

Strategies for Poor Responders in IVF Cycles

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Abstract

The desired objective of controlled ovarian stimulation (COS) is to allow the growth of a cohort of follicles and to facilitate the recovery of a large number of fertilizable oocytes. However, poor responders with low ovarian reserve often fail to respond adequately despite the maximal dose of gonadotropins administered, with the results that the number as well as quality of oocytes harvested may be very low. These results lead to a significant decrease of pregnancy rate in IVF cycles. Therefore, successful COS for poor responders continues to be a major challenge in IVF program. In this review, I will describe strategies for improvement of ovarian response to COS in poor responders. The strategies described may provide a means of augmenting follicular recruitment by endocrinological manipulation for poor responders undergoing IVF.

Keywords: Controlled ovarian stimulation; Poor responders; IVF; Endocrinological manipulation

The management for poor responders with diminished ovarian reserve is still a challenge, although many studies have been performed to seek for a method of efficient ovarian stimulation for infertile women with reduced ovarian reserve. A variety of stimulation regimes have been employed for the management of poor responders. It is generally believed that the starting dose of gonadotropins should be primarily increased for women with low ovarian reserve. Nevertheless, this strategy is often of limited effectiveness and moreover, clinical improvement obtained with doses more than 450 IU/day is very rare. The most prevalent protocols for treating poor responders at present are GnRH agonist (GnRH-a) low-dose long protocol (LP), GnRH-a luteal LP (stop protocol), GnRH-a flare-up protocols, GnRH-a micro-dose flare protocol and GnRH antagonist protocol [1-6]. GnRH antagonist protocols have recently received increasing attention, as the use of GnRH antagonists is associated with several advantages, including shorter duration of stimulation and reduced gonadotropin consumption [7]. Our recent study showed that GnRH antagonist multiple-dose protocol (MDP) with oral contraceptive pill (OCP) pretreatment is at least as effective as GnRH-a low-dose LP in poor responders and can be advantageous to poor responders because of the shortened time required for follicular maturation and the diminished amount of recombinant human FSH (rhFSH) required to provide adequate ovarian stimulation [8]. Recently, the combination protocol of the micro-dose GnRH-a flare protocol and a GnRH antagonist protocol was proposed as a valuable new tool for poor responders [9], and another protocol using GnRH-a/antagonist conversion with estrogen priming (AA CEP) was also proposed for poor responders [10].

Unfortunately, neither of these protocols has been especially effective in improving ovarian response in poor responders. Therefore, hormonal manipulations to augment a follicular recruitment and coordinate subsequent antral follicle growth during ovarian stimulation have been performed. Hormonal manipulations include concomitant growth hormone (GH) or pyridostigmine administration, LH supplementation, luteal estradiol pretreatment, LH pretreatment, DHEA supplementation, testosterone (T) pretreatment, and aromatase inhibitor co-treatment.

The use of human GH in panhypopituitary patient was reported in 1989 [11], and there has been much controversy about its use in poor responders. In 2009, a meta-analysis of data from 6 randomized controlled trials (RCTs) in which GH addition and controls were compared was reported. This meta-analysis by Kolibianakis et al

demonstrated that clinical pregnancy rate and live birth rate were significantly higher in patients treated with GH [12]. In 2010, meta-analysis in Cochrane review demonstrated a statistically significant difference favouring the use of GH adjuvant in poor responders undergoing IVF, when compared with placebo group [13]. However, in women who are not considered poor responders, there was no evidence to support the use of GH [13]. Further studies should be directed at defining the dose of human GH, and determining if selected populations may benefit from human GH co-treatment.

Considering the extra cost and limited data of GH addition, stimulation of endogenous GH secretion may be more cost-effective if pts have adequate endogenous GH reserve. Therefore, in poor responders with positive result of clonidine test, endogenous GH secretion can be stimulated by augmentation of central cholinergic pathway. Administration of acetylcholinesterase inhibitor, pyridostigmine increases acetylcholine levels, and thereby inhibiting somatostatin production in hypothalamus. Reduced somatostatin levels result in the increase of GH production and secretion from the anterior pituitary. Therefore, we performed RCT to investigate the effect of an acetylcholinesterase inhibitor, pyridostigmine cotreatment during COS in poor responders [14]. COS was performed using GnRH agonist LP in all subjects. For the study group, pyridostigmine was administered 60 mg twice a day from the 1st day of stimulation up to the day of HCG injection. Total ampules and days of gonadotropin used were significantly fewer in the pyridostigmine group than in the control group. Serum estradiol levels and number of follicles more than 14mm in diameter were significantly higher in the pyridostigmine group. Numbers of oocytes retrieved and oocytes fertilized were also significantly higher in the pyridostigmine group. Intrafollicular GH and IGF-1 levels were significantly higher in the pyridostigmine group [14]. Therefore, pyridostigmine cotreatment during COS in poor responders

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with adequate GH reserve may be a cost-effective alternative to GH cotreatment.

