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A Comparison between GnRH Agonist Long and GnRH Antagonist Protocol for *In vitro* Fertilization: A Review

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Abstract
In early years, for the in vitro fertilization (IVF), gonadotropin-releasing hormone (GnRH) agonist long protocol play a key role for poor ovarian responders and was used for ovarian stimulation to inhibit the premature surge of luteinizing hormone. Although it had a number of side effects, this method was widely accepted and used as a long duration protocol treatment, which also increased the pregnancy rate and a number of oocytes retrieved. With the administration of the agonist, follicular stimulating hormone (FSH) and LH increases. Different studies and meta-analysis have shown major complication leading to higher incidence of hospital admission associated with the ovarian hyperstimulation syndrome (OHSS). Thus, to overcome these complications, various studies were conducted using GnRH antagonist which had an immediate mode of action, shorter duration, decrease hospital stay and beneficial to patients undergoing ovarian stimulations. Comparative studies between these two analogues have shown antagonist being the "drug of choice" even though the probability of live births does not rely on the type analogue used. In recent years, it is anticipated that the protocol of GnRH antagonist could improve the achievement of pregnancy outcomes compared to GnRH agonist, however, after the introduction of GnRH antagonist it has proved and appreciated as an additional support to ovarian stimulation in IVF cycles on the basis of patient's benefits and the clinicians are taking advantage of these benefits.
Keywords: GnRH agonist, GnRH antagonist, IVF, follicular stimulating hormone, OHSS.

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Introduction

Gonadotropin–releasing hormone (GnRH) is a hormone secreted by the anterior pituitary gland and plays a vital role in monitoring the ovarian cycle in females [1]. About 9% of the women worldwide are suffering from infertility in their reproductive age [2]. Among 9% of infertile patients, poor ovarian response coming for in vitro fertilization (IVF) cycles accounts for 9-24% [3]. The primary reason for poor ovarian response is a reduction in ovarian function. The indicators relating to the poor ovarian response are the levels of the basal follicular stimulating hormone (FSH), antimullerian hormone, inhibin B, and the count of the antral follicle. Though there are many studies based on assisted reproductive technology for the patients with the poor ovarian response, there are still controversies for their treatments regimens [1, 4-6].

To fulfill the requirement of patients, they classify groups from low, intermediate and higher responders. Studies continues to publish numerous treatment regimens such as including GnRH analogue, CC (clomiphene citrate), and gonadotropin mixture, or combining therapy regimens consisting of CC, recombinant follicle stimulating hormone (FSH) and Luteinizing hormone (LH). Depending on the usage of GnRH agonist versus GnRH antagonist, GnRH analogues in IVF protocols are classified as GnRH agonist or GnRH antagonist protocols [7, 8]. The use of agonist and antagonist has become the most debating issues for the present generation and clinicians. The use of these drugs gives the highest success rate for IVF outcome in comparison to other treatment cycles [2].

Gonadotrophin is also taken in a positive way for the use of the therapeutic treatment in patients suffering from an ovulatory PCOS. The patients who has already gone through the treatment with anti-estrogens, failed to ovulate, didn't respond to CC and other factors decreasing chances of conception. The standard step-up treatment regimens has been traditionally used as 75-150 IU/day and increment by 75 IU/day every 3-5 days but it was replaced by either "low-dose called step-up" or "low-dose called step-down" regimens so as to avoid risks of multiple

pregnancies and over stimulation with gonadotropin therapy [9, 10]. Suppression of endogenous LH was accepted in stimulation protocol, which were used in IVF before starting the initiation of stimulations due to unpredictable LH surge so women were given gonadotrophin treatment for several days but could not get retrieval of oocytes. Also, some of them have to cancel the treatment due to premature luteinization by pituitary downregulation and there was a sudden decline in the proportion of 2 in 100 women [11]. GnRH analogs were proved useful in endogenous gonadotropin suppression and it was very much successful. This was only possible after isolating GnRH decapeptide by Fujino et al in 1971 [12]. After remodeling decapeptide, it synthesizes with agonistic and antagonistic effecting on gonadotrophic cells of the anterior pituitary gland and two types of analogues are obtained GnRH agonist and GnRH antagonist [13, 14]. However, the mechanism of action of both the agonist and antagonist acts in a complete different way by suppressing the gonadal steroids that decreases [1, 15]. Hence, the aim of this review is to show the benefits and efficacy of GnRH antagonist over GnRH agonist long protocol in terms of results achieved in IVF stimulation cycles.

