Discussion: GnRH agonists and antagonists in ovarian stimulation

Ovarian stimulation using GnRH agonists

Gonadotrophin-releasing hormone (GnRH) agonists have been used for several years, yet many aspects of the preferred clinical protocols and treatments are still a matter for intense debate. Down-regulation beginning in the luteal phase is believed by many clinics to have the advantage of utilizing the circulating progesterone concentrations to reduce flare-up of luteinizing hormone (LH), moderating the immediate response of ovarian follicles and avoiding the luteinization of large follicles. The value of initiating treatment with agonists in the follicular phase is also contentious. Some clinicians believe that it accentuates disorders in the follicles, and causes the formation of many ovarian cysts. The short protocol may be less effective in clinics who use it without checking progesterone concentrations in their patients, since incompletely-regressed corpora lutea may be revived and produce a rise in plasma progesterone concentrations. This problem is avoidable by recording concentrations of plasma progesterone before the agonist is given, and if necessary by delaying the treatment for a day.

The nature of the short protocol is still undecided. Some clinics use the ultra-short protocol to take advantage of flare-up to induce follicle growth, whereas others use a slightly longer treatment period, and wait until the pituitary is down-regulated before starting treatment with human menopausal gonadotrophin (HMG). Disagreements persist about comparative pregnancy rates after using the agonists for either a luteal or follicular onset of down-regulation, since these rates appear to be similar with either form of the treatment. One apparent advantage of long-term protocols, i.e. a lower rate of ectopic pregnancy, seems to be an artefact.

Some matters of the subsequent health of patients require further study. Long-term effects could arise after the prolonged use of agonists, e.g. on the subsequent activity of the pituitary gland. Some data from rats indicates that pituitary adenomas may be a consequence of such a therapy. The nature of other clinical situations arising in patients after the chronic use of agonists, e.g. prostate carcinoma, is still under review.
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Even after 10 years of using various forms of pituitary suppression, with the GnRH agonists, there is still no defined minimizing effective dose. Every clinic seems to have its own formula for ovarian stimulation. Some clinics permit follicles to grow to 17–18 mm, whereas others prefer a diameter of >20 mm. Other clinics continue long-term down-regulation treatment with agonists for 3 weeks or more, to suppress oestradiol output. Often, a shorter period is used, from 10–14 days. There are no clinical data showing an advantage of 3 weeks versus shorter treatment periods.

The use of GnRH antagonists in ovarian stimulation protocols

Some of the GnRH antagonists are hydrophobic, and they gel in solutions of sodium chloride. This characteristic may contribute to the depot action of these compounds when injected into patients. Cetrorelix rarely gives irritation marks on the skin, and when it does they last for only a few minutes. Some other antagonists are more hydrophilic, but evoke a higher histamine release and local adverse reactions.

The antagonists offer a rapid, simple, easy to use and inexpensive form of pituitary suppression when given at virtually any stage of the menstrual cycle. The initial doses used to suppress plasma LH for 3 days have gradually been reduced from 5–2 or even 1 mg, and the introduction of various dosage combinations may be the final answer.

The exact stage to give the GnRH antagonists has not been clarified. They can be started at any phase of the cycle, and survival of a growing follicle or a corpus luteum is immediately impaired. Uterine bleeding begins within 48 h. The LH surge is blocked within 1 h of administration, so that any premature LH surges that are threatened during HMG stimulation are blocked immediately.

A single dose of antagonist given during ovarian stimulation as oestrogen concentrations pass 400 pg/ml is immediately effective, and this form of treatment may offer a routine method for patient care. Perhaps 500 or 600 pg would be a better start point for those patients who do not have either polycystic ovaries (PCO) or an elevated LH concentration. Oestrogen concentrations as high as 900 pg/ml have occasionally been used as a starting point for the administration of an antagonist. A more optimal response in the patient may be gained by starting the antagonist as late as possible, since it has an immediate effect on blocking pituitary receptors. It may even be possible to delay the antagonists until close to the expected onset of the LH surge, but this will require detailed monitoring. The effects of such a single dose of antagonist given in the mid-follicular stage will prevent spontaneous LH surges until the time when HCG is normally given to induce ovulation. Exceptions may include patients with polycystic ovarian syndrome (PCOS) who have high plasma LH concentrations.

