Clinical Role of the GnRH Antagonist

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Introduction

Ovulation induction is one of the major advances in the treatment of subfertility. The one aspect of premature LH surge required attention in this OI, and attempting to inhibit it, has been an integral part of treatment since the inception of Assisted Reproductive Technology. A failure to suppress the LH surge inevitably resulted in cycle cancellation. This led to the use of Gonadotrophin-releasing hormone antagonists since 1984.

Mechanism of action

In contrast to the long-acting agonists, which fi rst stimulate and later inhibit pituitary gonadotropin secretion by desensitizing gonadotropes to GnRH via receptor down-regulation, the antagonists (e.g. Cetrorelix and Ganirelix) block the GnRH receptor in a dose-dependent competitive fashion and have no similar flare effect. Gonadotropin suppression is almost immediate.

At the beginning of the stimulation cycle endogenous gonadotropins initiate the ovarian stimulation with a normal early follicular phase recruitment of a cohort of follicles, without any pituitary block.(5) Thus, the endogenous intercycle FSH rise is utilised rather than suppressed, resulting in a reduction in the amount of medication needed and in the total length of the treatment.

GnRH antagonist protocols:

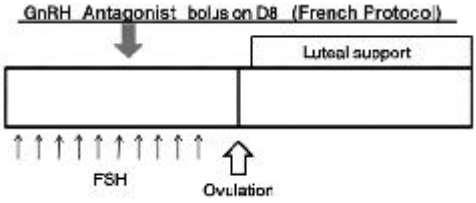
GnRH antagonists use is characterised by an immediate suppression of gonadotrophin secretion from the pituitary, and a rapid recovery of normal gonadotrophin secretion when the drug is withdrawn. This results in a dramatic reduction in treatment cycle duration. (5)

Three general approaches for the GnRH antagonist co-treatment in IVF:

1. *Single large dose (subcutaneously) (French protocol):*

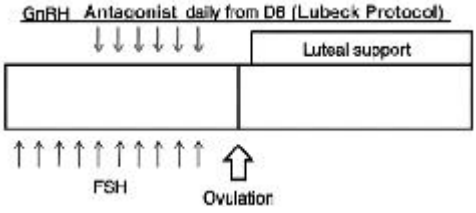
   Gonadotrophins are started as usual and a single dose (3 mg) of antagonist is given on day 8 or when the serum E2 level is about 150-200 pg/ml and the follicular size is 14 mm.

   Administration of a single dose antagonist is effective in suppressing endogenous LH for 4 days. If the criteria to trigger final oocyte maturation have not been met before the end of this 4 day period, then daily antagonist dose can be administered accordingly. Theoretically however, this single dose might result in unnecessary antagonist administration, if the criteria to trigger final oocyte maturation are met before the effectiveperiod of 4 days is over. And so, though the daily antagonist protocol necessitates multiple injections, it allows using the minimally necessary dose of antagonist in a treatment cycle.



2. *Fixed daily dose protocol (Lubeck protocol):*

   Gonadotrophins are started as usual and the antagonist is started from a fixed day (the 6th day of stimulation) onwards in a daily dose of 0.25mg / day till the day of HCG injection.



3. *Flexible daily dose protocol:*

   Daily small doses initiated depending on the size of the dominant follicle (>_14mm) or on estradiol levels, and continued till and including the day hCG is administered for final oocyte maturation

GnRH antagonist dosages

The optimal dose is 0.25 mg subcutaneously, at the same time of the day (preferably around 2 pm), for the daily dose scheme and 3 mg for the single dose scheme. Higher antagonist doses for daily administration have been associated with very low LH levels, and a lower probability of pregnancy. Also, they lead to detectable antagonist in circulation on the day of embryo transfer, which could be detrimental for embryo implantation.

Antagonist vs agonist protocol

Advantages over the Agonist protocol:

1. The duration of treatment for an antagonist is substantially shorter than for an antagonist. Since its only purpose is to prevent a premature endogenous LH surge and its effects are immediate, antagonist treatment can be postponed until later in follicular development (after 5–6 days of gonadotropin stimulation), after estradiol levels are already elevated, thereby eliminating the estrogen deficiency symptoms that may emerge in women treated with an agonist.
2. Because any suppressive effects that agonists may exert on the ovarian response to gonadotropin stimulation also are eliminated, the total dose and duration of gonadotropin stimulation required is decreased. For the same reason, GnRH antagonist stimulation protocols may benefit women who are poor responders when treated with a standard long protocol.
3. By eliminating the flare effect of agonists, GnRH antagonists avoid the risk of stimulating development of a follicular cyst. Finally, the risk of severe OHSS associated with use of antagonists also appears lower than with agonists.
4. It is more convenient for the patient with fewer injections and fewer side effects. For the physician and the nursing staff, stimulation protocols that include recombinant FSH and a GnRH antagonist are much easier to implement, schedule, and manage.

