

Strategies for Pituitary Down-regulation to Optimize IVF/ICSI Outcome in Poor Ovarian Responders

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Abstract

The ovarian stimulation of poor responders still remains a challenging task for clinicians. There are numerous strategies that have been suggested to improve the outcome in poor responders but there is still no one pituitary down-regulation protocol that best suits all women with such condition. Traditional GnRH agonist flare and long luteal phase protocols do not appear to be advantageous. Reduction of GnRH agonist doses, "stop" protocols, and microdose GnRH agonist flare regimes all appear to improve outcomes, although the proportional benefit of one approach over another has not been convincingly established. GnRH antagonists improve outcomes in this patient population, although, in general, pregnancy rates appear to be lower in comparison to microdose GnRH agonist flare regimes.

Keywords: ICSI, IVF, Poor ovarian responders.

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Introduction

Despite improvements in stimulation protocols in IVF program, the stimulation of poor responders still remains a challenging task for clinicians. There are numerous strategies that have been suggested to improve the outcome in women with the poor ovarian responses (Table 1).

GnRH agonist protocols

1. Short and ultra-short flare-up regimens

The flare-up regimens involve early follicular phase beginning of the GnRH agonist, with minimal delay before the onset of gonadotrophin administration (1, 2). In this protocol, the ovarian suppression is not excessive, therefore, better response to gonadotrophin stimulation could be achieved. The initial stimulation of GnRH receptors by the secretion of endogenous gonadotrophins enhances the effects of the exogenously administered gonadotrophins. These regimens would be appropriate to patients with low ovarian response. To our knowledge, there seems to be no decent prospective randomized controlled trials of flare-up protocols to assess their value compared

with standard protocols (3, 4).

Standard-dose flare-up regimens: By standard-

Table 1. Strategies for optimizing the outcome of IVF/ICSI in poor responders

Flare-up GnRH agonist regimens
Standard-dose flare-up regimens
Reduced-dose GnRH agonist flare-up regimens
GnRH agonist stop regimens
GnRH antagonists
High doses of gonadotrophins
Use of recombinant FSH
Recombinant LH administration
Luteal initiation of FSH
Estradiol in the luteal phase
Addition of letrozole to the protocol
Addition of growth hormone to the protocol
Modified natural protocol
Addition of androgen to the protocol

dose flare up protocol we mean use of a standard dose of GnRH on the first 3 days of the cycle. In a prospective study with historical controls using an ultra short protocol, pregnancy rate was 42.9% (1). Another non-controlled prospective study on 53 poor-responders showed low cancellation and good pregnancy rates despite the low number of retrieved oocytes (5). Toth et al. compared the flare-up versus the long GnRH agonist regimen, and observed higher pregnancy and lower cancellation rates with the flare-up protocol (6).

On the other hand, other researchers have failed to show any considerable value for using a classic flare-up protocol. In a historically controlled prospective study on poor responders treated with classic flstu-up GnRH agonist regimen Karande et al. found an increased number of retrieved oocytes but with high cancellation and low pregnancy rates (7).

Small dose flare-up regimens: This protocol is also known as 'mini' or 'micro' dose regimen. This protocol involves utilization of oral contraceptive (OC) priming followed by diluted doses of GnRH agonists, e.g. leuprolide acetate (LA) 40 µg, given twice daily. Two days later, stimulation is initiated by adding high doses of gonadotropins. Enhanced outcome was observed in a prospective controlled trial by Surrey et al. The patients had no pregnancies in previous IVF attempts with the long luteal regimen (8). Notable results using the same microdose protocol were also reported by Schoolcraft et al. on poor responders who were pretreated for 21 days with a combined oral contraceptive (COC); on day 3 post COC, each patient received leuprolide (40 µg twice daily) and growth hormone (GH, 4 IU/day intramuscularly) followed on day 5 post-COC by a high dose of gonadotropins (450 IU purified FSH) (9). Another retrospective study compared a microdose flare-up regimen with a long luteal protocol with decreasing doses of GnRH agonist, and observed higher cancellation rates, lower clinical pregnancies and decreased numbers of oocytes retrieved per cycle with the microdose flare-up regimen (10). Scott and Navot, used lower doses of leuprolide (ie. 20 µg b.i.d.) from cycle day 3, followed by high doses of FSH from cycle day 5, and reported a good number of retrieved oocytes (11).

The results derived from the use of reduced-dose GnRH agonist flare-up regimens are divisive. In a systematic review based on the results of a single study comparing short GnRH protocol versus long

GnRH agonist protocol, Kyrou et al. found that the probability of clinical pregnancy did not seem to be reliant on the type of GnRH agonist protocol used (12).

