Ovulation Induction for Poor Responder in IVF program

Sang-Hoon Lee

Depart. of Obstetrics & Gynecology Chung Ang University College of Medicine

I. Introduction

Women who respond poorly to controlled ovarian hyperstimulation (COH) regimens have a diminished chance for conception in cycles of assisted reproductive technologies (ARTs). Poor responders comprise 9~30% of patients going through ART cycles. Although most fertility specialists "know a poor responder when we see one," there are actually no well-accepted objective parameters which define the poor responder. Poor response to ovarian stimulation is one of the important factors for repeated failure to achieve pregngncy in consecutive IVF cycles. Those patients undergoing IVF whose E2 on the day of HCG was $\leq$1000 pg and oocyte recovered in that cycle were $\leq$4 were considered as poor responders. Advancing age, poor embryo quality and decreasing endometrial receptivity appear to be the main factors for a poor response and failure to achieve pregnancy. Everyone involved in assisted reproduction has been surprised by the young patient who unexpectedly produced few eggs as well as by women in their forties who produce many eggs. While this variability in ovarian responsiveness to stimulation has been clear from the beginning, given the costs involved, accurate markers of this variability of ovarian reserve have been sought.

The review will present current methods of evaluation ovarian reserve as a means to identify the low responder, and describe their limitations and uses. Such information is important for women of all ages as a means to realistically asscess their chances for successful pregngncy in assisted reproduction. Accordingly, women in their forties with significant ovarian reserve can be identified and encouraged to proceed with their family building, while those with limited ovarian reserve could be counseled to consider other options.

It is important to remind readers that the values of FSH and estradiol reported to be clinically useful in the following material are assay- and institution-specific. Do not presume that an FSH value of 25 IU/L will be the appropriate cutoff in your setting until the assays have been compared.

Despite the lack of a consensus regarding the definition of a poor responser, multiple therapeutic regimens have been proposed in an attemt to improve these patient's response to COH.

1. High dose Menotropin protocol
2. Long term GnRH agonist suppression and gonadotropin protocol
3 Flare-up protocol
4. Cotreatment with growth hormone
5. Combined naltrexone and clomiphene citrate protocol
6. Pulsatile intravenous gonadotropin protocol

7. Combination low-dose GnRHa and high-dose menotropin protocol

II. Evaluation of the ovarian reservoir

1. Serum basal FSH level

Subtle FSH elevations signal declining ovarian reserve despite regular menses. Flood et al. and Cameron et al. among others, have reported that such unexpected elevations of FSH associated with unexplained infertility.

Though FSH was superior as a single predictor than age, taking account of basal FSH does not eliminate the need to consider age effects. Both FSH and age (and probably E2) need to be considered simultaneously for optimal prediction of ovarian reserve. There is a gradual decline in IVF performance with increasing age even at the same levels of FSH. For instance, women with FSH between 10 and 15 IU/L have a 47% chance of pregnancy if they are <30 years old but only a 21% chance if 40 or older.

2. Serum basal E2 and LH level

LH and E2 on cycle day 3 also show a relationship with IVF performance, but in a less clear cut fashion. Basal LH levels above 25 IU/L are often associated with PCO-type response in which many eggs of poor quality are produced. Basal E2 levels above 50 pg/ml are also associated with poor response; fewer than half as many pregnancies were observed and many of these were miscarried. This premature E2 elevation signifies early recruitment and is a common perimenopausal pattern. Note that women with high basal E2 only rarely gave a concomitant elevation of their basal FSH, since the inappropriate E2 elevation effectively supresses FSH secretion in the menopausal transition. This means that meaningul interpretation of basal FSH values requires knowing that the E2 is not elevated.

3. Serum basal FSH and E2 level

As indicated above, basal E2 elevations above 50 IU/L portend poor response to stimulation regardless of the basal FSH. However, together they improve the prediction of IVF outcome, as Licciardi et al. have recently stressed. In a study of 592 cycles at Cornell, they reported ongoing pregnancy rates per retrieval of 0% when both FSH and LH were elevated (FSH <17 IU/L, E2 <45 pg/ml), 22.8% when both were in the normal range, and intermediate when only one of the two was elevated (FSH alone = 16.7%; E2 alone = 17.4%). No pregnancies were observed when the FSH exceeded 26 IU/L or the E2 75 pg/mL.

4. Clomiphene citrate challenge test (CCCT)

Ovarian responsiveness to controlled ovarian hyperstimulation (COH) plays a major role in IVF-ET results. Indeed, a suboptial IVF-ET outcome is obsered in caes of poor ovarian response to COH, likely due to a decreased oocyte/embryo quality. Moreover, poor responses to COH could represent an indirect sign of ovarian aging and early evidence of a reduction in the women's fertility potential. Hence, to avoid inadequate prescription of COH to women whose ovarian responsiveness to stimulation is definitely hindered, some approaches aiming to predict

the performance of the ovaries under COH mave been proposed.

