Gnrh Agonist Protocol Versus Gnrh Antagonist Protocol

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Abstract:

The availability of gonadotrophin-releasing hormone (GnRH) antagonists for ovarian stimulation protocols has generated many meta-analyses comparing it to GnRH agonist long protocols. These meta-analyses have yielded conflicting results for pregnancy rate, with a tendency toward a better outcome for GnRH agonists. Recently, a Cochrane review seems to have settled the conflicts by demonstrating no evidence of statistically significant differences in the rates of live births or ongoing pregnancies when comparing GnRH agonist long protocols with GnRH antagonist protocols. This paper disputes the equivalence of these two protocols as discussed in the latest meta-analysis and argue that the GnRH agonist still has a demonstrable superiority over GnRH antagonist protocols.

Keywords: GnRH agonist, GnRH antagonist, ovarian stimulation.

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Introduction:

There are two different kinds of GnRH analogs that have been found: agonists and antagonists. Because they have the ability to inhibit gonadotropin secretion and the concomitant generation of sex steroids, these deca-peptides have different therapeutic use. The main function in controlled ovarian hyperstimulation is to prevent the occurrence of premature LH surge. This function improves the results of in vitro fertilization (IVF) cycles while reducing the cycle cancellation rate. Moreover, these molecules offer physicians the freedom to arrange the moment for oocyte retrieval **(1).**

GnRH agonisits:

The native GnRH molecule's amino- and carboxy-terminal sequences are essential for binding to the receptor, whereas the amino-terminal domain is crucial for activating the receptor. Numerous GnRH agonists have been produced; they differ from one another by altering the amino acid at position 6. The resultant molecule has benefits from this new characteristic. According to **Narayan et al. (2),** the agonist analogs have a greater affinity for the GnRH receptor and become more resistant to enzymatic degradation.

The GnRH agonist first increases pituitary secretion (flare effect), then it reduces pituitary gonadotropin production by downregulating GnRH receptors on the gonadotropic cell's cell

membrane. Pituitary secretion normally resumes two weeks after therapy is stopped because the receptors are temporarily attached to the agonist; full restoration of ovarian function occurs after more than six weeks (3).

In order to achieve simultaneous maturation, early antral follicles grow synchronously in response to exogenous gonadotropins, as the endogenous GN are profoundly suppressed by GnRH agonists during the early follicular phase. As a result, the FSH window widens, more mature follicles are recruited and more oocytes are retrieved (4).

There are two most popular GnRH agonist regimens. First one is the long mid-luteal GnRH agonist protocol (Fig. 1). The GnRH agonist is administered in this procedure during the mid-luteal phase of the preceding cycle. The GnRH analogs in Table 1(5).

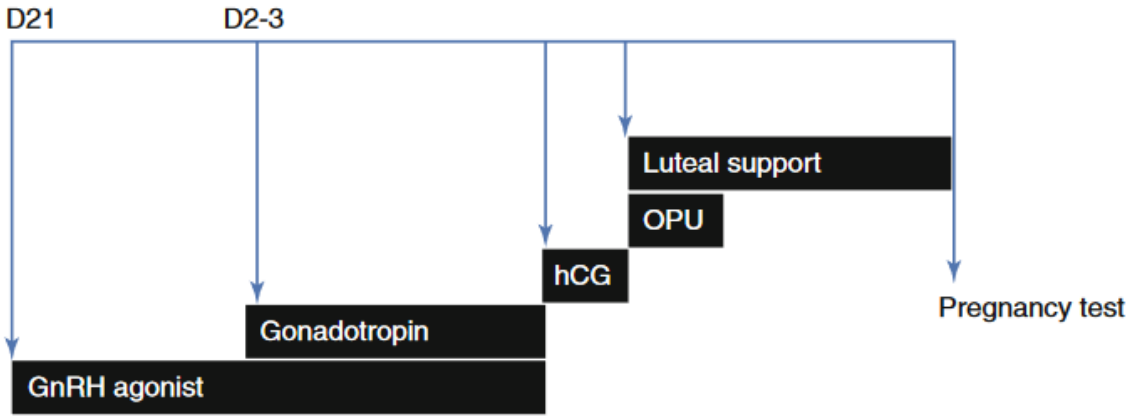

Figure (1): GnRH agonist downregulation protocol.

Table (1): GnRH analogs (6).

GnRH agonists	GnRH antagonists
Triptorelin	Nal-Glu-GnRH
Leuprolide	Antide
Buserelin	Azaline B
Goserelin	Cetrorelix
	Ganirelix

Second one is the short flare agonist down-regulation protocol, where the GnRH agonist is given on day 2 of menstruation (Fig. 2) (7).