Mechanism of action of GnRH analogues

2.1 Agonist

GnRH agonist was addressed first in the early 1990s as an alternative to human chorionic gonadotropin (HCG) for induction of oocyte maturation during the *invitro* fertilization [16, 17]. During IVF cycles treatment, GnRH agonist may trigger which correspond with similar endocrine profiles and oocyte measures in females with or without polycystic ovarian syndrome (PCOS) patients. Agonist also been used to trigger for the final initiation of follicular maturation and ovulation as purpose to reduce the risk for OHSS [18]. For more than 20 years, it is being used as prevention of mid-cycle LH for multiple follicular developments [19]. Acting on to pituitary receptors in hypophysis it binds to make flare up effect that induces to release large amount of FSH and LH, later increases in quantity of GnRH receptors called up-regulation, prolong internalization can cause decrease in quantity of GnRH receptors called down-regulation where pituitary becomes able to stimulate by GnRH which leads to declining in circulating gonadotropins [20]. The initiation and administration of agonist cause an early flare of gonadotropins which follows down-regulation of GnRH- receptors and is given on the first day of the cycle or on mid-luteal phase as a long GnRH agonist protocol. The release of gonadotropins also reduces and inhibits the release of androgen and estrogen production which helps pituitary desensitization to occur after 2 weeks of treatment and after that ovarian stimulation with exogenous gonadotropins can be started [19].

2.2 Antagonist

GnRH antagonist absolutely acts in completely different way than agonist and have a complex mechanism to block gonadotropin secretion. GnRH receptors completely bind and prevent the initiation of endogenous GnRH pulses on pituitary and within hours of administration, no flare up effect occurs which cause decreased secretion [21]. Thus, after ceasing the treatment, pituitary receptor remains intact and the recovery on pituitary-gonadal axis is fast and predictable [22]. Antagonists are highly dosed dependent in comparison to agonist, which also depend on the stability between present endogenous GnRH and the administration of antagonist [23]. Once GnRH antagonist goes through the circulation, each growing follicle or corpus luteum present comes in contact immediately. Thus due to antagonist effect uterine bleeding occurs within 48 hours as expected and the important factor to notice is after administration which causes blocking of LH surge within 6-8 hours of period [24]. By this way, many clinicians take advantage of GnRH antagonist; the outcome is fast and convenient to the patients who undergo for the treatment of IVF cycles.

Criteria for poor IVF protocol selection

The use of GnRH agonist long protocol and GnRH antagonist protocol totally depends on the clinicians after observing patient's condition, treatment option, its benefits and response of patients to the treatment. Gonadotropin stimulation patients can be divided based on their response; i.e. High, Intermediate and Poor responders [25, 26]. The criteria for poor responders may vary according to the clinicians. Malmusi et al. [27] described a patient having a low number of oocytes (less than 4) and no ovarian response with FSH greater than 300IU as poor responders. Elderly maternal age is associated with the poor response that affects in oocyte quality and follicle numbers and young patients but the cause is unclear. However, which treatment protocol is suitable for poor responders is not very clear as each protocol have both limitations and benefits.

GnRH agonist long protocol versus GnRH antagonist protocol for poor responders

For the success of IVF embryo transfer, ovarian stimulation plays a major role. GnRH agonist and antagonist both act by preventing from the premature rise in LH surge [4]. Raoul et al. [28] has shown the advantages of GnRH antagonist over agonist on the basis of hypoestrogenism, less treatment course, low gonadotropin requirement and lesser incidence of severe ovarian stimulation syndrome (OHSS). Various studies and meta-analysis has also been done comparing GnRH agonist and antagonist protocols which has shown various conflicting results in terms of pregnancy rate [29-33]. However, previous results have confirmed no evidence of a statistically significant difference in rates of live births or ongoing pregnancy comparing between agonist as long protocol with GnRH antagonist protocols [34]. Some studies have also shown a comparison between classical long GnRH agonist protocol treatment with the GnRH antagonist indicating faster result in earlier follicular growth but slightly lower in number of follicles on the day of HCG administration[35-38]. Similar to the antagonist, GnRH agonist also utilizes their effect by producing pituitary down-regulation phenomenon [21].