Plasma FSH measurement on cycle-day 3, has been routinely used to screen ovarian responsiveness to COH by a number of IVF-ET centers. Correlation of this test with COH results are, however, often disappointing. In fact, FSH levels during the early follicular phase can show marked intercycle fluctuations. To overcome this contingency of basal FSH measurements, some "dynamic" approaches for the evaluation of the ovarian reserve have been proposed, as the clomiphene citrate challenge test (CCCT) and the GnRHa stimulation test.

5. GnRH agonist stimulation test (GAST)

More recently, another approach based on the E2 response to the endogenous flare-up of gonadotropins induced by the administation of a GnRHa was proposed by Padilla etal. (Lrpron test). This test aims at evaluation the increase in plasma E2 levels after the administration of a GnRH agonist (leuprolide acetate, 1 mg s.c.) on days 2, 3 and 4 of the menstrual cycle.

The authors have found a good correlation between the E2 response and the ovarian response to COH: four distinct patterns of serum E2 response to the leuprolide acetate were identified, a lack of response of a sustained rise in peripheral E2 levels prognosticates a diminished pregnancy rate, whereas E2 levels elevation followed by a drop on the 3rd day of GnRHa therapy bodis well.

III. Suggested Treatment Modalities

1. High-Dose Menotropin protocol

The "if a little is good, more must be better" approach was first examined by Steptoe and Edwards in 1970. They evaluated laparoscopic oocyte retrieval rates in women stimulated with different doses of human menopausal gonadotropin (hMG) and found no significant differences. Laufer et al subsequently noted a higher oocyte retrieval rate when they increased the initial hMG dose from 150 IU per day to 225 IU per day. Benadiva et al retrospectively evaluated six poor responders (women with peak E2 levels <1000 pg/ml) who initially underwent COH for in vitro fertilzation (IVF) with 150 IU hMG daily for 5～7 days.

All six patients failed to conceive, and subsequently underwent another IVF cycle during which COH was achieved with 225 IU hMG daily for 5～7 days. These investigators were unable to detect any improvement in response, in terms of either peak E2 levels or the number of oocytes recoveed by increasing the hMG dosage.

The investigators concluded that it may be deffective to increase the hMG dose in patient who respond poorly during an initial CC/hMG. Pantos et al performed a similar trial in 271 patients receiving CC and hMG. In their retrospective evaluation, they increased the hMG dose from 150 to 225 IU for women who produced fewer than five oocytes in their previous IVF cycle, in an attempt to inerease oocyte yield. Although interpretation of their results is complicated, as only 45% of the patients in the study actually received a higher dose of hMG, there did not appear to be any measurable improvement resulting from the higher gonadotropin dosage.

There is only one report in the literature evaluating the effect of increasing the dose of pure FSH in poor responders. Hofmann et al prospectively evaluated 23 women who had previously

demonstrated a poor response to 300 IU FSH in an IVF cycle.

To date, only one study has examined the effect of inereasing the gonadotropin dosage in women who are also receiving a GnRHa. Jenkins, et al retrospectively observed that 61 poor responders developed higher peak E2 levels when they received 450～600 IU hMG daily, as compared to levels they produced when stimulated with 300 IU daily. No comparison ws made with regard to oocyte yield, fertilization rates or pregnancy rates. In addition, when compared to 250 matched "good responders," the poor responders receiving high dose hMG still produced significantly fewer oocytes, and had significantly lower fertilization and pregnancy rates.

2. Long term GnRH agonist suppression and gonadotropin protocol

Use of the long protocol for poor responders was predicated on the assumption that ovarian stimulation prior to the selection and dominance of a leading follicle could encourage development of secondary follicles. With the notable exception of women with an elevated level of follicle-stimulation hormone (FSH), this does appear to be the case, since poor responders appear to produce about twice as many follicles, and the number of oocytes retrieved is routinely greater than with gonadotropins given alone. Since endogenous gonadotropins are suppressed, but the average daily requirement for gonadotopins is not increased, the ovary does indeed appear to be more sensitive. Since androgens are implicated in atresia of secondary follicles, the suppression of bioactive LH and testosterone during stimulation may explain this improved response. The apparent increased incidence of ovarian hyperstimulation with combination theray is also consistent with inceresed ovarian sensitivity to gonadotropins.

3 Flare-up protocol

No consensus is available in the literature about the definition of poor responders. Moreover, patients who have presented E2 levels <1000 pg/ml at the end of COH with a daily dose of exogenous gonadotropins of at least 300 IU, whose total amount of exogenous gonadotropins execcded 60, and who have produced <5 oocytes may be included in this group of patients.

Based on the theoretical benefits of the gonadotropin flare effect on the improvement of the follicular recruitment, short GnRHa protocols have been proposed for the treatment of poor responders. Katayama et al. have reported encouraging results using GnRHa/hFSH/hMG in short association for COH in seven patients who had not previously developed a follicle larger than 15 min or a peak E2 level >300 pg/ml in response to hFSH or hMG alone. Further publications, however, failed to confirm these preliminary results.