Several investigators demonstrated that androgen promotes initiation of primordial follicle growth and increases the number of growing preantral and small antral follicles in the primate ovary [15,16]. These results suggest that androgen has a folliculotropic action. Therefore, in women with diminished ovarian reserve who undergo assisted reproductive technology treatment, boosting intraovarian androgens might increase the number of follicles available to enter the recruitment stage as well as the process of follicle recruitment itself [17]. Barad and Gleicher treated poor responders with DHEA at a dose of 25 mg three times a day for 4 to 48 weeks before COS and observed an increase in the number of oocytes and good quality embryos in the DHEA-treated group [18]. The beneficial effect of androgen treatment on the ovarian response was also observed by Fabregues et al. [19]. In their randomized trial, transdermal T patch used for 5 days before gonadotropin treatment decreased the percentage of cycles with low response in low responders undergoing IVF. Recently, we performed RCT to investigate the effectiveness of treatment with transdermal T gel (TTG) before COS using GnRH antagonist MDP in poor responders undergoing IVF/intracytoplasmic sperm injection (ICSI) [20]. For TTG pretreatment group, TTG at a dose of 12.5 mg/d for a 1.25 mg/d delivery rate of testosterone was applied daily for 21 days in the cycle preceding COS for IVF/ICSI. The percutaneous absorption of testosterone ranges from ~9% to ~12% of the applied dose. Following percutaneous absorption, testosterone diffuses into the systemic circulation at relatively constant concentrations during the 24-hour cycle, and this transdermal delivery system maintains stable serum T levels within narrow ranges with little intra- and intersubject variation. In our RCT, total dose and days of gonadotropin used were significantly fewer in the TTG pretreatment group than in the control group. The numbers of oocytes retrieved, mature oocytes, fertilized oocytes, and good-quality embryos were significantly higher in the TTG pretreatment group. Embryo implantation rate and clinical pregnancy rate per cycle initiated also were significantly higher in the women pretreated with TTG [20]. Therefore, we concluded that TTG pretreatment improves the ovarian response to COS and the clinical pregnancy rate with fewer doses and days of rhFSH used, and thus it can be a cost-effective and patient-friendly treatment option to maximize the ovarian potential of low responders undergoing IVF/ICSI. So far, there are very limited data on androgen pretreatment for poor responders, and therefore larger studies with standardized methods will be needed.

Aromatase inhibitors were initially approved to suppress oestrogen levels in postmenopausal women with breast cancer. They inhibit the enzyme by competitive binding to the heme of the cytochrome P450 subunit, blocking androgen conversion into estrogens so that there is a temporary accumulation of intraovarian androgens [17]. Mitwally et al showed that aromatase inhibition improves ovarian response to FSH in poor responder patients undergoing ovulation induction and IUI [21]. In 2005, Garcia-Velasco, et al. [22] treated poor responders with an aromatase inhibitor and observed significantly higher levels of follicular fluid testosterone and androstenedione in aromatase inhibitor-treated patients [22]. Also their study showed a higher number of oocytes retrieved as well as a higher implantation rate in a treatment group despite similar doses of gonadotropins. Our RCT showed comparable IVF/ICSI outcomes with shorter duration and smaller dose of rhFSH in letrozole/GnRH antagonist MDP, when compared with the standard GnRH antagonist MDP.

Whatever ovarian stimulation protocol is used in poor responders,

they mostly require a large dose of gonadotropins and also show lower-quality oocytes and poor pregnancy rates. Therefore, poor responders may benefit from IVF treatment in natural or minimal stimulation cycles. We performed prospective randomized study to investigate the effectiveness of minimal stimulation compared with GnRH antagonist MDP in poor responders [23]. For the minimal stimulation, cycle monitoring was started on cycle day 7 or 8 by transvaginal ultrasound and repeated daily or every other day, according to the size of the dominant follicle. Subcutaneous injections of 0.25 mg GnRH antagonist cetrorelix and 150 IU recombinant human FSH (rhFSH) were started concomitantly when the lead follicle reached 13–14 mm in a mean diameter and was continued daily until the day of hCG injection. When the mean diameter of the lead follicle reached 17–18 mm, 250 mg recombinant hCG (rhCG) was administered to trigger follicular maturation. Our study demonstrated that the minimal stimulation protocol provides similar pregnancy rates to GnRH antagonist MDP with a fewer dose and days of rhFSH in women of advanced age or with low ovarian reserve undergoing IVF/ICSI [23].

In addition, co-transfer of fresh and collected cryopreserved embryos (COFACCE) can be performed for poor responders [24]. Oocytes retrieved in minimal stimulation or natural cycles were inseminated and 2 pronucleate zygotes were cryopreserved and collected. When fresh oocytes were retrieved and fertilized in the next cycle after two or three cryopreserved embryos were collected, co-transfer of a fresh and two or three cryopreserved-thawed embryos was performed 2-3 days after fresh oocyte retrieval. In our retrospective analysis, 12 COFACCE cycles were performed in 12 patients. For COFACCE cycles, oocyte retrieval was successfully performed in 45 cycles out of 53 initiated cycles (84.9%) and a mean of 1.0 ± 0.5 oocytes per initiated cycle was retrieved. The mean number of initiated cycles required for one COFACCE cycle was 4.4 ± 0.7 . Total dose and days of rhFSH used per initiated cycle were 397.6 ± 138.4 IU and 2.8 ± 0.9 days. Cumulative total dose of rhFSH used per COFACCE cycle were significantly lower in COFACCE group, with 1775.0 ± 200.6 IU compared with 2812.5 ± 247.6 IU in standard GnRH antagonist MDP group ($P < 0.0001$). The mean numbers of mature eggs and grade I/II embryos per completed ET cycle were significantly higher in COFACCE group ($P < 0.0001$, $P = 0.005$, respectively). The clinical pregnancy rate was higher in COFACCE group, with 41.7% (5/12) per COFACCE cycle compared with 16.7% (2/12) per ET cycle in control group, but statistical significance was not found [24]. Therefore, COFACCE may be a cost-effective and patient-friendly alternative for poor responders and can be considered as the last chance before oocyte donation.

Although oocyte donation is a successful alternative treatment for infertile women with diminished ovarian reserve, we must devote our best efforts to use patients' own oocytes for successful pregnancy. The strategies using pharmacogenomics and endocrinological manipulation may provide a means of maximizing follicular recruitment and cytoplasmic integrity of oocytes in patients' own ovaries, and thus improve the prognosis for these patients. There is no universally accepted COS protocol for poor responders, and individualized approach is necessary to increase the cost-effectiveness.

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