysing 1353 embryos from 179 IVF-PGD cycles undergone by 156 patients with a maximum age of 37 years and who needed PGD, but among whom the cases of chromosomal translocation had been excluded. We found that the patients who consumed more than 1500 IU of gonadotrophins had a similar

**Table I. Multivariate logistic regression. Influence of the number of oocytes retrieved on pregnancy rate (\( n = 5476 \) OPU).**

<table>
<thead>
<tr>
<th>Oocytes retrieved</th>
<th>OR</th>
<th>Significance</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \leq 5 )</td>
<td>0.57</td>
<td>&lt;0.001</td>
<td>0.46–0.70</td>
</tr>
<tr>
<td>6–8</td>
<td>1</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>9–12</td>
<td>1.01</td>
<td>0.9</td>
<td>0.83–1.23</td>
</tr>
<tr>
<td>( \geq 13 )</td>
<td>1.13</td>
<td>0.2</td>
<td>0.94–1.36</td>
</tr>
</tbody>
</table>

Adjusted for age, basal FSH and Gns consumption.

**Table II. Multivariate logistic regression. Influence of gonadotropin consumption on pregnancy rate (\( n = 5476 \) OPU).**

<table>
<thead>
<tr>
<th>GNS dose (IU)</th>
<th>OR</th>
<th>Significance</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \leq 2626 )</td>
<td>1</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>2627–3225</td>
<td>0.9</td>
<td>0.23</td>
<td>0.76–1.07</td>
</tr>
<tr>
<td>3226–4125</td>
<td>0.6</td>
<td>&lt;0.001</td>
<td>0.57–0.81</td>
</tr>
<tr>
<td>( \geq 4126 )</td>
<td>0.5</td>
<td>&lt;0.001</td>
<td>0.43–0.67</td>
</tr>
</tbody>
</table>

Adjusted for age and basal FSH.

Figure 1. Influence of gonadotrophin consumption on pregnancy rate.

**Table III. Influence of GNS dose on cumulative pregnancy rates (fresh + frozen cycles) (\( n = 529 \) patients).**

<table>
<thead>
<tr>
<th></th>
<th>( \leq 1500 ) IU</th>
<th>( &gt; 1500 ) IU</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preg/fresh cycle (%)</td>
<td>43.3</td>
<td>35.1</td>
<td>–</td>
</tr>
<tr>
<td>Cumulative preg/fresh + frozen cycles</td>
<td>63.3</td>
<td>43.5</td>
<td>&lt;0.002</td>
</tr>
</tbody>
</table>

Figure 2. Cumulative pregnancy rate (fresh + frozen) according to the number of oocytes retrieved.
number of oocytes retrieved and of valid embryos for biopsy at the same time as a practically identical number of normal embryos (Figure 3). Nevertheless, there was a tendency towards lower-quality embryos when the number of oocytes retrieved was more than 20 though this did not achieve statistical significance.

In our experience, the cycles in which gonadotrophin consumption was lower did not involve a lower pregnancy rate, provided that six or more oocytes had been retrieved. The strategy is to combine these mild stimulation cycles with the selective transfer of a small number of embryos and the freezing of the remaining embryos. In these cycles, good implantation and pregnancy rates are obtained with accumulated rates after the fresh transfer plus cryotransfer that show no significant differences between selectively transferring one embryo or two (66.2% vs. 69.7%, Table IV).

Discussion

It is accepted that there are now more than 3 million children born following IVF and the use of Assisted Reproduction Techniques continues to grow [11,12]. We are in a position to identify the more negative aspects of ART and we must try to avoid them. There can be no doubt that the application of mild stimulation protocols will help to make it easier for patients to follow the treatment without their possibilities of pregnancy being compromised.

Drawbacks of the mild stimulation protocols for IVF

With the mild ovarian stimulation protocols, it is obvious that the duration of the treatment and the total dose of gonadotrophins used are reduced [13]. However, these strategies can involve a decrease in ovarian response and a higher risk of cancellation of the cycle because of inadequate or insufficient response. While it has been shown that reducing the intensity of the stimulation lowers the number of oocytes retrieved in the aspiration, as long as a sufficient number of oocytes is achieved there is no reason why the final pregnancy rate should be compromised [14].

Another potential drawback of the mild of stimulation strategies is the lower possibility of embryo freezing. Although this is a theoretical possibility, there is no doubt that it can compromise the accumulated rate that can be achieved by combining the results of the fresh cycles with the cryotransfer cycles. This is more apparent in countries where ART is covered by the public health service, and the patients receive numerous attempts at treatment with no personal financial cost [15].

This situation gives rise to a series of questions about the efficiency of these therapeutic alternatives. Questions as to the ideal number of oocytes to retrieve and their quality, the possibility of applying selective transfer policies of a single embryo and the advantages of having frozen embryos for later transfer must be answered in the light of accumulated clinical experience. This was our point of view in analysing the recent results of our IVF programme.

Moreover, the application not only of milder protocols but also the use of in vitro maturation programmes or even of spontaneous cycles accompanied by very little stimulation will make it possible to improve pregnancy rates while greatly simplifying the procedures. This strategy will be very useful not only in improving patient comfort but also in reducing the cost of the treatment. In this regard,
the reduction in the rate of multiple pregnancies that will result from combining the mild stimulation strategies with selective transfer of a small number of embryos will also help to reduce the obstetric and neonatal costs involved in dealing with these patients [16].

We believe that the time has come to apply protocols that make this treatment friendlier for the patients through mild stimulation protocols with simpler monitoring and with the transfer of a small number of embryos. If we can reach these goals without reducing the pregnancy rates, that will be the time for the general use of these strategies.

Acknowledgements

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References