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.\(^7\) 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 \textit{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.
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).\textsuperscript{13–15} 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.\textsuperscript{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.\textsuperscript{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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