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Editorial

Early initiation of GnRH antagonist administration in a flexible protocol: Is it better?

Gonadotropin-releasing hormone (GnRH) antagonist protocol is a popular and patient-friendly regimen for controlled ovarian stimulation (COS) during in vitro fertilization (IVF). This is due to several advantages of this protocol, including reducing the duration of GnRH analogue treatment, decreasing the amount of gonadotrophins required for stimulation, lowering the incidence of ovarian hyperstimulation syndrome (OHSS), and avoiding hypo-estrogenic symptoms and ovarian cyst formation.[1,2] GnRH antagonist can effectively prevent a premature luteinizing hormone (LH) surge by competitive blockage of the GnRH receptors in the pituitary gland directly and immediately.[3,4] GnRH antagonist is commonly given using a fixed or a flexible regimen.[1,2] In the fixed regimen, the GnRH antagonist is introduced daily from a fixed day of ovarian stimulation, regardless of follicular size. In the flexible regimen, GnRH antagonist is initiated based on the follicular size and/or the serum estradiol (E2) level. A randomized controlled trial revealed that no significant difference was observed between the flexible and fixed groups regarding the incidence of LH rise.[5] Furthermore, a meta-analysis showed there was no significant difference regarding pregnancy rate between the flexible and fixed protocols, but a significant reduction in both GnRH antagonist and gonadotropin requirements was observed when the flexible antagonist regimen was used.[6] In the flexible regimen, GnRH antagonist may be given on the different stimulation days. Which day is better? Is there any difference between an early initiation (<stimulation day 6) or a late initiation (≥stimulation day 6) of GnRH antagonist administration? The retrospective cohort study by Ozturk and colleagues in this issue of the *Journal of the Chinese Medical Association* attempted to investigate the issue.[7]

Ozturk and co-workers suggested that an early initiation of GnRH antagonist administration seemed to be more cost-effective, compared to a late initiation of GnRH antagonist administration due to lower required dosage of gonadotropins and shorter stimulation duration.[7] Additionally, the authors observed no difference between the early or late initiation of GnRH antagonist administration regarding the number of retrieved oocytes, the number of metaphase II oocytes, the number of fertilized oocytes, the fertilization rates, the number of transferred embryos, and clinical pregnancy rates.[7] However, these results and conclusions should be carefully explained. First, Ozturk et al. enrolled patients who underwent a GnRH antagonist flexible protocol, in which GnRH antagonist was initiated when the diameter of the leading follicle ≥13 mm or the serum E2 level ≥300 pg/ml. Then, the enrolled patients were divided into an early initiation or a late initiation of GnRH antagonist administration. Based on the study design, the aim of this study was not to compare different fixed antagonist protocols, but to compare the difference between patients who met the criteria of flexible antagonist protocol, early or late. Therefore, it is more suitable to conclude that in a flexible antagonist protocol, if patients reached the criteria earlier, an earlier initiation of GnRH antagonist administration led to a reduced gonadotropin requirement and shorter stimulation period. The original conclusion proposed by Ozturk and colleagues may be misunderstood as a fixed antagonist protocol. Second, the authors enrolled patients who were 20–39 years of age, with a body mass index between 18 and 29 kg/m^2. Old and obese patients were excluded from this study. However, diminished ovarian reserve and obesity were major risk factors for breakthrough LH surge, despite GnRH antagonist suppression in IVF cycles.[8,9] Thus, the results and conclusions reached in Ozturk et al.'s study cannot be applied to the elderly or obese women. Third, in terms of cost-effectiveness, it is typically expressed as an incremental cost-effectiveness ratio, the ratio of change in costs to the change in effects,[10] not just assessed using the dosage of gonadotropins. Taken together, it is believed that the results and conclusions in Ozturk et al.'s study should be interpreted cautiously.

In a flexible antagonist protocol, Ozturk and colleagues demonstrated that patients with an early antagonist start had decreased gonadotropins dosage and shorter stimulation duration than those with a late antagonist start, although the pregnancy rate did not differ between the two groups.[7] Likewise, in the retrospective study of Tannus et al.,[11] comparable implantation, clinical, and ongoing pregnancy rates were observed between an early initiation and a late initiation of GnRH antagonist administration. However, an early initiation resulted in reduced gonadotropin amount, shorter stimulation period, more oocytes and two pronuclei oocytes.[11] A prospective observational cohort study conducted by Lainas et al.

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showed that in addition to shorter stimulation period, patients who initiated the GnRH antagonist early (on stimulation days 4 or 5) achieved a higher pregnancy rate, compared to those who initiated the GnRH antagonist late (on stimulation day 6).[12] It is quite reasonable regarding the above results because an early initiation of GnRH antagonist administration indicates that follicles obtained good response to gonadotropins, and grow rapidly to reach the criteria of the flexible regimen earlier. Therefore, a reduced dosage of gonadotropins and shorter stimulation period are needed when patients earlier initiated the GnRH antagonist. Moreover, the high-dose gonadotropins or longer stimulation duration during the IVF cycles may have negative effects on reproductive outcomes.[13–15] Thus, an early initiation of GnRH antagonist administration may be associated with better IVF outcomes. However, additional studies are needed to confirm the concept.

In conclusion, in recent years, the GnRH antagonist protocol have become the most popular regimen for COS in the IVF cycles due to its flexibility, patient-friendliness and a lower risk of developing OHSS without reducing the chances to achieve a live birth. In a flexible antagonist protocol, an early initiation of GnRH antagonist administration seems to have beneficial effects on IVF outcomes, compared to a late initiation of GnRH antagonist administration, which is supported by the study of Ozturk et al.[7] We welcome more large-scale, prospective research to further confirm the results.