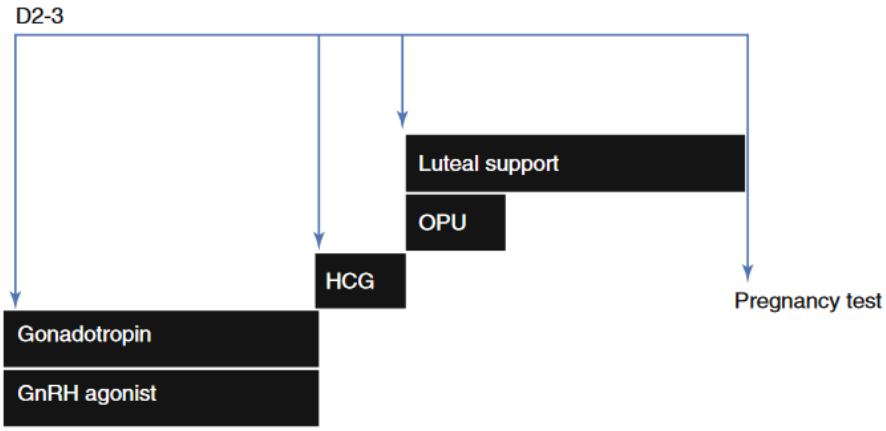

Figure (2): Short flare GnRH agonist protocol

In the long protocol, injections or a depot formulation of a GnRH agonist are started in mid-luteal phase of the previous cycle. Currently, this protocol remains the most widely utilized in the world for assisted reproductive procedures. Its goal is to completely desensitize the pituitary gland before initiating stimulatory therapy. Although it works well to stop the early LH surge and permits strict cycle management, it has many drawbacks, including the following:

(a) Length: the course of treatment should last at least 14 days beyond the average menstrual cycle.

(b) Using the agonist while a potential early pregnancy is present.

(c) Cyst formation: ovarian function may be hampered by the flare-up effect.

(c) Symptoms of hormone withdrawal.

(e) Gonadotropin use: Compared to cycles without the use of GnRH agonists, more gonadotropins are used.

(f) Due to pituitary desensitization, ovulation induction is only feasible by human chorionic gonadotropin (hCG) and LH; GnRH cannot induce ovulation.

(g) Pituitary desensitization necessitating luteal phase support.

(h) Higher frequency of moderate and severe OHSS compared to cycles in which GnRH agonists were not used.

(i) Pituitary suppression that lasts longer after desensitization disrupts subsequent menstrual cycles. **(8).**

The GnRH agonist protocol may suppress endogenous FSH levels, resulting in a follicular cohort of all small follicles at the onset of FSH stimulation and a synchronized follicular development. It may also produce stable and low levels of LH and progesterone (P) throughout the stimulation phase. This protocol's benefits include better patient scheduling, more oocyte collection, and higher chances of conception from cryopreserved embryos **(9).**

GnRH antagonists:

Multiple amino acid changes at positions 1, 2, 3, 6 and 10 in the decapeptide yield antagonistic analogs of GnRH. High dosages of these substances are required in order to counteract endogenous GnRH activity. The initial generation of GnRH analogs stimulates the production of histamine, they may trigger anaphylactic responses. These negative effects are absent from Ganirelix and Cetrorelix, the next generation compounds. The levels of sex steroids decrease as a result of suppression of gonadotropin (FSH, LH) release. Gonadotropin levels do not initially rise in response to GnRH antagonists. Recent research suggests that long-term use of GnRH antagonists causes downregulation of GnRH receptors in addition to their ability to compete with GnRH for these receptors on gonadotroph cell membranes. GnRH antagonists work mainly by competing with native GnRH for the specific membrane receptors. **(10, 11).**

There are three GnRH antagonist procedures described:

(a) Single dose protocol: 3 mg of a GnRH antagonist on the seventh stimulation day.

(b) Fixed day six protocol: take 0.25 mg of GnRH antagonist every day up until hCG is administered.

(c) Flexible dose protocol: 0.25 mg GnRH antagonist when a follicle reaches 14 mm. **(12).**

The potential for making ovarian stimulation less aggressive and significantly "softer" than the long agonist regimen is one of the most encouraging elements of using GnRH antagonists **(1).**

An antagonist strategy has definite benefits, including a shorter stimulation duration, no sex steroid withdrawal symptoms, a decreased rate of OHSS. Compared to GnRH agonists, the pharmacological mode of action of GnRH antagonists is more physiological. GnRH antagonists provide great therapeutic flexibility by immediately suppressing gonadotropins. The same study recommended the use of a GnRH antagonist treatment in a subset of patients, particularly poor responders. **(13).**

According to **Depalo et al. (4),** the GnRH antagonist regimen is more efficient at delaying the rise in LH than the long agonist protocol, which means that the ovarian stimulation protocol is shorter and less expensive. The synchronization of follicular growth and recruitment in the GnRH agonist and GnRH antagonist regimens differs, nevertheless, with the GnRH antagonist therapy exhibiting superior follicular growth and oocyte maturation **(14).**