Potential 'Disadvantages' over the Agonist protocol:

When administered in small daily doses, strict compliance with the prescribed treatment regimen is essential. Antagonists suppress endogenous gonadotropin secretion more completely than agonists. Whereas the low levels of LH observed during agonist treatment are usually sufficient to support normal follicular steroidogenesis during stimulation with uFSH or rFSH, the even lower concentrations in women treated with an antagonist may not be. Indeed, serum estradiol levels may plateau or fall when antagonist treatment begins. Although follicular growth appears unaffected, most prefer to add or substitute a low dose of hMG (75 IU) at the same time if it was not already part of the stimulation regimen. Evidence also suggests that pregnancy rates in antagonist treatment cycles may be modestly lower than in cycles using agonists in the long protocol. It thus became a second choice for many clinicians. A Cochrane review 2007 concluded that GnRH antagonist protocols are short, simple, with good clinical outcomes and significant reduction in severe OHSS incidence and gonadotrophin amount; however, the lower pregnancy rate compared with the GnRH agonist long protocol necessitates counselling subfertile couples before recommending change from GnRH agonist to antagonist. (1)

Newer treatment concepts (2,3)

GnRH antagonists offer clinicians an alternative to the GnRH agonists, and also use of the following regimes.

1. The modified natural cycle: The natural cycle protocol involves no drugs whatsoever, and the LH surge is used to decide the timing of the oocyte retrieval. The modified natural cycle protocol is also with no stimulation medications, but only the hCG trigger is used, prior to the oocyte retrieval. Antagonist and FSH / HMG add-back can be used. Several studies published recently have shown that natural / modified natural cycles are beneficial in poor responders, those with repeated failure of implantation, and in those where stimulation is contraindicated.(4) It should preferably be offered as a series of cycles, as it is safer, cost-effective and less stressful to the patient.
2. Mild IVF: Mild stimulation is defined as "FSH or HMG administered at lower doses and/or for a shorter duration in a GnRH antagonist co-treated cycle, or when oral compounds are used alone or with gonadotrophins". Ovulation induction with hCG or alternative medications, and luteal phase support is part of the protocol.

   Although the use of GnRH antagonists is probably not absolutely required for "mild" ovarian stimulation, their introduction in clinical practice since the 1990s has represented the key event to start using "mild" protocols in IVF. (5)
3. GnRH agonist for triggering the final oocyte maturation, in patients at risk of developing OHSS.
4. Antagonists during the luteal phase for management of severe OHSS.
5. In IUI cycles: For control of endogenous LH with GnRH antagonists.

Ovulation trigger in the antagonist protocol

Replacing hCG as the trigger with recombinant LH or GnRH agonists can be done in an Antagonist protocol cycle. This has been found to significantly reduce the incidence of OHSS.

Luteal phase support (lps) in the antagonist protocol

The GnRH agonist protocol though will need LPS always, since these cycles are generally associated with luteal phase defect. The natural cycle IVF does not require LPS. And so also to some extend in the antagonist protocol, though most prefer to support the LP in this cycle also. The short LH inhibition should ideally produce low disturbance on the luteal phase. But the fact that Antagonists have also been suggested to produce negative effects on endometrial receptivity, and the initial attempts with no LPS in the antagonist cycle, indicated that it would indeed be a better idea to use LPS. Progestogens

and progesterone are now preferred, as against the previously used hCG.

GnRH antagonists in special populations

1. Patients at risk of OHSS:
   - Coasting can be used to prevent OHSS in Antagonist cycles. However, prolongation of the follicular phase by deleying hCG administration results in a higher incidence of endometruial advancement on the day of the oocyte retrieval in GnRH antagonist cycles.
   - GnRH agonists can be used as an ovulation trigger (instead of hCG) in an antagonist protocol cycle. This significantly reduces the incidence of OHSS.
   - Antagonists administered during the luteal phase of cases with severe OHSS, is an effective management method. But all the embryos need to be frozen, and transferred at a later date.
2. The older patient and the poor responder: The agonist microdose flare-up protocol seemed to be more effective in the poor responder patients with a significantly higher mean number of mature oocytes and higher implantation rates. But more recently the flexible Antagonist protocol was found to be associated with significantly higher ongoing pregnancy rates than the flare-up protocol.(9)

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