The gonadotropin-releasing hormone antagonist protocol – the protocol of choice for the polycystic ovary syndrome patient undergoing controlled ovarian stimulation

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Abstract
Polycystic ovary syndrome (PCOS) patients are prone to develop ovarian hyperstimulation syndrome (OHSS), a condition which can be minimized or completely eliminated by the use of a gonadotropin-releasing hormone agonist (GnRHa) trigger. In this commentary paper, we maintain that the gonadotropin-releasing hormone antagonist protocol should be the protocol of choice for the PCOS patient undergoing ovarian stimulation with gonadotropins for in vitro fertilization. If an excessive ovarian response is encountered, the clinician will always have two options: either to trigger final oocyte maturation with a bolus of GnRHa and supplement the luteal phase with a small bolus of human chorionic gonadotropin (hCG) in addition to the standard luteal phase support and transfer in the fresh cycle or, alternatively, to trigger with GnRHa and perform a total freeze, resulting in a complete elimination of OHSS and high ongoing pregnancy rates in the subsequent frozen–thawed transfer cycles.

Abbreviations: GnRH, gonadotropin-releasing hormone; GnRHa, gonadotropin-releasing hormone agonist; hCG, human chorionic gonadotropin; IVF, in vitro fertilization; LH, luteinizing hormone; OHSS, ovarian hyperstimulation syndrome; PCOS, polycystic ovary syndrome; RCT, randomized controlled trial.

Following its introduction at the turn of the millennium, the gonadotropin-releasing hormone (GnRH) antagonist protocol has been used successfully in assisted reproductive technology. Although, previously, it was debated whether or not the long GnRH agonist (GnRHa) protocol was superior to the GnRH antagonist protocol in terms of the reproductive outcome (1,2), the latest meta-analysis showed no difference in the live birth rate between the two GnRH analogs (3). Moreover, the GnRH antagonist protocol is associated with a significant reduction in the occurrence of ovarian hyperstimulation syndrome (OHSS; 3,4). Importantly, GnRH antagonist cotreatment allows final oocyte maturation to be triggered with a bolus of GnRHa instead of human chorionic gonadotropin (hCG; 5); a procedure which is known...
Table 1. Main characteristics and OHSS rate in studies on GnRHa triggering vs. hCG triggering of final oocyte maturation.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Trial type</th>
<th>Oocyte source</th>
<th>Ovulation trigger</th>
<th>n</th>
<th>Cumulus oocyte complex (mean)</th>
<th>OHSS risk</th>
<th>OHSS [% (n)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acevedo et al. (2006)</td>
<td>RCT</td>
<td>Donors</td>
<td>GnRHa</td>
<td>30</td>
<td>9.1</td>
<td>Low</td>
<td>0 (0/30)</td>
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<td>Babayof et al. (2006)</td>
<td>RCT</td>
<td>Own</td>
<td>GnRHa</td>
<td>15</td>
<td>19.8</td>
<td>High</td>
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<tr>
<td>Engmann et al. (2006)</td>
<td>Retrospective</td>
<td>Own</td>
<td>GnRHa</td>
<td>23</td>
<td>20</td>
<td>High</td>
<td>0 (0/23)</td>
</tr>
<tr>
<td>Orvieto et al. (2006)</td>
<td>Retrospective</td>
<td>Own</td>
<td>GnRHa</td>
<td>82</td>
<td>22.3</td>
<td>High</td>
<td>0 (0/82)</td>
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<tr>
<td>Griesinger et al. (2007)</td>
<td>Observational</td>
<td>Own</td>
<td>GnRHa</td>
<td>69</td>
<td>16.8</td>
<td>High</td>
<td>7 (5/69)</td>
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<tr>
<td>Shapiro et al. (2007)</td>
<td>Retrospective</td>
<td>Donors</td>
<td>GnRHa</td>
<td>42</td>
<td>21.7</td>
<td>High</td>
<td>1 (1/42)</td>
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<tr>
<td>Bodri et al. (2009)</td>
<td>Retrospective</td>
<td>Donors</td>
<td>GnRHa</td>
<td>1046</td>
<td>13.6</td>
<td>Intermediate</td>
<td>0 (0/1046)</td>
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<td>Humaidan et al. (2009)</td>
<td>RCT</td>
<td>Own</td>
<td>GnRHa</td>
<td>152</td>
<td>8.9</td>
<td>Low</td>
<td>0 (0/152)</td>
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<td>Hernandez et al. (2009)</td>
<td>Retrospective</td>
<td>Donors</td>
<td>GnRHa</td>
<td>254</td>
<td>13.2</td>
<td>Intermediate</td>
<td>0 (0/254)</td>
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<td>Melo et al. (2009)</td>
<td>RCT</td>
<td>Donors</td>
<td>GnRHa</td>
<td>175</td>
<td>8.7</td>
<td>Low</td>
<td>6 (10/175)</td>
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<td>Simanoglu et al. (2009)</td>
<td>RCT</td>
<td>Donors</td>
<td>GnRHa</td>
<td>50</td>
<td>17.1</td>
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<td>Observational</td>
<td>Own</td>
<td>GnRHA, luteal rescue with hCG (1500 IU)</td>
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<td>21.5</td>
<td>High</td>
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<td>Galindo et al. (2009)</td>
<td>RCT</td>
<td>Donors</td>
<td>GnRHa</td>
<td>106</td>
<td>11.4</td>
<td>Low</td>
<td>0 (0/106)</td>
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<td>Manzanares et al. (2010)</td>
<td>Retrospective</td>
<td>Own</td>
<td>GnRHa</td>
<td>42</td>
<td>12.6</td>
<td>High</td>
<td>0 (0/42)</td>
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<td>Tehaninejad et al. (2010)</td>
<td>RCT, high risk</td>
<td>Own</td>
<td>GnRHa</td>
<td>45</td>
<td>13.4</td>
<td>High</td>
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<td>Griesinger et al. (2010)</td>
<td>Prospective cohort study</td>
<td>Own</td>
<td>GnRHa</td>
<td>40</td>
<td>18</td>
<td>High</td>
<td>0 (0/40)</td>
</tr>
</tbody>
</table>

