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).
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 GnRHa protocol was associated with higher pregnancy rates and lower cancellation rates (5). However, Duvan et al. (2008), concluded that COC pretreatment plus microdose GnRHa 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 GnRH 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 GnRHa 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). Wiser 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-responder 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 two above mentioned studies done by Massin et al. (2006); and Fábregues 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:

1. Lok IH, Yip SK, Cheung LP, Yin Leung PH, Haines CJ. Adjuvant low-dose aspirin therapy in poor responders undergoing in vitro fertilization: a prospective, randomized, double-blind, placebo-controlled trial. Fertil Steril. 2004; 81(3):556-61.
2. Scott, R. and Navot, D. Enhancement of ovarian responsiveness with microdoses of gonadotropin-releasing hormone agonists during ovulation induction for in vitro fertilization. Fertil. Steril. 61; 1994, 880–885.
3. Gonen, Y., Jacobsen, W. and Casper, R. Gonadotropin suppression with oral contraceptives before in vitro fertilization. Fertil. Steril. 1990; 53, 282–287.
4. Biljan MM, Mahutte NG, Dean N, Hemmings R, Bissonnette F, Tan SL. Effects of pretreatment with an oral contraceptive on the time required to achieve pituitary suppression with gonadotropin-releasing hormone analogues and on subsequent implantation and pregnancy rates. Fertil Steril. 1998; 70(6):1063-9.
5. Lindheim, S., Barad, D., Witt, B., Ditkoff, E. and Sauer, M. (1996) Short-term gonadotrophin suppression with oral contraceptives benefits poor responders prior to controlled ovarian hyperstimulation. J. Assist. Reprod. Genet., 1996; 16, 745–747.
6. Duvan CI, Berker B, Turhan NO, Satiroglu HOral contraceptive pretreatment does not improve outcome in microdose gonadotrophin-releasing hormone agonist protocol among poor responder intracytoplasmic sperm injection patients. J Assist Reprod Genet. 2008; 25(2-3):89-93.
7. Bendikson K, Milki AA, Speck-Zulak A, Westphal LM.Comparison of GnRH antagonist cycles with and without oral contraceptive pretreatment in potential poor prognosis patientsClin Exp Obstet Gynecol. 2006; 33(3):145-7.
8. Jia X, Kalmijn J, Hsueh A. Growth hormone enhances folliclesti mulating hormone -induced differentiation of cultured rat granulosa cells. Endocrinology 1986; 118:1401 –6. granulosa cells. Endocrinology 1986; 118:1401 –6.
9. Adashi, E. and Rohan, R. Intraovarian regulation. Peptidergic signalling systems. Trends Endocrinol. Metab. 1993; 3: 243–248.
10. Ibrahim ZH, Matson PL, Buck P, Lieberman BA. The use of biosynthetic human growth hormone to augment ovulation induction with buserelin acetate/human menopausal gonadotropin in women with a poor ovarian response. Fertil Steril. 1991; 55(1): 202-4.
11. Hugues JN, Torresani T, Herve F, Martin-Pont B, Tamboise A, Santarelli J. Interest of growth hormone-releasing administration for improvement of ovarian responsiveness to gonadotropins in poor responder women. Fertil Steril 1991; 55:945 – 51.
12. Wu MY, Chen HF, H o HN, Chen SU, Chao KH, Huang SC, et al. The value of human grown hormone as an adjuvant for

ovarian stimulation in a human in vitro fertilization program. J Obstet Gynecol Res 1996; 22:443 – 50.
13. Owen EJ, Shoham Z, Mason BA, Ostergaard H, Jacobs HS. Cotreatment with growth hormone, after pituitary suppression, for ovarian stimulation in in vitro fertilization: a randomized, double-blind, placebo-control trial. Fertil Steril 1991; 56:1104–10.
14. Zhuang GL, Wong SX, Zhou CQ. The effect of co-administration of low dosage growth hormone and gonadotropin for ovarian hyperstimulation in vitro fertilization and embryo transfer. Chin J Obstet Gynecol 1994 510; 29:471–4.
15. Tesarik J, Hazout A, Mendoza C. Improvement of delivery and live birth rates after ICSI in women aged >40 years by ovarian co-stimulation with growth hormone.Hum Reprod. 2005; 20(9):2536-41.
16. Kucuk T, Hakan Kozinoglu, and Ayten Kaba Growth hormone co-treatment within a GnRH agonist long protocol in patients with poor ovarian response: a prospective, randomized, clinical trial J Assist Reprod Genet. 2008; 25(4): 123–127.
17. Kotarba D, Kotarba J, Hughes E. Growth hormone for in vitro fertilization (Cochrane Review). In: The Cochrane Library, 1 : Update Software. Oxford: The Cochrane Collaboration; 2002.
18. Harper K, Proctor M, Hughes E. Growth hormone for in vitro fertilization. Cochrane Database Syst Rev 2003; 3:CD000099.
19. Kyrou D, Kolibianakis EM, Venetis CA, Papanikolaou EG, Bontis J, Tarlatzis BC. How to improve the probability of pregnancy in poor responders undergoing in vitro fertilization: a systematic review and meta-analysis. Fertil Steril. 2009; 91(3):749-66.
