

AGONIST OR ANTAGONISTS? WHAT IS PREFERABLE?

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Introduction: Gonadotrophin releasing hormone analogs (GnRH-a) are widely used in ovarian stimulation protocols for assisted reproductive techniques (ART) in order to control the premature endogenous luteinizing hormone (LH) surge and therefore, to decrease the cycle cancellation rate from 15-20% to 2% (Porter et al., 1987; Stanger and Yovich., 1985; Wildt et al., 1986). For more than 20 years, GnRH agonists have been the "gold standard" protocol in ovarian stimulation (Biljan and Tan., 1998), but GnRH antagonist have been recently introduced (Felberbaum and Diedrich., 2002), offering several advantages such as: lower total dosages of gonadotrophins, less incidence of hyperstimulation syndrome, lower cost, lack of side effects, shorter duration of treatment and more individualized and less aggressive protocol (The European Orgalutran Study Group., 2001). With the GnRH agonist used in the long protocol (started either in the mid luteal phase or in the early follicular phase of the preceding cycle), pituitary desensitization is achieved only after 2 or 3 weeks of treatment, because of the initial stimulatory effect ("flare-up") that may also lead to ovarian cyst formation (Feldberg et al., 1989; Ben-Rafael et al., 1990) On the other hand, GnRH antagonists cause an immediate suppression of gonadotrophin secretion, without the initial stimulatory effect; hence, they can be given after starting gonadotrophin administration. It has been demonstrated that antagonists inhibit successfully premature surges of LH during stimulation (Diedrich et al., 1994; Olivennes et al., 1994, 1995; Albano et al., 1996, 1997; The Ganirelix dose-finding group., 1998).

GnRH agonists vs antagonists: Several studies have directly compared these new stimulation protocols against the long GnRH agonist protocol mainly in terms of pregnancy rate and incidence of ovarian hyperstimulation syndrome (OHSS).

Pregnancy rates: Despite the theoretical advantages of GnRH antagonists, their use was hampered due to the results obtained in a Cochrane review of the initial five randomized studies, which indicated a trend towards slightly lower implantation and pregnancy rates for the GnRH antagonist treatment group compared to those in the GnRH agonist group (Al-Inany and Aboulghar, 2002). The most recent Cochrane review (Al-Inany et al., 2006), has included 27 randomized controlled trials (RCT), and still shows similar results: clinical pregnancy rate was significantly lower in the antagonist group and the ongoing pregnancy/live-birth rate showed the same significantly lower pregnancy in the antagonist group. However, another recently published meta-analysis (Kolibianakis et al., 2006) based on the analysis of 22 published RCTs, compared the effectiveness of GnRH agonist and GnRH antagonists in IVF with respect to the probability of live birth per patient randomized, and concluded that the probability of live birth between agonists and antagonists was not significantly different. These results are in disagreement with the ones exposed in the review mentioned before (Al-Inany et al., 2006). Various theories have been put forth to explain the lower pregnancy rates observed in antagonist cycles, but consensus has not yet been reached: The uptake of GnRH antagonists has been slow and a great number of ovarian stimulation cycles are still performed in GnRH agonist long protocols. This means that clinicians are less trained to use antagonists and need to overpass the learning curve to reach similar outcomes. It has been suggested that GnRH antagonist is an inhibitor of the cell cycle by decreasing the synthesis of growth factors and, therefore, compromising the mitotic programme of follicles, embryo blastomere and endometrium (Hernández et al, 2000). This mechanism of action might be a reason for the poorer pregnancy outcome. It has been clearly demonstrated that premature luteinization (defined as elevation of serum progesterone the day of hCG administration) during GnRH antagonist IVF-ET cycles is a frequent event that is associated with lower pregnancy and implantation rates (Bosch et al., 2003). We should take into account that GnRH antagonists as compared with GnRH agonists have been usually prescribed in patients with a worse prognosis, who are older, poor responders and have performed more IVF cycles (Griesinger et al., 2005). It hence follows the worse results in terms of clinical outcome.

How to optimize the use of GnH antagonists: In order to optimize the cycle outcome when antagonists are used, several strategies have been classically proposed, such as: Pre-treatment with an oral contraceptive (OC) to allow greater control over patient response rate and to avoid follicular asynchrony. One study compared an OC pre-treatment versus a flexible-start regimen on antagonist and found a decrease in pregnancy rate in the second

group. They noted an increase in the LH serum area under the curve and speculated that the use of OC pre-treatment may blunt the elevated serum LH and normalize the pregnancy rate (Kolibianakis et al, 2003). Some authors have proposed the need of developing flexible antagonists regimens designed for individual patients (Felberbaum et al, 2002). However, our group demonstrated that there are no differences in cycle outcome according to the starting time of GnRH-a administration in a multiple dose protocol using 0,25 mg/d (fixed manner - stimulation day 6- versus starting when the leading follicle is ≥ 14 mm). On the other hand, this conclusion is applicable for young patients with normal cycle length and normal basal hormone profiles. (Escudero et al, 2004). Serum progesterone must be controlled during the ovarian stimulation cycle in order to avoid premature luteinization (PL). Nevertheless, according to studies performed in donors with PL (Melo et al., 2006), we must take into account that the effects of PL seem to be worse on the endometrium than on the embryo, so PL reaches more importance in cycles performed in patients that in donors. Regarding the effect of GnRH antagonists on human endometrium, Simón et al (2005) studied the gene expression profile on the endometrium of women undergoing ovarian stimulation for oocyte donation, and observed that the endometrial development after GnRH antagonist mimics the natural endometrium more closely than after GnRH agonist.

OHSS risk: Concerning the risk of OHSS, a statistically significant reduction in its incidence with the antagonist protocol as compared to the long protocol has been described (Ludwig et al., 2001). A recent review (Al-Inany et al., 2006) confirmed that there is a statistically reduction in the incidence of severe OHSS with the antagonist protocol, and even of the interventions to prevent it (e.g. coasting, cycle cancellation).

Conclusion: Considering the previous data, we can conclude that GnRH antagonist protocol is a handy protocol with good clinical outcome and noteworthy reduction in incidence of severe OHSS. However, GnRH antagonists could be more accepted in ovarian stimulation protocols if the probability of pregnancy reached similar rates to GnRH agonist ones. Other important issue is the necessity of perform an economical analysis with cost benefit comparisons, in order to decide the most convenient protocol, once the chance of pregnancy, that is the main objective, is similar between the two analogues.

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