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

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Conflict of interest
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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 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.

Reference	Trial type	Oocyte source	Ovulation trigger	*n*	Cumulus oocyte complex (mean)	OHSS risk	OHSS [% (*n*)]
Acevedo et al. (2006)	RCT	Donors	GnRHa	30	9.1	Low	0 (0/30)
			hCG	30	10.3	Low	17 (5/30)
Babayof et al. (2006)	RCT	Own	GnRHa	15	19.8	High	0 (0/13)
			hCG	13	19.5	High	31 (4/13)
Engmann et al. (2006)	Retrospective	Own	GnRHa	23	20	High	0 (0/23)
			hCG	23	18	High	4 (1/23)
Orvieto et al. (2006)	Retrospective	Own	GnRHa	82	22.3	High	0 (0/82)
			hCG	69	16.8	High	7 (5/69)
Griesinger et al. (2007)	Observational	Own	GnRHa	20	16.4	High	0 (0/20)
Shapiro et al. (2007)	Retrospective	Donors	GnRHa	32	28.8	High	0 (0/32)
			hCG	42	21.7	High	1 (1/42)
Engamnn et al. (2008)	RCT	Own	GnRHa	33	20.2	High	0 (0/33)
			hCG	32	18.8	High	31 (10/32)
Bodri et al. (2009)	Retrospective	Donors	GnRHa	1046	13.6	Intermediate	0 (0/1046)
			hCG	1031	9.8	Low	1.3 (13/1031)
Humaidan et al. (2009)	RCT	Own	GnRHa	152	8.9	Low	0 (0/152)
			hCG	150	9.3	Low	2 (3/150)
Hernandez et al. (2009)	Retrospective	Donors	GnRHa	254	13.2	Intermediate	0 (0/254)
			hCG	175	8.7	Low	6 (10/175)
Melo et al. (2009)	RCT	Donors	GnRHa	50	17.1	High	0 (0/50)
			hCG	50	18.1	High	4 (2/50)
Sismanoglu et al. (2009)	RCT	Donors	GnRHa	44	38.2	Very high	0 (0/44)
			hCG	44	36.7	Very high	7 (3/44)
Humaidan et al. (2009)	Observational proof of concept	Own	GnRH, luteal rescue with hCG (1500 IU)	12	21.5	High	8 (1/12)
Galindo et al. (2009)	RCT	Donors	GnRHa	106	11.4	Low	0 (0/106)
			hCG	106	12	Low	8 (9/106)
Manzanares et al. (2010)	Retrospective case–control	Own	GnRHa hCG – cancelled	42	12.6	High	0 (0/42)
Tehraninejad et al. (2010)	RCT, high risk	Own	GnRHa	45	13.4	High	0 (0/45)
			hCG	45	10.9	High	15 (33)
Griesinger et al. (2010)	Prospective cohort study	Own	GnRHa	40	18	High	0 (0/40)

Abbreviations: GnRH, 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).

Regardign the concept of a GnRHa trigger and the subsequent reproductive outcome, the results of the first RCT in normogonadotropic 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 ($\geq$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.

Radesic 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 $\geq$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 Humaidan 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 vaginal progesterone has been shown to result in live birth rates comparable to those seen after hCG triggering in both normogonadotropic 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 cumulative pregnancy rate was seen following this procedure in IVF patients (10,31). Moreover, in several thousand oocyte donation 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 intervention 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 associated 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 complaints (mostly abdominal discomfort), whereas this percentage 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 protocol 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 development.

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