Treatment protocol of GnRH agonist in poor responders

GnRH agonist allows continuous stimulation of gonadotropin secretion prevent from spontaneous LH surge [39]. GnRH agonist is used during IVF programs which reduce cancellation rate cycle and also improves treatment result [40]. For ovarian stimulation it combines with gonadotropin and this combination can be divided into two categories termed as “SHORT” and “LONG” protocols. Both protocols are effective to prevent spontaneous LH surge and both are significantly different in term of cycles dynamics range [41].

In short protocol, treatment starts by GnRH agonist on the 2ndday of the cycle and is continued till the day of HCG administered and is continued for 2-3 days. Gonadotrophins are then given after the action of GnRH agonist is seen. Advantages of using short protocol is the initial stimulatory effect of GnRH agonist on pituitary gonadotrophin release, which stimulates follicular development.

In the long protocol, treatment starts on mid-luteal phase to achieve pituitary down-regulation by suppressing endogenous gonadotrophin secretion. Once the suppression of pituitary-ovarian axis is achieved, the ovarian stimulation with exogenous gonadotrophins are initiated and GnRH agonist administration can be continued until the day of HCG administration [42-44].

According to previous retrospective or prospective studies, the debate about that long protocol is effective than the short protocol for IVF cycles increase in terms of pregnancy rate. A short protocol, which increases the LH activity, also have the effect on oocyte quality. However, HCG also have an equal role on FSH and LH used before [45]. Nowadays, long protocol treatment is one of the most commonly used assisted reproductive treatment (ART) such as in vitro fertilization, IVF/intracytoplasmic sperm injection (ICSI) worldwide. Many studies have shown the establishment of agonist long protocol in having a significant number of oocytes retrieved, mature oocytes production (with p-value <0.05) and cycle cancellation rate being similar to antagonist [27, 46]. The best treatment for the ovarian stimulation as long protocol is also accepted for young normal gonadotropic females but it must be started in the mid-luteal phase of the initial cycles [47]. The drawback with high doses of GnRH agonist is, it may cause deactivation of ovarian receptors in healthy or underweight patients [48]. For some patients using GnRH-agonist as long protocol has some disadvantages such as; (a) Long duration of treatment until deactivation occurs [49], (b) Increased risk of OHSS [50], (c) Adding the chances of frequent side effects such as: hot flushes, headache, bleeding, and cyst development during the deactivation period [51, 52] and (d) More ampoules of gonadotropin are required [53]

The incidence of a severe form of OHSS has been reached up to 3.1-8% [54]. High-risk patients should be selected for initial prevention by individualizing them for ovarian stimulation. This method of individualization helps to choose for proper protocol and to minimize gonadotropin dose required to achieve adequate oocyte maturation [55]. After reviewing different agonist treatment protocols, it is observed that the long protocol is much more effective than stimulating ovary without the administration of GnRH analogues.It is also more effective than other GnRH agonist protocols used, such as the short and ultra- short protocols [45]. The exact mechanism of suppression is still unclear though the GnRH agonist acts by down-regulation of GnRH receptors [15]. It also accompanies the administration of initial gonadotropin and gonadal hormone surge which is known as “FLARE” that acts by delaying the suppression for 7-14 days [15]. GnRH agonist is the modeled synthetic peptide,

which also reacts with GnRH receptors to produce its biologic response and to deliver pituitary hormones such as FSH and LH. After the earlier "FLARE" response, GnRH agonist desensitizes the pituitary gland by continuing the stimulation that causes GnRH receptor down-regulation. By desensitizing, pituitary decreases the secretion of LH and FSH and enhances hypo-gonadotropic hypo-gonadal anovulation known as "pseudo" menopause or medical "oophorectomy". For poor responders, GnRH agonist may cause over suppression without any additional IVF outcome. For the treatment of reproduction faculty, numerous regimens and interventions have been introduced and made lots of effort to improve ovarian response for the outcome of IVF. These treatment protocols also include high doses of gonadotropin, changed to "FLARE-UP" protocols, combining with oral contraceptives (OC) pretreatment and use of growth hormone or growth releasing factor or aspirin as additional therapies. Thus the clinician's special interest in GnRH antagonist due to the need of rapid control of LH surge and to escape the complex though GnRH agonist was already established as the treatment protocol in IVF. Hence, new GnRH antagonist types were introduced by Antide and Nal-Glu [56, 57].

