

Changing attitudes in ovarian stimulation

“Since safety issue always comes first, it is recommended to shift from the standard long agonist protocol to GnRH antagonist regimen. The absence of significant differences in efficacy between the long agonist and antagonist protocol would be reassuring that results would not be compromised by that shift.”

The standard protocol

Gonadotropin-releasing hormone agonists (GnRHa) were introduced in ovarian stimulation for IVF to suppress the premature surge of luteinizing hormone (LH). Among the different protocols that have been proposed, the long protocol of GnRHa has been the standard treatment for controlled ovarian hyperstimulation in assisted reproduction because of the associated increase in pregnancy rates. In such long protocols, GnRHa is started either in the mid-luteal phase or in the early follicular phase of the preceding cycle and continued until pituitary desensitization has been achieved; usually after 2–3 weeks, at which point gonadotropin administration will be started [1].

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Despite being widely accepted in practice, the use of GnRHa hasn't been without drawbacks. Among them, flare up (initial rise in follicle-stimulating hormone and LH) with possible cyst formation, the long periods needed to achieve downregulation and the troublesome manifestations of estrogen deprivation (hot flushes, headaches and sleep disturbances). However, more importantly, alongside the increased rates of pregnancy, an increase in the incidence of ovarian hyperstimulation syndrome (OHSS) has been noticed with the long GnRHa protocols [2].

OHSS: the reproductive health physician's nightmare

Ovarian hyperstimulation syndrome is considered the most serious complication of ovulation induction in IVF-embryo transfer. It can

vary from being a mild illness to a severe, life-threatening disease requiring hospitalization. It can occur as soon as a few days after receiving human chorionic gonadotropin ('early OHSS') or later ('late OHSS'). Severe manifestations of OHSS may include massive fluid shifts, hemoconcentration or renal and liver dysfunction. The syndrome may be ultimately complicated by thromboembolic events and adult respiratory distress syndrome [3]. Thus, a serious morbidity and even mortality can pursue a nonvital infertility treatment, making such complications of OHSS unacceptable.

Is there a safer alternative?

The fear from such serious and potentially life threatening complications has motivated researchers to study other alternative protocols that would achieve better safety with at least equivalent results, thus improving the outcome of IVF.

Gonadotropin-releasing hormone antagonists have emerged as an alternative treatment for preventing premature LH surges during controlled ovarian hyperstimulation. While the agonist acts by downregulation of pituitary GnRH receptors and desensitization of the gonadotropic cells, GnRH antagonists act by directly and rapidly inhibiting gonadotropin release within several hours through competitive binding to pituitary GnRH receptors. This mechanism of action is dependent on the equilibrium between endogenous GnRH and the applied antagonist and is highly dose dependent in contrast to the agonists [4]. The competitive blockade of the receptors leads to an immediate arrest of gonadotropin secretion; therefore, they can be given after starting gonadotropin administration. This will result in dramatic reduction in the duration of treatment cycle as well as avoiding flare up and estrogen deprivation symptoms associated with GnRHa-induced downregulation.

The first generation of GnRH antagonists showed allergic side effects owing to induced histamine release, which hampered the clinical



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Keywords

- GnRH antagonist • infertility
- IVF • live birth • ovarian hyperstimulation syndrome

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development of these compounds. However, third generation GnRH antagonists including ganirelix (NV Organon, Oss, The Netherlands) and cetrorelix (ASTA Medica AG, Frankfurt am Main, Germany) have resolved these issues and are approved for clinical use [5].

Several different regimes have been described in the literature for using GnRH antagonists in controlled ovarian hyperstimulation, including multiple-dose fixed (0.25 mg daily from day 6 to 7 of stimulation), multiple-dose flexible (0.25 mg daily when leading follicle is 14–15 mm) [6], and single-dose (single administration of 3 mg on day 7–8 of stimulation when LH surge is most feared) [7] protocols, with or without the addition of an oral contraceptive pill. Starting GnRH antagonist very early at the beginning of the stimulation with the aim to reduce LH levels early in the follicular phase has been suggested. However, no advantage to this regimen was demonstrated in a prospective randomized study [8]. In addition, prolonged antagonist administration will actually abolish one of its real benefits, which is the shorter period of administration.

“More accumulating evidence is currently ensuring the safety of GnRH antagonists compared with long agonist protocols, as the former was associated with remarkable reduction in the incidence of severe OHSS.”

A lower pregnancy rate has been anticipated by some authors when the flexible approach was proposed [9]. A meta-analysis by Al-Inany *et al.* did not find differences in the pregnancy rates between the flexible and fixed approaches, although there was a trend towards higher pregnancy rates with fixed protocols [10].

GnRH antagonist versus GnRHa: Cochrane reviews

The first Cochrane review comparing GnRH antagonist to the more widely used long agonist protocols was published in 2001 [11] and was updated in 2006 [12]. As many more randomized controlled trials have been published, it was updated again in 2011 [13], this time focusing on patient-oriented value mainly safety and ongoing pregnancy/live birth rate.

The previous two versions of that review showed lower efficacy for GnRH antagonists while the most recent one showed lower

pregnancy in antagonist but did not reach statistically significant level. This improved performance for antagonist may be attributed to improvement in LH instability in antagonist cycles. LH instability is defined as any fluctuation in LH level, either a LH surge or rise in LH concentration as defined by the study protocol per woman randomized. There is supportive evidence regarding possible better pregnancy outcomes when using the fixed GnRH antagonist compared with the flexible protocol from two studies [9,10], where fixed versus flexible GnRH-antagonist protocol had been compared directly. From both studies, the trend towards better performance in fixed protocols was notified, with odds ratios for the difference that could possibly account for the difference between antagonist and agonist cycles in general. Since these studies were published, there was a trend for using fixed protocol in subsequently conducted trials. Thus, a decrease in the relative incidence of LH instability can possibly have improved pregnancy outcomes in antagonist cycles. This observation warrants the strive for improvement of the LH suppressive effects of the antagonist comedicated stimulation protocols.

More importantly, there were a statistically highly significant lower incidence of OHSS in the GnRH antagonist group (29 randomized controlled trials, odds ratio: 0.43; 95% CI: 0.33–0.57; $p < 0.00001$; $I^2 = 19\%$). The incidence was reduced by 50% in antagonist group (1.91 vs 3.74%). The corresponding number needed to harm was 25 (95% CI: 19–36) with an absolute risk reduction of 4% (95% CI: 2.79–5.13). This means for every 25 women undergoing downregulation by agonist, one more case of severe OHSS may be expected. In addition, the cancellation rate owing to high risk to develop OHSS was significantly higher in GnRHa group. This means that the difference would be highly significant if cancellation was not done [11].

Conclusion

More accumulating evidence is currently ensuring the safety of GnRH antagonists compared with long agonist protocols, as the former was associated with remarkable reduction in the incidence of severe OHSS. Since safety issue always comes first, it is recommended to shift from the standard long agonist protocol to GnRH antagonist regimen. The absence of significant differences in efficacy between the long agonist and antagonist protocol would be reassuring

that results would not be compromised by that shift. Other privileges that can further motivate physicians to take on such change in practice are the development of new GnRH antagonists free of side effects, the prompt mode of action and the shorter period of administration. All these advantages would offer patients a more favorable, safer and efficient method of ovarian stimulation.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

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