Abbreviations: GnRHa, gonadotropin-releasing hormone; GnRHa, gonadotropin-releasing hormone agonist; hCG, human chorionic gonadotropin; OHSS, ovarian hyperstimulation syndrome; PCOS, polycystic ovary syndrome; and RCT, randomized controlled trial.
to either totally eliminate or significantly reduce the risk of OHSS in the high-risk patient. Thus, of 2034 patients triggered with a GnRHa in published studies only one patient developed mild OHSS (after hCG rescue), whereas 83 of 1810 patients triggered with hCG (4.6%) developed OHSS (Table 1).

In the era of “personalized treatment”, clinicians are obliged to consider each individual patient prior to stimulation to determine the most appropriate protocol, combining the lowest treatment burden and risk with the highest chance of conception. Thus, for the oocyte donor it is now generally recommended that ovarian stimulation should be performed with GnRH antagonist cotreatment, while final oocyte maturation should be accomplished with a bolus of GnRHa instead of hCG, because this protocol eliminates OHSS and gives less discomfort for the donor in the “luteal phase”, i.e. the days following oocyte aspiration, as well as an excellent reproductive outcome in the recipient (6–10).

Regarding the polycystic ovary syndrome (PCOS) patient, a meta-analysis including four randomized controlled trials (RCTs), comparing the two GnRH analogs in 305 PCOS patients, reported no difference in the reproductive outcome (11), a finding which has been corroborated by others (12–14). As previously mentioned, the main advantages of GnRH antagonist cotreatment are a significant reduction in the risk of OHSS as well as the possibility of using a GnRHa trigger for final oocyte maturation (15).

The total OHSS incidence (mild, moderate and severe) in a high-risk population, mainly consisting of PCOS patients, undergoing ovarian stimulation for in vitro fertilization (IVF) after either a long pituitary suppression with GnRHa or cotreatment with a GnRH antagonist and having final oocyte maturation triggered with hCG has been reported to be as high as 17–31% (16,17), whereas the incidence of severe OHSS has been reported to be 15% in the PCOS IVF patient (18). This number should be compared with the general IVF population, in which the incidence of moderate OHSS has been described to be ~5% and the severe cases in need of hospitalization ~2% (19).

Regardin the concept of a GnRHa trigger and the subsequent reproductive outcome, the results of the first RCT in normogonadotrophic patients revealed an extremely high early pregnancy loss rate (80%) despite a standard luteal phase support (20). The finding was interpreted as a luteal phase “insufficiency” caused by low circulating endogenous luteinizing hormone (LH) levels in the early to mid-luteal phase (21–23), and during the following years, focus was directed towards rescuing the luteal phase, by an increase in the luteal LH activity after the initial GnRHa trigger with hCG, recombinant LH or repeated boluses of GnRHa; so-called modified luteal phase support after GnRHa trigger. In the normogonadotropic as well as the OHSS high-risk patient, this intervention has resulted in a reproductive outcome comparable to that seen after hCG triggering (21–27). Thus, although a recent meta-analysis on earlier studies using a GnRHa trigger did not recommend the use of GnRHa trigger in fresh cycles owing to an expected lower birth rate (28), we maintain that this statement was too premature, because the newer studies, using the modified luteal phase support, were not included in the analysis. This issue was thoroughly addressed in a recent debate regarding the performance of meta-analyses during the development of new concepts (29).

