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Editorial

The benefit of individualized low-dose human chorionic gonadotropin support for high responders in gonadotropin-releasing hormone agonist-triggered *in-vitro* fertilization/intracytoplasmic sperm injection cycles

Ovarian hyperstimulation syndrome (OHSS) is one of the major complications in artificial reproductive technology, especially in high responders. Exogenous human chorionic gonadotropin (hCG) for triggering final oocyte maturation during controlled ovarian stimulation (COS) is primarily responsible for the pathogenesis of early-onset OHSS.[1] Several strategies were offered to prevent OHSS, including reducing the gonadotropin dose, individualizing *in-vitro* fertilization/intracytoplasmic sperm injection (IVF/ICSI) treatment protocols, using adjuvant metformin therapy, and further considering alternatives for triggering ovulation, coasting, cryopreservation of embryos, avoiding hCG for luteal phase support (LPS), cryopreservation of embryos, albumin infusion, cabergoline administration, and others.[1] Recently, gonadotropin-releasing hormone agonist (GnRHa) used to induce final oocyte maturation and ovulation presented an alternative to hCG to effectively reduce OHSS risk in COS. The Cochrane Review revealed that GnRHa trigger was associated with a lower incidence of OHSS than was hCG [odds ratio (OR) 0.15, 95%, confidence interval (CI) 0.05−0.47].[2] However, the critical disadvantage of GnRHa trigger is early luteolysis and consequently luteal phase insufficiency, resulting in impaired endometrial receptivity and worse conception rates. The Cochrane Review indicated that GnRHa trigger was associated with a lower ongoing pregnancy rate (OR 0.70, 95% CI 0.54−0.91) and a higher early miscarriage rate (OR 1.74, 95% CI 1.10−2.75) than was seen with hCG.[2] To improve reproductive outcomes in GnRHa trigger protocol, some strategies of modified LPS were suggested as follows[3]: (1) intensive LPS with aggressive exogenous administration of estradiol (E2) and progesterone (P)[4]; (2) dual trigger with both GnRHa and low-dose hCG[5]; and (3) hCG rescue after oocyte retrieval.[6] All approaches have been shown to be effective in generating pregnancy rates similar to conventional hCG trigger and leading to a very low OHSS risk.[7] However, combined modified LPS in GnRHa trigger protocol seems to be popular in Taiwan.[8]

The study by Huang and colleagues[9] in this issue of the *Journal of the Chinese Medical Association* presented a protocol of GnRHa trigger with individualized low-dose hCG support and intensive LPS. The authors concluded that the protocol provides satisfactory pregnancy rate with an extremely low OHSS risk, and emphasized that individualized low-dose hCG supply may provide a patient-friendly method for LPS.[9] The individualized low-dose hCG supply in the study of Huang et al[9] represented hCG for ovulation triggering with a dose depending on the serum level of E2 and the number of follicles $\geq$ 11 mm on the trigger day (500 IU for cycles with peak E2 > 5000 pg/mL or follicle number $\geq$ 25; 750 IU for cycles with peak E2 3500−5000 pg/mL and follicle number < 25; and 1000 IU for cycles with peak E2 < 3500 pg/mL and follicle number < 25) and hCG for luteal rescue with an additional 300 IU of hCG, which was administered if the serum E2 level dropped to < 800 pg/mL before the sixth day of oocyte retrieval. The authors found no OHSS cases occurred in this protocol, with even more high responders in the group.[9] When compared with a protocol of GnRHa trigger alone with intensive LPS, the authors observed that GnRHa trigger with individualized low-dose hCG support and intensive LPS had a tendency toward improved pregnancy outcomes. The authors provided an explanation for the result. In addition to the apparent benefit to LPS, the authors suggested that dual trigger seemed to contribute to better oocyte maturation than GnRHa trigger alone. However, a significantly higher fertilization rate found in the protocol of GnRHa trigger with individualized low-dose hCG supplementation supported the idea[9]; nonetheless, more studies are needed to confirm the result. In contrast, the authors provided the criteria for hCG trigger dosage according to serum E2 level and the number of follicles $\geq$ 11 mm on trigger day. Moreover, the authors recommended hCG rescue with an additional 300 IU of hCG from their own experience.[9] These criteria have given us a great reference in clinical practice. However, more studies have to be undertaken to verify the criteria.

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It has been established that induction of final oocyte maturation with a bolus of GnRHa can be effective in the prevention of OHSS. However, no consensus on GnRHa trigger type or dose emerged. A randomized investigator-blinded trial compared different dosage of triptorelin (Ipsen, Paris, France; 0.2 mg, 0.3 mg, and 0.4 mg) for ovulation trigger and found that there were no significant differences in the number of mature oocytes and top-quality embryos between triptorelin doses of 0.2 mg, 0.3 mg, and 0.4 mg.[10] However, more studies are needed to explore the issue. GnRHa trigger with modified LPS provided satisfactory pregnancy rate. Studies have shown that the early luteal phase steroid levels and the endometrial gene expression following GnRHa trigger and modified LPS were similar to those seen after hCG trigger.[11] Therefore, modified LPS is necessary for GnRHa as an oocyte for final maturation and ovulation trigger, but likewise, there is no consensus on this point. Engmann and colleagues[12] indicated that GnRHa trigger and LPS with intramuscular (IM) P and E2 patch provided a similar pregnancy rate to hCG trigger. The study conducted by Griffin et al[5] revealed that dual trigger with GnRHa and 1000 IU hCG and LPS with IM P and E2 patch obtained better pregnancy outcome than GnRHa trigger alone. Two prospective randomized controlled multicenter studies demonstrated that a GnRHa trigger followed by early luteal hCG support with one bolus of 1.500 IU hCG appeared to achieve a pregnancy rate similar to that with traditional hCG trigger.[6,13] Severe early OHSS can still occur when low-dose hCG is used for luteal rescue.[14] Development of individualized LPS regimens in the GnRHa trigger protocol is required. In the study by Huang and colleagues,[9] a protocol of GnRH agonist trigger with individualized low-dose hCG support and intensive LPS was proposed. Additionally, Engmann and co-authors[15] recommended an LPS protocol after GnRHa trigger as follows: intensive LPS with transdermal E2 and IM P alone if peak serum E2 is $\geq$ 4000 pg/mL after GnRHa trigger; dual trigger with GnRHa and hCG 1000 IU if peak serum E2 is $<$ 4000 pg/mL; hCG 1500 IU 35 h after GnRHa trigger if there are $<$ 25 follicles; and freeze all oocytes or embryos if there are $>$ 25 follicles.

In conclusion, OHSS, primarily stemming from hCG trigger, is a potentially life-threatening complication during COS. Instead of conventional hCG trigger, GnRHa for induction of final oocyte maturation and ovulation significantly reduces OHSS risk. Through overcoming luteal phase insufficiency, GnRHa trigger with modified LPS can achieve a satisfactory conception rate. Huang et al[9] offered a protocol of GnRHa trigger with individualized low-dose hCG support and intensive LPS, resulting in good pregnancy outcomes and no OHSS cases. However, optimal GnRHa type or dose and individualized modified LPS regimens need to be more comprehensively investigated.

Conflicts of interest

The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

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