The primary benefit of antagonist regimens is that they prevent the side effects associated with the first flare-up and subsequent downregulation by providing rapid and reversible inhibition of gonadotropin secretion. The IVF procedure may be started by the doctors during a normal menstrual cycle. With a much lower effective dosage and a shorter course of treatment. The primary drawback of antagonist treatments is the potential for high variation in inter-cycle FSH concentrations which might stimulate the recruitment of additional follicles and result in asynchronous follicular growth **(4).**

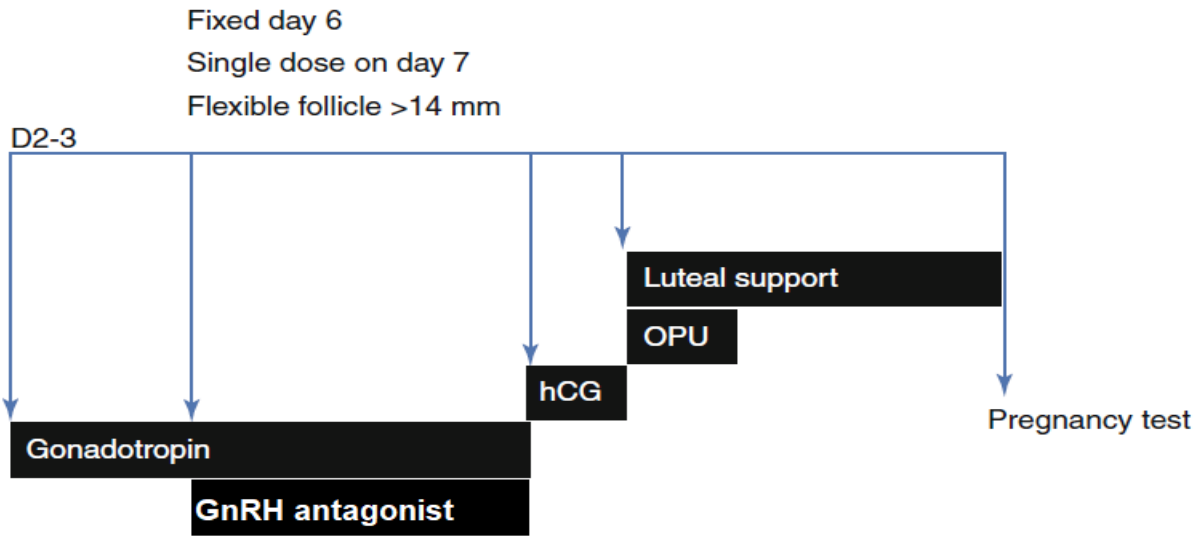

Figure (3): GnRH Agonist Protocol (4).

GnRH Antagonist versus GnRH Agonist Protocol

The outcome parameters of patients who were expected to be good responder to stimulation based on baseline characteristics and who used either an antagonist or agonist strategy for their first IVF cycle were compared in recent retrospective research. The authors unequivocally stated that in good responders using either a GnRH agonist or antagonist during their first cycle of IVF, clinical pregnancy rates (43.6 % vs. 48.6 %) and live birth rates (34.9 % vs. 40.1%) were comparable **(15).**

The cycle outcomes of oral contraceptive (OC) pill pretreatment in recombinant FSH/GnRH antagonist versus recombinant FSH/GnRH agonist stimulation in IVF patients were reported in another prospective randomized research. According to **Barmat et al. (16),** the patients in both methods had comparable numbers of two pronuclei (2PN) oocytes, cryopreserved embryos, transplanted embryos, and rates of implantation and pregnancy.

A meta-analysis clarified how antagonist regimens have a positive impact on OHSS rate reduction. In terms of continuing pregnancy rates and live birth rates, the authors were unable to find any statistically significant results based on the results of 45 randomized controlled trials (RCTs). Nonetheless, it was made evident by the authors that using an antagonist was linked to a significant decrease in OHSS when compared to long GnRH agonist protocols **(17).**

Another study addressed the topic of whether cycle outcomes for the same patient undergoing IVF differed depending on the GnRH agonist and GnRH antagonist strategy. The results of this retrospective analysis showed that the implantation rate and clinical pregnancy rate in the antagonist protocol (15.82 % and 30.26%, respectively) were considerably greater than those in the agonist protocol (5.26% and 10.64 %, respectively). It was determined that older patients with a history of numerous IVF-ET failures would most likely have a better pregnancy outcome when using the GnRH antagonist strategy **(1).**

A meta-analysis provided a study of Agonists vs Antagonists in COH results showed that both the GnRH antagonist and the GnRH agonist long regimen had comparable implantation, clinical pregnancy, and pregnancy loss rates. Nonetheless, in the GnRH agonist group as opposed to the

GnRH antagonist group, a notably greater quantity of oocytes and a higher percentage of mature MII oocytes were recovered per patient who was randomly assigned. Furthermore, a statistically significant correlation was found between the age of the patient and the quantity of oocytes recovered in the antagonist group. This suggests that the GnRH antagonist promotes a more spontaneous recruitment of follicles in the follicular phase in an unstimulated ovary, while the agonist treatment improves the synchronization of the follicular cohort. **(4).**

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