4. Cotreatment with growth hormone (GH)

The summary of the clinical trials described here provides a clearer idea of which patients may benefit from cotreatment with GH and hMG. In general, patients suffering from a blatant or more sutbtle disturbance of GH kinetics causing a dysfunction of the putative GH/IGF-I intraovrian regulatory system are a small but select group who may benefit. This distrubance may have been induced by surgical (e.g., hypophysectomy), pathological (e.g., idiopathic hypothalamic hypogonadism) or medical (e.g., the use of GnRHa) reasons. Thus, clear evidence of an adjuvant effect of GH in increasing ovarian response to gonadotropins has been obtained in women with

hypopituitarism. The positive effect of GH in these series may be regarded as successful substitution theraphy for GH insufficiency.

Poor responders to conventional GnRHa/hMG therpy for IVF have been reported to gave a mixed response to additive GH therapy. While some have shown a significant improvement in ovarian sensitivity and number of oocytes collected, fertization rates pregnancy rates or a selective improvement in women with polycystic ovaries, others have shown on effect. Without the use of GnRHa, younger poor responders gave accelerated ovarian response with additive GH but in older patients and in a further controlled series no significant effect was noted. Older patients, those with incipient ovarian failure or normal responders have shown no improvement.

It was perhaps over optimistic to expect that additive GH to hMG in normal responders would improve ovarian responsiveness to gonadotropins. These patients have a balanced pituitary-ovarian axis with normal GH kinetics. Follicular development is already maximal in patients with a normal response to hMG and the system is already saturated.

However, in poor responders for whom GnRHa was employed, a relative GH deficiency may have been created, thus explaining the benefit achieved in a number of these patients from GH cotreatment. In addition to the induced hypoestrogenic state, despite the fact that GnRHa does not affect IGF-I or GH peripheral circulation levels, the pituitary GH response to GHRH is reduced. In addition, GnRHa has been shown to redue the number of IGF-I receptors induced by FSH in granulosa cells.

5. Combined naltrexone and clomiphene citrate protocol

Ovulation can be induced successfully using naltrexone alone or naltrexone in combination with an anti-estrogen in clomiphene citrate resistant anovulatory patients. Compared to gonadotrophin induction of ovulation, this method is safe, simple and inexpensive.

Naltrexone (Nalorex; Dupont, Nemours, France) was administered orally in a dose of 25 mg twice daily. If the patient did not respond to naltrexone alone, 100 mg of clomiphene citrate for 5 days was added to the contimuous naltrexone therapy. Naltrexone was discontinued in the case of a positive pregnancy test or when patients had on follicular growth after 21 days of combined naltrexone and colmiphene citrate treatment. The dramatic effects of the opiate antagonist naltrexone on gonadotrophin secretion in hypothalamic ovarian failure and on insulin resistance and hyperandrogenism, suggesting a critical role of endogenous opioids in the pathogenesis of both disorders.

6. Pulsatile intravenous gonadotropin protocol

In the natural follicular phase, GnRH is released in a pulsatile fashion every 90~120 minutes. Hoping to mimic this phenomenon, Ho Yuen, et al evaluated the use of pulsatile intravenous gonadotropins in 107 cycles in 30 women previously unresponsive to CC and/or hMG. While the pulse frequency was kept constant, the pulse dosage was adjusted based on serial serum E2 levels and transvaginal ultrasonography. The mean daily hMG dose was 113 IU, and the mean duration of infusion was 8.7 days. Overall, 88% of all cycles resulted in ovulation, with a cycle fecundity of 14%. A similar regimen, using pure FSH, was evaluated in eight poor responders undergoing IVF. Edelstein, et al did not observe any improvement in peak E2 levels, oocyte re-

covery or fertilization rates or pregnancy rates in patients treated with pulsatile FSH.

7. Combination low-dose GnRHa and high-dose menotropin protocol

Kaylen M. suggested that it may be possible to combine some of the aforementioned protocols in the hope of improving stimulation regimens for poor responders.

IV. Conclusion

Responses of infertile patients are unpredictable. Old, not so old and sometimes young patients show poor response.

As with many other topics in infertility there is no clear cut answer to the question - How do we best stimulate the poor responder? The literature is, unfortunately, relete with small, uncontrolled series - many combining different therapeutic regimens in populations combining poor, normal, and high responders. Small studies which support to show no difference between different therapeutic regimens do not include power calculations or address the issue of beta error. It may, therefore, be inappropriate to assume that just because a majority of the studies that address one particular issue reach a similar conclusion, that they are statistically correct. When interpreting this literature, one must pay careful attention to study design, patient selection, and statistical analysis.

Offering a variety of treatment protocols and remembering that there is a time to call it a day, will help many patients to achieve pregnancy and spare them from heavy financial committments and psychological stress. " Reproductive life span is today long and so is the art."

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