Regarding OHSS high-risk patients, who are mainly PCOS patients, different approaches for luteal phase rescue have been suggested after GnRHa trigger. Humaidan (22), in a proof-of-concept study including 12 OHSS high-risk patients (≥25 follicles on day of trigger), rescued the luteal phase with a combination of a bolus of 1500 IU hCG on the day of oocyte retrieval (21) and conventional luteal phase support consisting of vaginal progesterone and estradiol; so-called modified luteal phase support. This modified approach after the GnRHa trigger resulted in a live birth rate of 50%. One patient developed moderate late-onset OHSS, and the patient was treated on an outpatient basis.

Radesci and Tremellen (27), in a retrospective study, analysed 71 consecutive OHSS high-risk patients who had been treated according to the protocol suggested by Humaidan et al. (21–23). Forty-five per cent of the patients were PCOS patients, and the mean anti-Müllerian hormone level of patients was 48 pmol/L. A high risk of developing OHSS was defined as the presence of at least 14 follicles ≥12 mm on the day of triggering final oocyte maturation. All patients were triggered with a bolus of GnRHa (leuprolide acetate, 2 mg), followed by 1500 IU hCG administered subcutaneously, after the oocyte retrieval. A mean of 17 oocytes were retrieved, and all 71 patients received a single embryo transfer. This resulted in a clinical pregnancy rate of 52% per transfer and a miscarriage rate of 8%. One patient (one of 71) developed a late-onset severe OHSS, requiring hospital admission on day 16 post-oocyte retrieval. The patient was treated according to guidelines for severe OHSS and was discharged 7 days later.

Likewise, Shapiro et al. (30) retrospectively reported the effect of a so-called “dual trigger” in OHSS high-risk patients, mainly patients with a polycystic ovary-like ultrasonography pattern and PCOS patients. A total of 182 patients were treated according to this protocol, receiving on the day of triggering final oocyte maturation 4 mg leuprolide acetate as well as a mean of 1428 IU hCG as a trigger. Patients had a mean of 28 follicles on the day of triggering, and a mean of 20 oocytes were retrieved. After blastocyst transfer, an ongoing pregnancy rate of 58% per transfer was obtained. One patient (one of 182) in this high-risk group of patients developed a late onset OHSS.

Taken together, the optimal protocol for luteal phase support after GnRHa trigger is currently under investigation and
still needs to be fine-tuned. The protocol developed by Hu-
maidan et al. (21,23) of administration of a bolus of 1500 IU hCG immediately after the oocyte pick-up, followed by a
standard luteal phase support with 4 mg estradiol and vagi-
ral progesterone has been shown to result in live birth rates comparable to those seen after hCG triggering in both nor-
magonadotropic patients and PCOS patients (21–23,27).

An alternative solution in patients at high risk of OHSS is
to freeze all embryos after GnRHa triggering, and transfer in
subsequent either natural or substituted freeze–thaw cycles.
No incidence of OHSS was reported, and a high cumula-
tive pregnancy rate was seen following this procedure in IVF
patients (10,31). Moreover, in several thousand oocyte do-
nation patients triggered with GnRHa, some of whom were
at high risk of developing OHSS, not a single OHSS case
was recorded (6,8,32) Thus, this simple medical interven-
tion after ovarian stimulation seems to eliminate OHSS and
thus provides the clinician with a good alternative to a fresh
transfer, provided that the clinic has a good cryopreservation
program.

“Patient-friendly” IVF is a repeated theme in the field of
assisted reproductive technology and is a driving force for the
development of new stimulation protocols. In this context, it
should be emphasized that the GnRHa trigger is associ-
ated with a significantly lower mid-luteal ovarian volume
(17), which is directly correlated with patient comfort, even
if an OHSS condition does not develop. Thus, in oocyte
donors triggered with hCG, 42% reported subjective com-
plaints (mostly abdominal discomfort), whereas this per-
centage was 0% in those who received GnRHa to trigger
ovulation (33). Therefore, we propose that even if OHSS is
not an immediate threat, GnRHa should be considered for the
triggering of final oocyte maturation in the PCOS patient,
simply in the interest of patient comfort.

In conclusion, based on the results of current clinical
research, we maintain that GnRH antagonist cotreatment
should be recommended instead of the long GnRHa proto-
col when stimulating PCOS patients for IVF. If an extreme
response is encountered, the clinician will always have the
option of triggering final oocyte maturation with GnRHa,
followed by either a modified luteal phase support or a total
freeze of embryos and transfer in subsequent thaw cycles.
Both approaches will ensure a good reproductive and clinical
outcome, with very little or no risk at all of OHSS develop-
ment.

References