20. Venetis CA, Kolibianakis EM, Tarlatzi TB, Tarlatzis BC. Evidence-based management of poor ovarian response. Ann N Y Acad Sci. 2010; 1205:199-206.
21. Howles CM, Loumaye E, Germond M, Yates R, Brinsden P, Healey D, et al. Does growth hormone releasing factor assist follicular development in poor responder patients undergoing ovarian stimulation for IVF? Hum Reprod 1999; 14:1939 – 43.
22. Chung-Hoon K, Hee-Dong C, Yoon-Seok C. Pyridostigmine cotreatment for controlled ovarian hyperstimulation in low responders undergoing in vitro fertilization± embryo transfer. Fertil Steril 1999; 71:652 –7.
23. Weiner, Z., Thaler, I. an Levron, J. Assessment of ovarian and uterine blood flow by transvaginal colour Doppler in ovarian stimulated women: correlation with the number of follicles and steroid hormone levels. Fertil. Steril. 1993, 59, 743–749.
24. Moncada, S., Palmer, R.M.J. and Higgs, E.A. Nitric oxide: physiology, pathophysiology and pharmacology. Pharmacol. Rev. 1991; 43, 109–142.
25. Anteby EY, Hurwitz A, Korach O, Revel A, Simon A, Finci-Yeheskel Z, et al. Human follicular nitric oxide pathway: relationship to follicular size, oestradiol concentrations and ovarian blood flow. Hum Reprod 1996; 11:1947–51.
26. Ben-Shlomo I, Adashi EY, Payne DW.The morphogenic/cytotoxic and prostaglandin-stimulating activities of interleukin-1 beta in the rat ovary are nitric oxide independent. J Clin Invest. 1994; 94(4):1463-9.
27. Battaglia C, Salvatori M, Maxia N, Petraglia F, Facchinetti F, Volpe A. Adjuvant l-arginine treatment for in-vitro fertilization in poor responder patients. Hum Reprod 1999; 14:1690–7.
28. Smith, M.P., Mathur, R.S., Keay, S.D., Hall, L., Hull, M.G. and Jenkins, J.M. Periovulatory human oocytes, cumulus cells and ovarian leucocytes express type-I but not type-II 11b-HSD RNA. Fertil. Steril. 2000, 73, 825–830.
29. Miell JP, Taylor AM, Jones J, Holly JM, Gaillard RC, Pralong FP, Ross RJ, Blum WF. The effects of dexamethasone treatment on immunoreactive and bioactive insulin-like growth factors (IGFs) and IGF-binding proteins in normal male volunteers.J Endocrinol. 1993; 136(3):525-33.
30. Polak de Fried E, Blanco L, Lancuba S, Asch RH. Improvement of clinical pregnancy rate and implantation rate of in-vitro fertilization-embryo transfer patients by using methylprednisone. Hum Reprod. 1993; 8(3):393-5.
31. Keay SD, Lenton EA, Cooke ID, Hull MG, Jenkins JM. Low-dose dexamethasone augments the ovarian response to exogenous gonadotrophins leading to a reduction in cycle cancellation rate in a standard IVF programme.Hum Reprod. 2001; 16(9):1861-5.
32. Suzuki T, Sasano H, Kimura N, Tamura M, Fukaya T, Yajima A, et al. Immunohistochemical distribution of progesterone, androgen and oestrogen receptors in the human ovary during the menstrual cycle: relationship to expression of steroidogenic enzymes. Hum Reprod 1994; 9:1589–95.
33. Casson PR, Lindas ay MS, Pisarka MD, Carson SA, Buster JE. Dehydroepiandros terone su pp lementation augmrnt s ovarian stimulation in poor responders: A case series. Hum Reprod 2000; 15(10):2129 – 32.
34. Van Weering HGI, Gutnecht DR, Schats R. Augmentation of ovarian respon se by dehy droepi andros terone. Hum Reprod 2001; 16(7):1537 – 9
35. Balasch J, Fabreques F, Penarruba J, Carmona F, Casamitjana R, Creus M, et al. Pretreatment with transdermal testosterone may improve ovarian response to gonadotrophins in poor-responder IVF patients with normal basal concentrations of FSH. Hum Reprod 2006; 21(7):1884 – 93
36. Wiser A, Gonen O, Ghetler Y, Shavit T, Berkovitz A, Shulman A. Addition of dehydroepiandrosterone (DHEA) for poor-responder patients before and during IVF treatment improves the pregnancy rate: A randomized prospective study. Hum Reprod. 2010; 23: 234-8.
37. Fábregues F, Peñarrubia J, Creus M, Manau D, Casals G, Carmona F, Balasch J.Transdermal testosterone may improve ovarian response to gonadotrophins in low-responder IVF patients: a randomized, clinical trial.Hum Reprod. 2009; 24(2):349-59.
38. Massin N, Cedrin-Durnerin I, Coussieu C, Galey-Fontaine J, Wolf JP, Hugues JN. Effects of transdermal testosterone application on the ovarian response to fsh in poor responders undergoing assisted reproduction technique—a prospective, randomized, double-blind study. Hum Reprod 2006; 21:1204–11.