Modified flare-up protocol: Weissman et al. suggested high doses of triptorelin (500 µg/day) for the first 4 days, followed by reduced dose of the medication (to 100 µg/day) together with the administration of hMG. They compared this regimen with the standard agonist dose. Clinical pregnancy rate was higher in the long GnRH protocol compared with the modified short protocol, but the difference was not statistically significant (13).

2. GnRH agonist stop regimens

These regimens are characterized by the use of relatively low doses of GnRH agonists starting in the mid-luteal phase of the cycle and usually ending at the time of menses or soon afterward, in combination with high doses of gonadotropins. Reduced effects of GnRH agonists on ovarian receptors may result in reduced ovarian suppression and consequently, increased ovarian response. It is claimed that the occurrence of untimely LH surge is still low (14, 15).

The results are rather contradictory; two prospective randomized controlled trials for the 'stop' versus 'non-stop' GnRH agonist protocols showed no statistically significant increase in pregnancy rates, (16, 17). Conversely, different prospective trials using different drugs demonstrated better outcomes. Faber et al. and Pu-Tsui et al. used 'stop-Lupron protocol', in which a low-dose mid-luteal GnRH agonist (leuprolide 0.5 mg, subcutaneously) was administered but later discontinued with the onset of menses (18, 19). Schachter et al. used nafarelin (0.6 mg/day), started in the mid-luteal phase and discontinued on day 5 of ovarian stimulation (20). Pinkas et al. used the same GnRH agonist with the same dosage but discontinued it on day 1 of the next cycle (21). In a meta-analysis using two randomized controlled trials done by Dirnfeld et al. and Garcia-Velasco et al. which compared the effect of the "stop" versus "non-stop" long GnRH protocol in poor responders, Kyrou et al. found no improvement in pregnancy rates with the stop agonist protocol (12, 16, 17).

3. GnRH agonist step-down regimen

Olivennes et al. used leuprolide (0.1 mg/day, s.c.) from day 21 and reduced it (to 0.05 mg/day) on stimulation. However, the cancellation rate remained high and the pregnancy rate was relatively low (22). Another study of 106 cycles in the same

step-down fashion (from 0.1 to 0.05 mg/day) showed higher number of oocytes and improved pregnancy rates (23).

4. Single dose depot GnRH agonist

Administration of a single dose depot of GnRH agonist preparation (leuprolide 3.75 mg) on day 21 of a pre-stimulated cycle was assessed in a Cochrane review. The authors observed no evidence for differences between the long protocols using depot or daily GnRH agonist for IVF cycles. Nonetheless, the use of depot GnRH agonist is associated with increased requirements for gonadotrophins and a longer time for ovarian stimulation. If these differences could be shown to decode into economic benefit, depot GnRH agonist would increase the overall costs of IVF treatment which is not in favor of this protocol (24).

GnRH antagonist protocols: Gonadotropin-releasing hormone antagonists result in internalization and subcellular translocation of the GnRH receptor to the cell nucleus, and down-regulation of messenger ribonucleic acid (mRNA) expression for the GnRH receptor leading to immediate and rapid suppression of gonadotrophin production (25, 26). Gonadotropin-releasing hormone antagonists are typically initiated either in a flexible protocol when the lead follicle is 14 mm in mean diameter, or in a fixed protocol on stimulation days 5–6. The treatment cycle is significantly shorter with GnRH antagonist than with GnRH agonist treatment (27). GnRH antagonists are associated with simpler stimulation protocols, lower gonadotropin requirements, reduced costs, and shorter intervals between successive cycles. There is always the possibility of assessing ovarian reserves immediately prior to deciding whether or not to initiate gonadotropin stimulation for poor responders (28).

Craft et al. reported stimulation of poor responders by a combination of gonadotropins, clomiphene citrate, and multiple flexible GnRH antagonists (29). There had been modest improvements in cycle cancellation rates and oocyte yield with the GnRH antagonists. Another retrospective analysis of poor responders treated with GnRH antagonists showed lower gonadotropin consumption and shorter stimulation durations in antagonist cycles, compared to previous cycles using a GnRH agonist (30). A prospective randomized study by Akman et al. reported that the use of GnRH antagonists, together with high doses of gonadotrophins in previous poor responders, was associated with lower cancellation and increased

pregnancy rates, as compared with gonadotrophins alone. These differences were not statistically significant and no change was observed in the number of retrieved oocytes (31).

Meta-analyses of studies comparing agonist and antagonist protocols by Sunkara et al. (2007) did not show a consistent benefit for any particular pituitary suppression regimen over other protocols in improving outcome measures. Currently available evidence does not favour any particular pituitary suppression regimen for women with poor ovarian response undergoing IVF/ICSI treatment (32).

GnRH antagonist or short GnRH agonist protocol?

