The role of adjuvant therapy to optimize the outcome in poor ovarian responders undergoing IVF/ICSI

Alaa wageah, MSc
Mohamed ElGharib, MD
Ezz Din Osman, MD
Ahmed Badawy, MD FRCOG PhD
Department of Obstetrics & Gynecology,
Mansoura University

Does aspirin have a role?

The effect of adjuvant low-dose aspirin on utero-ovarian blood flow and ovarian responsiveness in poor responders undergoing IVF was evaluated and it was concluded that supplementation with low-dose aspirin failed to improve either ovarian or uterine blood flow or ovarian responsiveness in poor responders (1).

Is pretreatment with COC or progesterons worthwhile?

It was postulated that COC administration aims to suppress endogenous gonadotrophins preventing salvage of the corpus luteum from the previous cycle or a rise in progesterone with initiation of the follicular phase microdose GnRH-a and, at the same time (through its estrogen component), generate and sensitize more estrogen receptors (2) delivery and
A few RCTs have shown that COC pretreatment may be worthy for ovarian response and clinical pregnancy rates, but these data were obtained from a patient cohort which excluded poor responders (3,4). Lindheim et al. (1996) showed that COC administration prior to the GnRH protocol was associated with higher pregnancy rates and lower cancellation rates (5). However, Duvan et al. (2008), concluded that COC pretreatment plus microdose GnRH flare-up protocol does not offer advantages over non COC microdose GnRHa flare-up protocol among poor responder ICSI patients (6). Bendikson et al. (2006) in a retrospective study found that pregnancy outcome in GnRHa antagonist protocol with and without COC were comparable (7).

Adjunctive use of Growth Hormone (GH)

The hypothesis that GH stimulates ovarian steroidogenesis, follicular development and enhances the ovarian response to FSH was proposed in 1986 (8). This action of GH is believed to be mediated via the IGF-1 that acts in synergy with FSH, amplifying its effects on granulosa cells (9). These were the theoretical basis for the introduction of GH or GH-releasing factor (GHRF) in the IVF treatment of poor responders.

Initial results in small groups of poor responders were optimistic reporting higher number of oocytes collected and improved pregnancy rates (10-14). In a RCT, similar number of oocytes, embryos and pregnancies has been reported but improvement of delivery and live birth rates after ovarian co-stimulation with GH has been noticed in 50 women older than 40 years old who have undergone ICSI (15). Kucuk et al. (2008) studied the efficacy of GnRHa long protocol with and without GH co-stimulation in poor responders and found higher fertilization rate in the group co-stimulated with GH. However, the clinical pregnancy rate was not significantly increased (16).

Kotarba et al. (2002), in a Cochrane Review, conducted a meta-analysis of the trials assessing the effectiveness of GH adjuvant therapy in poor responders, and showed no significant difference in either the number of follicles and oocytes, or gonadotrophin usage (17). In another Cochrane review, a significant improvement in live birth rate in poor responders was found with GH adjuvant therapy despite no effect in normal responders has been noticed (18). Kyrou et al. (2009) in their systematic review evaluating GH addition in poor responders stimulated for IVF based on five RCTs suggested that live birth rates are improved when GH is coadministered during ovarian stimulation for IVF in poor responders (19). Recently, Venetis et al. (2010), in their metaanalysis found that addition of GH significantly increased probability of live birth and clinical pregnancy in poor responders (20).

Addition of GH-releasing factor (GHRF)

No statistically significant difference in live birth rates was observed between patients who did or did not receive GHRF (21).
Addition of pyridostigmine

Pyridostigmine is an acetyl cholinesterase inhibitor which by enhancing the action of acetylcholine can increase GH secretion. Chung-Hoon et al. (1999) used pyridostigmine (120 mg/day orally from the day of down-regulation until the day of HCG). The results showed significant higher number of oocytes collected and improved pregnancy rates despite being statistically insignificant (22).

Adjunctive use of nitric oxide (NO)-donor (L-arginine)

Increased vascularization appears to play a critical role in the selection, growth and maturation of follicles in both natural and IVF cycles. L-Arginine, acting as a NO-donor, is a potential vasodilator. In fact, NO is derived in vivo from L-arginine by a NO-synthetase enzyme (23,24). It is also thought that NO is involved in follicular maturation and selection, possibly due to its participation in periovulatory vasodilatation (25,26). Battaglia et al. (1999), in a prospective randomized study, in which two groups of poor responders were compared, each of which was treated with the GnRHs flare-up regimen and only one group orally administered L-arginine (27). Higher numbers of collected oocytes and higher pregnancy rate were found in the L-arginine group, although the increase in pregnancy rate was not statistically significant.

Adjunctive use of glucocorticosteroids (dexamethasone)

It has been suggested that dexamethasone may affect follicular development and oocyte maturation either directly via its isoform (11bHSD) in the granulosa cells or indirectly, by increasing serum GH and consequently intrafollicular IGF-1. In addition, it may provoke immunosuppression within the endometrial microenvironment (28-30).

To our knowledge, no studies have been reported involving poor responders. In one double-blind, placebo-controlled prospective randomized study in 290 cycles of normal responders (aged <41 years), dexamethasone was administered at 1 mg/day in the long luteal protocol until the day prior to oocyte retrieval and a significantly lower cancellation rate was found (31). These findings are encouraging, as they reveal a very low incidence of poor response with the use of corticosteroids; however, the data are limited and can only be considered as preliminary.

What is the role of androgen?

It has been suggested that androgens play a role on follicular growth. Androgen receptors have been identified in the human ovary (32). The addition of androgen during the early follicular phase may have a beneficial effect on the number of small antral follicles as well as on the ovarian sensitivity to FSH. Dehydroepiandrosterone (DHEA) has been used 2 months prior to ovarian stimulation in patients who previously had a poor response with promising results (33,34).

In a study by Balasch et al. (2006) who investigated the usefulness of testosterone pretreatment in poor responders via transdermal application, it was found that this may be a useful approach for patients known to be poor responders with normal basal FSH concentrations (35). Wisser et al. (2010) evaluated the effect of DHEA supplementation on IVF data and outcomes among 33 poor-responder patients and they concluded that DHEA supplementation can have a beneficial effect on ovarian reserves for poor-responder patients on IVF treatment (36).

A RCT comparing transdermal application of testosterone preceding standard gonadotrophin ovarian stimulation to high-dose gonadotrophin in association with a minidose GnRHa protocol in poor responders concluded that pretreatment with transdermal testosterone may improve the ovarian sensitivity to FSH and follicular response to gonadotrophin treatment in previous low-responding IVF patients. This approach leads to an increased follicular response compared with a high-dose gonadotrophin and minidose GnRHa protocol (37). In contrast, another study reported that live birth/delivery rates are not improved with the addition of transdermal testosterone (38). The above mentioned studies done by Massin et al. (2006); and Fabregues et al. (2009) were reanalyzed by Venetis et al. (2010), using a stratified analysis, clinical pregnancy rates did not differ significantly between the testosterone pretreatment group and the placebo group (20, 37).

References:
12. Wu MY, Chen HF, H o KN, Chen SU, Chao KH, Huang SC, et al. The value of human growth hormone as an adjuvant for


