The Egyptian Journal of Hospital Medicine (April 2023) Vol. 91, Page 4543-4545

Use of Gonadotropin-Releasing Hormone Agonists in Induction of Ovulation: Review Article

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ABSTRACT
Gonadotropin-Releasing Hormone Agonists (GnRH -a) are now frequently used in addition to ovulation induction. With the help of these analogues, a variety of regimens can be utilized to increase the quantity and/or quality of follicles that can be stimulated, lower rates of early luteinization, lower cancellation rates, and eventually increase the likelihood of pregnancy. The current review summarizes the mode of action of GnRH –a, and the three types of superovulation protocols; the ultrashort, short, and long protocols.
Keywords: Gonadotropin-Releasing Hormone Agonists, Ovulation, Luteinization, Review, Zagazig University.

INTRODUCTION

It has been demonstrated that the presence of an elevated basal level of luteinizing hormone (LH) has little to do with the effectiveness of an IVF cycle. Premature LH surges, which led to premature luteinization and were causes for discontinuing the treatment cycle, were brought on by the positive feedback of growing estradiol levels brought on by the gonadotropins [(1)].

The initial clinical trials of GnRH analogues have shown their efficacy in lowering the incidence of low responders and removing the basal levels of LH. Cycle cancellations became much less common, and GnRH analogs quickly became widely used [(2)].

Mode of Action:

Agonists were first created to have a more potent and pervasive effect on the pituitary; as a result, they boost the initial release of FSH and LH reserves and temporarily upregulate the membrane-based gonadotropic cell receptors [(3)].

A longer duration of administration of agonists simulates a chronic infusion of GnRH, neutralizing the pulsatile impact. The number of receptors decreases as the agonist receptor complexes are integrated, commonly referred to as downregulation [(4)].

The biological activity of FSH and LH is reduced, their serum levels fall, and postmenopausal levels of estradiol are reached. By giving GnRH agonists daily intranasally, subcutaneously, or monthly as part of a Depot regimen, follicular maturation can be persistently suppressed [(4)].

The Flare up Effect:

The GnRH agonists always have an initial stimulatory impact before having an inhibitory effect. After 12 hours, this flare-up results in a five-fold spike in FSH concentration and a roughly ten-fold increase in serum LH levels. Estradiol levels briefly increase to around four times the baseline at the same time [(5)].

About 15 to 20 percent of stimulated cycles were lost before the development of GnRH agonists as a result of an early LH surge. Pretreatment by down-regulation caused this rate to drop to under 2% [(6)].

GNRh Protocols for Controlled Ovarian Stimulation:

Three types of superovulation protocols—the ultrashort, short, and long protocols—combine the use of GNRH agonists and hMG, originally and now recombinant FSH (r-FSH) [(7)]. Both the short and ultrashort protocols attempt to stimulate follicles by utilizing the initial flare-up in gonadotropin release [(7)].

The Short Protocol:

From the first day of the cycle until the induction of ovulation with HCG, GnRH agonist is administered subcutaneously or intranasally. To prolong follicular growth when the pituitary gonadotropins become desensitized, exogenous gonadotropins such as hMG or r.FSH must be administered by day 2 of menstruation, or even better, day 3 [(5)].

The Ultra Short Protocols:

Only days 2 through 4 of the cycle are used in the ultrashort protocol to administer GnRH agonist subcutaneously or intranasally, and days 2 mark the beginning of hMG stimulation [(3)].

Starting on day 5 of the cycle, the patient is assessed every day by evaluating serum levels of estradiol and LH together with vaginal ultrasonography to gauge follicular growth up to the HCG day, both agonist and hMG are sustained for an average of 13 to 14 days [(8)].

Induction of Ovulation:

When the leading follicle measures 17 mm in diameter ovulation induction begins by giving 5000–

Received: 20/11/2022
Accepted: 22/01/2023

10000 IU of HCG, with oocyte retrieval following 34–39 hours later [9].

Oocyte maturity is obtained 36 hours after hCG injection in cycles promoted by human menopausal gonadotropin analogue agonist. Before 36 hours, oocyte retrieval should not be done, and between 36 and 37 hours, there is no possibility of spontaneous ovulation [9].