Several trials compared multiple GnRH antagonist protocols with the flare-up GnRH agonist protocol in poor responders. These trials reported significantly higher mean number of mature oocytes retrieved and higher implantation rate with flare-up GnRH agonist protocol when compared to antagonist protocols (33–35).

Martinez et al., Schmidt et al. and Kahraman et al. noticed no significant differences as regards with any outcome parameters (36–38). These results were confirmed by Devesa et al. in a prospective study and by Berin et al. in a retrospective one. They showed that the flare-up agonist and antagonist protocols were comparable regarding clinical pregnancy rates in poor responders (39, 40).

On the contrary, Lainas et al. concluded that the flexible multiple GnRH antagonist protocol is associated with significantly higher ongoing pregnancy rates compared with the flare-up GnRH agonist protocol in poor responders (41).

GnRH antagonist or long GnRH agonist protocol?

Cheung et al. compared the GnRH antagonist fixed multiple protocol with the long GnRH-agonist protocol in poor responders and reported that in the antagonist group, the number of transferred embryos was higher and there was a tendency toward higher clinical pregnancy rates but with no statistically significant differences (42). Two randomized trials comparing the effect of a GnRH flexible multiple antagonist protocol versus a GnRH-agonist long protocol in poor responders showed reduced duration of stimulation and consumption of gonadotrophins in the flexible, multi-dose antagonist group (43–45). While Marci et al.

showed increased number of retrieved follicles and oocytes and fewer cancelled cycles in the antagonist group, Sun and Zhu reported lower number of retrieved oocytes in the antagonist group (43, 44). On the other hand, Tehraninejad et al. showed that the duration of stimulation, consumption of gonadotrophins, and number of retrieved follicles and oocytes were similar in both agonist and antagonist groups. However, in the above mentioned trials pregnancy rates were similar in both the agonist and antagonist groups (46).

In a meta-analysis using GnRH-antagonist for ovarian stimulation in poor responders, no differences in clinical outcomes were found, except a significantly higher number of cumulus-oocyte complexes in the GnRH-antagonist multiple dose protocol as compared to GnRH-a long protocol (47). Another meta-analysis did not prove any difference between the two regimens with respect to cycle cancellation rate, number of mature oocytes or clinical pregnancy rate (48). Based on all the above results no firm conclusion could be obtained but better results were demonstrated with the use of GnRH antagonists.

Combined GnRH antagonist/ GnRH agonist

Orvieto et al. used the ultrashort GnRH_a regimen combined with a flexible multidose GnRH antagonist protocol in patients with previous failed IVF attempts. The results demonstrated a statistically significant higher number of retrieved oocytes and embryos transferred with a reasonable clinical pregnancy rate (14.3%) (49).

GnRH antagonist in the luteal phase

In an attempt to lengthen the follicular phase, GnRH antagonist was given in the luteal phase of the cycle preceding the ovarian stimulation (3 mg cetrorelix) followed by stimulation with rFSH starting on cycle day 2, followed by a flexible GnRH-antagonist protocol (CRASH protocol). The results were compared to the preceding long protocol. There were more follicles, more oocytes and embryos with the prior administration of the antagonist. Moreover, the implantation and pregnancy rates were increased approaching the clinical outcome of normal responder patients (50). Nilsson et al. used GnRH antagonist (ganirelix) daily, from days 3 to 5 before the expected onset of menstruation and continued for 4–7 days. At a leading follicle diameter of 14 mm, ganirelix administration was resumed until the final oocyte maturation was induced by 10,000 IU hCG.

GnRH antagonist only marginally affected the intercycle FSH rise; basal levels of FSH remained similar to those seen after 4 days of antagonist administration. The protocol effectively induced low LH levels and luteolysis, but it only led to the collection of 3 oocytes in 49 oocyte retrievals resulting in 5 pregnancies (4 delivered). Despite GnRH antagonist administration in the late luteal phase and menstrual bleeding, FSH was not sufficiently reduced to secure a more synchronic cohort of recruitable follicles (51).

Conclusion

There is no one pituitary downregulation protocol which is best suited for all poor responders. Traditional GnRH agonist flare and long luteal phase protocols do not appear to be advantageous. Reduction of GnRH agonist doses, "stop" protocols, and microdose GnRH agonist flare regimens all appear to improve outcomes, although the proportional benefit of one approach over another has not been convincingly established. GnRH antagonists improve outcome in poor responders, although, in general, pregnancy rates appear to be lower in comparison with microdose GnRH agonist flare regimens. Prediction of decreased response by a thorough assessment of ovarian reserve prior to cycle initiation allows selection of an appropriate COH protocol tailored for each individual patient.

Conflict of Interest

Authors declare no conflict of interest.

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