Article

GnRH antagonists in IVF

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Abstract

The present review summarizes existing knowledge on the use of gonadotropin releasing hormone (GnRH) antagonists based on experience gathered after the completion of phase III comparative trials with GnRH agonists. Available data suggest that prolongation of the follicular phase significantly decreases the probability of pregnancy. Moreover, patients with elevated progesterone at initiation of stimulation have significantly fewer chances of achieving an ongoing pregnancy. Luteal support remains mandatory, while the replacement of human chorionic gonadotrophin by GnRH agonist does not appear to be feasible. Although not conclusive, existing data are not in favour of increasing the starting dose of gonadotrophins, of LH supplementation or of using a flexible antagonist protocol.

Keywords: *flexible antagonist administration, GnRH antagonists, luteal support, luteinizing hormone, progesterone elevation*

Introduction

Need for down-regulation

During the early years of IVF, it became apparent that premature LH surge could complicate ovarian stimulation and decrease pregnancy rates (Loumaye, 1990). Gonadotrophin-releasing hormone (GnRH) antagonists could solve this problem by immediately suppressing endogenous LH (Karten and Rivier, 1986). The history of ovarian stimulation might have been written differently if antagonists did not also cause histaminic reactions (Kiesel and Runenbaum, 1992). This impeded their use in assisted reproductive technologies for almost a decade.

GnRH agonists in ovarian stimulation for IVF

It was GnRH agonists (Porter *et al*., 1984) that, in the mid-1980s, formed what is perceived today as the gold standard of performing ovarian stimulation: administering medication to avoid premature LH surge approximately 3 weeks before such an event is possible.

Pituitary down-regulation using GnRH agonists decreased the proportion of cycle cancellation due to premature LH surge from approximately 20% to 2% (Loumaye, 1990) and led to a significant improvement in IVF outcome (Hughes *et al*., 1992).

Agonist usage was accompanied by occurrence of ovarian cysts, oestrogen deprivation symptoms, increased consumption of gonadotrophins and lack of immediate pituitary responsiveness following agonist discontinuation (Smitz *et al*., 1992). In order to simplify ovarian stimulation, several modifications of the long agonist protocol were proposed; however, they were proven inferior in terms of pregnancy rates (Daya, 2000).

GnRH antagonists: reappearance

The third generation of GnRH antagonists devoid of histaminic problems affecting earlier forms was introduced into clinical practice in the form of a daily (Diedrich *et al*., 1994) or a single-dose protocol (Olivennes *et al*., 1994). This allowed suppression of the premature LH surge in the mid-follicular phase, when it was really necessary, thereby offering a rational way to perform ovarian stimulation.

GnRH antagonists versus GnRH agonists

Five large randomized controlled trials (RCT) were performed to

compare GnRH analogues (Albano *et al.*, 2000; Borm and Mannaerts 2000; Olivennes *et al.*, 2000; European and Middle East Orgalutran Study Group, 2001; Fluker *et al.*, 2001). It was confirmed that antagonists could effectively suppress endogenous LH and result in a decreased amount of gonadotrophins, a shorter period of stimulation, a similar incidence of severe ovarian hyperstimulation syndrome and similar multiple pregnancy rates compared to agonists. Although significantly fewer oocytes were retrieved in the antagonist group, similar numbers of embryos of similar quality were transferred between the two groups. However, the expectation that pregnancy rates with antagonists would be at least equal to those achieved by GnRH agonists was not realized (Al Inany and Aboulghar, 2001). This might be due to several differences present between the two analogue stimulation schemes, the impact of which on pregnancy rates was not known prior to phase III trials.

The antagonist cycle is not preceded by a period of gonadotrophin suppression such as that in the agonist long protocol, but instead by the luteal phase of a natural cycle. As a consequence, in a small proportion of patients, abnormal steroid concentrations can be observed on the day gonadotrophin stimulation is scheduled to start. The importance of these abnormal steroids concentrations at initiation of stimulation was unknown, while no guidelines were available as to what should be the appropriate management in these cases.