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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References

1. Wei LH, Ma WH, Tang N, Wei JH. Luteal-phase ovarian stimulation is a feasible method for poor ovarian responders undergoing in vitro fertilization/intracytoplasmic sperm injection-embryo transfer treatment compared to a GnRH antagonist protocol: a retrospective study. *Taiwan J Obstet Gynecol* 2016;**55**:50–4.
2. Al-Inany HG, Youssef MA, Ayeleke RO, Brown J, Lam WS, Broekmans FJ. Gonadotrophin-releasing hormone antagonists for assisted reproductive technology. *Cochrane Database Syst Rev* 2016;**4**:CD001750.
3. Lee TH, Lin YH, Seow KM, Hwang JL, Tzeg CR, Yang YS. Effectiveness of cetrorelix for the prevention of premature luteinizing hormone surge during controlled ovarian stimulation using letrozole and gonadotropins: a randomized trial. *Fertil Steril* 2008;**90**:113–20.
4. Luo S, Li S, Jin S, Li Y, Zhang Y. Effectiveness of GnRH antagonist in the management of subfertile couples undergoing controlled ovarian stimulation and intrauterine insemination: a meta-analysis. *PLoS One* 2014;**9**:e109133.
5. Kolibianakis EM, Venetis CA, Kalogeropoulou L, Papanikolaou E, Tarlatzis BC. Fixed versus flexible gonadotropin-releasing hormone antagonist administration in in vitro fertilization: a randomized controlled trial. *Fertil Steril* 2011;**95**:558–62.
6. Al-Inany H, Aboulghar MA, Mansour RT, Serour GI. Optimizing GnRH antagonist administration: meta-analysis of fixed versus flexible protocol. *Reprod Biomed Online* 2005;**10**:567–70.
7. Ozturk Inal Z, Yılmaz N, Inal HA, Hançerlioğullari N, Coskun B. Are there any differences between antagonist administrations on days < 6 and ≥ 6 of COH on assisted reproductive technique outcomes? *J Chin Med Assoc* 2018;**81**:53–8.
8. Lin LT, Wang PH, Tsui KH. The use of luteal-phase ovarian stimulation for poor ovarian responders undergoing in vitro fertilization/intracytoplasmic sperm injection-embryo transfer treatment. *Taiwan J Obstet Gynecol* 2016;**55**:307–8.
9. Roth LW, Bradshaw-Pierce EL, Allshouse AA, Lesh J, Chosich J, Bradford AP, et al. Evidence of GnRH antagonist escape in obese women. *J Clin Endocrinol Metabol* 2014;**99**:E871–5.
10. Fiddelers AA, van Montfoort AP, Dirksen CD, Dumoulin JC, Land JA, Dunselman GA, et al. Single versus double embryo transfer: cost-effectiveness analysis alongside a randomized clinical trial. *Hum Reprod* 2006;**21**:2090–7.
11. Tannus S, Weissman A, Boaz M, Horowitz E, Ravhon A, Golan A, et al. The effect of delayed initiation of gonadotropin-releasing hormone antagonist in a flexible protocol on in vitro fertilization outcome. *Fertil Steril* 2013;**99**:725–30.
12. Lainas T, Zorzovilis J, Petsas G, Stavropoulou G, Cazlaris H, Daskalaki V, et al. In a flexible antagonist protocol, earlier, criteria-based initiation of GnRH antagonist is associated with increased pregnancy rates in IVF. *Hum Reprod* 2005;**20**:2426–33.
13. Santana R, Setti AS, Maldonado LG, Valente FM, Iaconelli C, Iaconelli Jr A, et al. The impact of pituitary blockage with GnRH antagonist and gonadotrophin stimulation length on the outcome of ICSI cycles in women older than 36 years. *Int J Fertil Steril* 2014;**8**:135–42.
14. Alport B, Case A, Lim H, Baerwald A. Does the ovarian stimulation phase length predict in vitro fertilization outcomes? *Int J Fertil Steril* 2011;**5**:134–41.
15. Baker VL, Brown MB, Luke B, Smith GW, Ireland JJ. Gonadotropin dose is negatively correlated with live birth rate: analysis of more than 650,000 assisted reproductive technology cycles. *Fertil Steril* 2015;**104**:1145–52.e1-5.

Li-Te Lin
Department of Obstetrics and Gynecology, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan, ROC

Department of Obstetrics and Gynecology, National Yang-Ming University, Taipei, Taiwan, ROC

Department of Biological Science, National Sun Yat-sen University, Kaohsiung, Taiwan, ROC

Peng-Hui Wang
Department of Obstetrics and Gynecology, Taipei Veterans General Hospital, Taipei, Taiwan, ROC

Department of Obstetrics and Gynecology, National Yang-Ming University, Taipei, Taiwan, ROC

Institute of Clinical Medicine, National Yang-Ming University, Taipei, Taiwan, ROC

Kuan-Hao Tsui*

Department of Obstetrics and Gynecology, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan, ROC

Department of Obstetrics and Gynecology, National Yang-Ming University, Taipei, Taiwan, ROC

Department of Pharmacy and Graduate Institute of Pharmaceutical Technology, Tajen University, Pingtung, Taiwan, ROC

*Corresponding author. Dr. Kuan-Hao Tsui, Department of Obstetrics and Gynecology, Kaohsiung Veterans General Hospital, 386, Dazhong 1st Road, Kaohsiung 813, Taiwan, ROC.

E-mail address: khtsui60@gmail.com (K.-H. Tsui).