Treatment protocol of GnRH antagonist in poor responders

The use of GnRH antagonist is to save LH surge in Assisted Reproductive Technologies and is a new approach for more "familiar IVF" [58]. It is safe, cost effective and simple treatment protocol in controlled ovarian hyper-stimulation. It has also improved the quality of care for assisted reproduction and more importantly for the oocyte donors reducing the unnecessary treatment risks [49]. It also decreases estrogen level, short duration of treatment, lower gonadotropin requirement and reduces the incidence of severe OHSS [51]. One of the studies conducted in 2005 favored that the antagonist protocol significantly produces more numbers of oocytes ($p=0.022$) in poor responders who were already treated with the GnRH long protocol [59]. Another similar article published in 2012 advised antagonist is more effective compared to agonist long protocol in terms of OHSS prevention. Programming the GnRH antagonist cycles remains to be still challenged in adding pre-treatment with oral contraceptives in a condition like (COCS), which is aimed to achieve better coordinated response for the scheduled cycle. These are associated with significant low ongoing pregnancy rate, longer duration of stimulation and a higher dose of gonadotropin needed. It suppresses the premature LH-surge during ovarian stimulation unlike GnRH agonist, which causes instant and fast suppression of gonadotropin production [60]. The antagonist is given between 5-7 days of stimulation to lower the possibilities of the premature rise in LH surge. This escape the initial gonadotropin flare and following pituitary down-regulation associated with GnRH agonist [35]. Ovarian stimulation can be included in a spontaneous menstrual cycle which contributes to patient comfort. The GnRH antagonist protocol by using estrogen, OCP or pretreatment in the luteal phase prior to ovarian stimulation suggest a simple way gain endogenous gonadotropin suppression and succeeding synchronization during early follicular phase [61-63]. Due to unexpected induction of luteolysis, late luteal GnRH antagonist pretreatment was called "CRASH protocol".

Cetrorelix 3mg was administered as a single dose for 3-5 days before the expected onset of menses [64]. This administration succeeded to result in a prominent reduction in circulating gonadotropin levels during first few days partly showing a rise in endogenous FSH before the exogenous FSH administration [65]. A study conducted says using a low dose of 0.25mg GnRH antagonist, gives more reduction in endogenous FSH levels which later decided to administer GnRH antagonist daily for five consecutive days. For the ovarian stimulation, using prolong fix regimen has three benefits. First after three days of the treatment cycle, patients didn't have menstruation cycles, secondly administration during the early follicular phase, there was fast and reversible suppression of FSH, which contributes the improvement of follicular development [66]. Therefore, improvement of GnRH antagonist in early follicular phase might also ensure complete lute lysis and may have additional benefits on a more similar follicular development. Finally, the use of a fixed dosage also allowed us to adjust the treatment plan, long before controlled ovarian stimulation, which is easier and more patient friendly [64].

In 1991, published paper have shown some experiences by using Nal-Glu in healthy volunteers, the arrest of follicular growth were achieved after four days in late follicular phase, the level of estradiol was low and also the suppression of LH levels and after this observation, multiple doses of antagonist protocol was used frequently [67]. New IVF cycles with ET no OHSS was found after GnRH antagonist administration and the risk was only 5% when analyzed with agonist group [68]. For the future use, we can use as a tool towards eradication

of OHSS by Freezing and preserving oocytes. This reflects the new hope to future IVF [69]. There are two factors, which create the major treatment concern in IVF; the duration of treatment and side effect. It is an important factor for clinical effectiveness of IVF procedures, which gives importance to patients concern who are likely to prefer shorter cycles with minimum drug exposure [70]. For long agonist protocol, it generally takes 3 weeks duration of treatment per cycle, whereas antagonist protocol treatment per cycle takes only a few days of administration [28].

Conclusion

As discussed above, GnRH and its analogues play a key role for the poor ovarian responders in IVF treatment. Overall for poor responder's stimulation in IVF are in favor of using GnRH agonist as long protocol because it is more effective comparing to GnRH antagonist according to the oocytes number retrieved and pregnancy rates achieved. But after all criticism, the use of GnRH antagonist administration has also proved and appreciated as an additional support to ovarian stimulation because of low risk of OHSS, short duration of administration and decrease hospital stay. The above review proves that using GnRH antagonist against agonist have more advantages like low hypoestrogenism, shorter treatment duration, low gonadotropin requirement and reduces the incidence rate of severe ovarian hyperstimulation syndrome (OHSS). However, we need a large number of randomized controlled trials of sufficient evidence to conclude significant differences in pregnancy rates, which require ideal comparative study between GnRH agonist and GnRH antagonist for IVF treatment protocols.

Conflict of interest

All contributing authors declare that they have no conflict of interest.

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