Both procedures are effective at stopping an early LH surge. Their benefit is that they only marginally extend the stimulated cycle, using roughly 27 ampules of HMG each stimulated cycle. Both are economically advantageous, and the consumption increase compared to no analog pretreatment is barely noticeable [4].

One drawback is the elevated LH concentration in the early follicular phase brought on by increased endogenous gonadotropin release, which might negatively impact follicular maturation [10].

The Long Protocol:

The lengthy protocol has evolved into the norm at the majority of major hospitals [3]. Prior to hMG stimulation, this technique seeks to desensitize the pituitary. So, from the midluteal (day 22) of the previous cycle or early follicular phase, GnRH agonist is administered either daily subcutaneously or intranasally, or in the form of depot preparation subcutaneously or intramuscularly (day 1) [4].

Monitoring in the Long Protocol:

It can be presumed that the hypothalamic-pituitary ovarian axis has essentially been dissociated 14 days after starting GnRH agonist treatment. Now we evaluate the hormone state in the beginning. When estrogen and LH levels are below 400 pg/mL and 10 IU/ml, respectively, hMG stimulation may begin 50 pg/mL and progesterone below 1 ng/mL [4].

Ovulation Induction:

The leading two follicles need to be at least 18 mm in diameter before hCG can be administered, according to the main requirement. The administration of hCG can be timed with a great deal of flexibility. According to estradiol levels and the size of the other follicles, hCG is often administered when the leading follicle (or follicles) are 20 mm or 22 mm in diameter. Approximately 300-400 pg/mL of estradiol is secreted per follicle greater than 17 mm [9].

A dose of 5000–10,000 IU of HCG is taken in the morning and evening. In comparison to other protocols, the lengthy protocol allows for the synchronization of follicle maturation and the selection of a greater number of follicles or oocytes for IVF. The high hMG consumption, which averages 45 ampules per stimulated cycle, is a drawback. Because of this, the therapy is very expensive [11].

Monitoring of Gonadotropin:

In order to achieve a high rate of conceptions while avoiding hyperstimulation and lowering the incidence of multiple pregnancy to a tolerable minimum, proper monitoring is essential for the outcomes of gonadotropin therapy.

Three goals are pursued by monitoring the ovarian response to stimulation:

1. To establish the optimal gonadotropin dosage per day.
2. To establish how long gonadotropin administration will last.
3. To establish the best time to administer the HCG ovulatory dosage [12].

An ultrasound of the pelvic area is performed prior to the start of each session of treatment to rule out the presence of aberrant follicular formations or cysts. As these structures are linked to aberrant ovarian response to stimulation and/or sonographic treatment monitoring, they should either be punctured or the therapy should be postponed until they spontaneously vanish [13].

Between the third and fifth day of spontaneous or induced bleeding, treatment is initiated. When all pituitary ovarian downregulation has been achieved, concurrent GnRh analogue gonadotropin therapy is initiated [14].

The patient is checked every one to three days. According to the patient's reaction as revealed by estrogen, ultrasound, and clinical findings, the gonadotropin dose is modified [12].

It is done using ultrasound. The dose is decreased by one ampule if estrogen climbs too quickly or the day-to-day variation is greater than the geometric rise (75 IU FSH) and the reduced dosage of the medication is maintained. The same dose is continued until an E2 level between if the estrogen rise is gradual and not excessive 350 and 1200 pg/ml (1330-4500 p mol/L) is reached [15].

The third sonographic scan is carried out at this point in the therapy. If the combined number of detectable follicular structures in both ovaries is less than 10, and one to four follicles have a diameter greater than 17 mm, the ovulatory dosage of hCG will be administered (10000 IU) is administered [14].

Sources of funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of interest: There are no conflicts of interest, according to the authors.

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