Moreover, in the early follicular phase of an antagonist cycle, unsuppressed endogenous LH concentrations and significantly higher oestradiol concentrations are present as compared with an agonist cycle, while no data were available as to their potential effect on the probability of pregnancy. Similarly, the significance of the abrupt decrease in LH after antagonist initiation at a critical stage of follicular development was unknown, while the decision for the optimal moment at which final oocyte maturation should be triggered was arbitrary.

Meta-analysis considerations

The meta-analysis by Al-Inany and Aboulghar (2001) showed that the probability of clinical pregnancy was 5% lower with GnRH antagonists as compared with GnRH agonists. This was not expected and in order to optimize GnRH antagonist stimulation, the source of this difference had to be identified. On the other hand, its implications for clinical practice deserve further consideration.

According to the meta-analysis by Al-Inany and Aboulghar (2001), the number needed to treat with GnRH agonists to achieve one additional pregnancy as compared with the GnRH antagonists is 20 (the inverse of the 5% difference in clinical pregnancy rate observed in favour of the agonists). It was also shown by the same authors that for each patient treated with GnRH agonist, 21 days of additional treatment as compared with a patient treated with GnRH antagonist were required. Thus, 420 days of additional treatment are necessary to achieve an extra clinical pregnancy with agonists as compared with GnRH antagonists (number needed to treat times the additional duration of treatment, 20 times 21 days). This needs to be considered carefully in clinical practice before deciding what should be the preferred protocol for pituitary down-regulation.

It is also important to realize that the meta-analysis published by the Cochrane group (Al-Inany and Aboulghar, 2001) suggested that GnRH antagonists were associated with a lower pregnancy rate than GnRH agonists, in the way the two analogues were used and compared in phase III trials. GnRH agonists were employed in an optimal way, following approximately 15 years of experience. The same claim, however, cannot be made for GnRH antagonists.

The current review examines existing knowledge on the use of GnRH antagonists, the protocol modifications applied so far and their effectiveness in improving pregnancy rates, and delineates further research that needs to be carried out. Potential extra-pituitary effects of GnRH antagonists, as well as their safety, have been reviewed elsewhere (Ortmann *et al.*, 2000; Tarlatzis and Kolibianakis 2003; Tarlatzis and Billi 2004).

Elevated progesterone at initiation of stimulation

In all phase III trials, it is explicitly stated that ovarian stimulation was started only after down-regulation was confirmed in the agonist group. In what proportion of patients randomized to antagonist treatment abnormal steroid concentrations were present on the day stimulation should start, or how these patients were managed, is not mentioned in any of the phase III trials. It has to be assumed either that all patients had normal hormonal concentrations, or that stimulation was started in all patients regardless of their hormonal status. The second scenario does not ensure equality of these patients with those in the agonist group, while the first is probably not true.

Approximately 5% of patients planned to start an antagonist cycle will present with elevated progesterone concentrations on the day stimulation is scheduled to start (Kolibianakis *et al.*, 2004a). In a prospective study including 420 patients, initiation of stimulation was postponed for 1 or 2 days in the presence of elevated progesterone concentrations (20 patients) and was started only if repeat progesterone concentrations returned to normal range. Progesterone concentrations, despite normalization before stimulation was started, were significantly higher during the follicular phase compared with those observed in 390 patients with normal progesterone concentrations at initiation of stimulation (Kolibianakis *et al.*, 2004a). More importantly, the probability of pregnancy was significantly decreased in patients with elevated progesterone at initiation of stimulation (5%) as compared with those having normal levels (31.8%)

It appears that patients treated with GnRH antagonists should not start stimulation in the presence of abnormal progesterone concentrations, even if these concentrations return to normal within 1–2 days.

Increasing the starting dose of gonadotrophins

Significantly lower numbers of cumulus–oocyte complexes (COC) were retrieved in the antagonist as compared to the agonist group in phase III trials (Al-Inany and Aboulghar, 2001). This might have been a source of the difference in pregnancy rates observed between the two analogues. It was postulated that by increasing the starting dose of gonadotrophins, this difference might be eliminated leading to an improvement in pregnancy rates.