Ovarian follicles apparently fail to progress beyond the period of recruitment during treatment with antagonists, and the withdrawal of gonadotrophin support seems to cause their death. Migration from the ovarian follicle pool to the
gonadotrophin-dependent phases of growth continues unabated during the period of ovarian suppression. It is not known if the antagonists reach the ovarian follicles and exert any actions there. Despite the suppression of subsequent stages of folliculogenesis, the ovary responds immediately when HMG is given after a long treatment with GnRH antagonists. The uterus also responds immediately, with a normal growth phase and an excellent secretory phase.

Progesterone concentrations decline from days 6–7 of the luteal phase, and may remain low as pregnancy begins despite the secretion of HCG. In patients who do not become pregnant, the luteal phase lasts for about 11 days. This shortening is typical of other forms of exogenous ovarian stimulation. Progesterone supplementation might help to sustain the luteal phase, but there is no information about its efficacy.

The use of GnRH antagonists during pregnancy does not cause abortion. This implies that the control of placental HCG differs from the control mechanisms involved in the regulation of LH release from the pituitary gland, where the antagonists sharply reduce gonadotrophin output. Nevertheless, some LHRH receptors are evidently expressed in ovarian follicles, indicating that similarities exist in control systems in the ovary and pituitary gland.

Long-term treatment with GnRH antagonists leads to an accumulating LH deficiency, perhaps due to their actions on thecal cells. This deficiency may have to be corrected in patients given a subsequent cycle of ovarian stimulation, and this is achieved by adding some LH to the FSH priming in order to stimulate oestrogen secretion in certain patients. There is no carry-over when treatment with antagonists is withdrawn, and effects on the subsequent cycle or pregnancy have not been detected.

Advantages of the antagonists

Antagonists offer several advantages for controlling LH secretion during ovarian stimulation. In general, they involve the simplest treatment for a rapid but temporary LH suppression, and improvements in the formulation and preparation of antagonists may offer further clinical advantages. Such improvements also occurred with the agonists after they were introduced, which made them more effective and adaptable to various stimulation protocols. The antagonists may be less expensive, faster working, and more effective than the agonists.

Treatment with antagonists can begin simultaneously or soon after treatment with gonadotrophins has begun. The frequency of ovarian cyst formation is lower than with the agonists. There is no flare-up effect with the antagonists, in contrast to the agonists. Antagonists may introduce cheaper forms of ovarian stimulation such as clomiphene and HMG, although the antagonists will probably prevent the action of clomiphene. Less gonadotrophin might be required for ovarian stimulation after treatment with antagonists, which might be important when considering the risks of ovarian cancers. This matter is still debatable. Patient management, stress, cost, the number of injections and hyperstimulation may all...
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be reduced in frequency, although the antagonists may not synchronize follicle
development as effectively as long-term down regulation with agonists. Current
evidence is unconvincing.

Antagonists could offer important advantages for other forms of patient care.
Patients who might benefit include those with fibroids, endometriosis and
myomas. The better control exercised on LH output and oestrogen secretion by
GnRH antagonists will give a better control over myomas, enabling an earlier
surgery (e.g. 2–3 weeks) than with agonist pre-treatment which requires 5 weeks
or sometimes even longer. In cases of uterine bleeding, the decline in haemoglobin
concentrations may be prevented much earlier since the antagonists reduce
oestrogen concentrations more rapidly than do the agonists. Agonists may be
preferable for some clinical indications. This situation may arise with the
preferential use of a single injection of agonist for the prolonged suppression of
fibroids, prostate cancer, etc., because injections of antagonists will have to be
given repeatedly under these circumstances.

Current availability of the antagonists

At present, the antagonists seems to have a very limited availability. Their use
is restricted to a few clinics or companies who are able to carry out clinical
trials. Antagonists seem to offer so many advantages that questions arise as to
why they are not immediately available. Their development history has been
subject to a series of setbacks, in particular the high incidence of histamine
release following the first generation of antagonists. Another reason for their
limited availability may involve a lack of economic incentive in producing them,
since the agonists are proving to be so profitable.

On the other hand, their relative unavailability may not necessarily be due to
commercial reasons. Several companies have an active phase 2 programme, and
one is in phase 3, and the large-scale production of antagonists may begin when
their clinical advantages are more clearly defined. In one sense, this situation
arose with the commercial production of the agonists, for they became easily
available for reproductive medicine when vast amounts of them were produced
for the alleviation of prostatic cancer, endometriosis, fibroids, etc. Some of the
companies manufacturing antagonists are more interested in oncology and not in
reproductive medicine, and this may also limit their introduction into routine
ovarian stimulation.