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Supplementation with Dehydroepiandrosterone as a Promising Treatment for Poor Responders

Paolo Giovanni Artini[1,2*], Sara Pinelli[1,3], Francesca Papini[1,3], Giovanna Simi[1,3], Vito Cela[1,3] and Andrea Riccardo Genazzani[1,2,3]

[1]*Department of Reproductive Medicine and Child Development, Division of Obstetrics and Gynecology, University of Pisa, Pisa, Italy*
[2]*Professor of Obstetrics and Gynecology, University of Pisa, Italy*
[3]*Medical Doctor*

Abstract

DHEA represents a promising option for the treatment of a large number of women who are really challenging for IVF specialists.

Keywords: Dehydroepiandrosterone; Poor Responders; Ovarian aging; Ovarian reserve

Introduction

One of the goals of Assisted Reproduction Techniques (ART) is the recruitment of multiple follicles and the recovery of good quality oocytes.

Ovarian response (OR) can be defined as the reaction of the ovaries to an exogenous stimulus: it changes substantially among women and in the same woman between various cycles [1]. Thus, ovarian response to controlled ovarian hyperstimulation (COH) may vary from a patient to another. The opposite of the spectrum of possible results are respectively "poor ovarian response" (POR) and "ovarian hyperstimulation syndrome" (OHSS).

Hence, POR indicates a reduced follicular response resulting in a low number of retrieved oocytes, despite the high dose of gonadotropins administered.

In literature there are several publications on poor ovarian response, but the conclusions of all these papers are the same: for the time being, there is not enough evidence to support the use of any particular regime in poor responders patients.

Incidence of poor response to ovarian stimulation during IVF treatments has been reported from 9 to 24% [2,3], but we have to consider that until ESHRE consensus in 2010 and the drafting of "Bologna criteria" on the definition of "poor response" to ovarian stimulation, the lack of a uniform definition of POR resulted in comparisons of heterogeneous groups of patients, making it very difficult to compare studies and to draw any definitive conclusions on pathogenesis, diagnosis and treatment. The prevalence of POR increases with age, and it is >50% in patients over 40 years [4], even if young age is not a completely protective factor.

Dehydroepiandrosterone

Dehydroepiandrosterone (DHEA) is a weak androgen produced by the conversion of cholesterol by the adrenal cortex, central nervous system and the ovarian theca cells, and is converted predominantly in peripheral tissue to more active forms of androgen or estrogen [5].

DHEA is abundant during female reproductive life, and progressively declines by approximately 2 percent per year [6], leading to the hypothesis that supplementation with DHEA may slow down aging process [7], considering the decrease in the ability of women to respond to ovulation-inducing medications with age. In fact, older women produce few oocytes and yield few normal embryos even when exposed to maximal gonadotropin stimulation [8]. Even after 70 years of research, the physiology of DHEA is not fully understood.

Physiology of DHEA

As a result of the cited studies, in recent years approximately one third of all IVF centers in the world have started to use DHEA supplementation in poor responder patients [9].

DHEA beneficial effects increase over time, and best results are obtained after four to five month of supplementation with 75 mg of micronized DHEA daily, a time period similar to the complete follicular recruitment cycle [10].

Numerous hypotheses have been made on how DHEA promotes fertility. Besides serving as an essential pro-hormone in ovarian follicular steroidogenesis, facilitating follicular function and growth [11,12], DHEA seems to increase follicular insulin-like growth factor-I (IGF-I) concentrations by ≅150%, probably independently of changes in GH secretion [13,14]. This may indicate that DHEA stimulates hepatic and end organ IGF-1 response to GH, which can promote the gonadotropin effect.

In animal models, DHEA has also shown to promote a polycystic environment in the ovaries, with promotion of antral follicle growth, increased levels of active oocytes and decreased atretic effects [8,13,15,16].

Androgens, long considered antagonist of normal follicle recruitment and development, thus assume a crucial role in female fertility: some reports demonstrated that androgens act on folliculogenesis by increasing the number of FSH receptors expressed in the granulosa cells [17]. On the other hand, the addition of androgens in COH is thought to have a positive role in follicular recruitment and granulosa cell proliferation [18].

Moreover, studies have shown the beneficial effect of DHEA administration on vascular function. In fact, DHEA increases vascular endothelial proliferation, migration and vascular tube formation. DHEA also promotes nitric oxide synthesis, at physiological levels,

***Corresponding author:** Paolo Giovanni Artini, Department of Reproductive Medicine and Child Development, Division of Obstetrics and Gynecology, University of Pisa, Via Roma 56, 56126 Pisa, Italy. Tel.: ++39.050.554104; Fax: ++39.050.551293; E-mail: paolo.artini@med.unipi.it

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in intact vascular endothelial cells, inducing vasodilatation [19]. This effect can be very important for vascular function also in the female reproductive system, considering that ovarian folliculogenesis is accompanied by a very finely regulated angiogenesis.

Side effects

Patients using DHEA may experience possible androgenic side-effects, such as acne vulgaris, oily skin, deepening of voice, hair loss and facial hair growth, but these effects appear minimal with a dose of 75 mg/day [20]. Nevertheless, Gleicher and Barad reported more frequently improved energy levels and better sex drive in patients treated with DHEA [21]. However, one study in literature reported a case of seizure in a patient using DHEA, suggesting need for special attention in women prone to convulsions, although more investigation is needed [22].

Long term effects of DHEA supplementation have not been clarified so far. Since DHEA is a precursor of sex steroids, its use could increase the risk of hormonal-dependent malignancies [23].

POR definition

Poor responders can be patients with low ovarian reserve as well as patients with normal ovarian reserve, but inherent low response to gonadotrophin. Failure to recruit adequate follicles is called "poor (or 'low') response".

Many terms that have been interchangeably used to describe poor responders, including "low responder", "bad responder" and "non-responder".

The original definition of low response was based on low peak estradiol level (A maximum E_2 concentration of <300–500 pg/ml) after the use of a standard stimulation protocol, with a small number of follicles and oocytes retrieved [24]. However, measuring E_2 level is liable for large inter-laboratory variations, as it is assay-dependent.

The number of developed follicles and/or number of oocyte aspirated are two of the most important criteria for defining ovarian response [25]. Various threshold values have been used in the literature, ranging from <3 to <5 for dominant follicles on the day of HCG [26-28] or for retrieved oocytes [29,30].

The ESHRE consensus reached in Bologna in March 2010 establishes that at least two of the following three features must be present, in order to diagnose POR:

i. Advanced maternal age (≥ 40 years) or any other risk factor for POR;

ii. A previous POR (<3 oocytes) with a conventional stimulation protocol;

iii. An abnormal ovarian reserve test (ORT) (i.e. AFC <5-7 follicles or AMH <0,5-1,1 ng/ml).

Two episodes of POR after maximal stimulation are sufficient to

Publication	Type of study	Characteristics of patients	No. of cases and controls	DHEA protocol	Ovarian stimulation protocol	Outcomes reported
Casson et al. (2000)	Case series	<41 years old Day-3 FSH <20mIU/ml Unexplained infertility Previous POR (peak E2 <500 pg/ml; ≤2 mature follicles)	5 cases; No controls	80 mg/day oral micronized DHEA for 2 months	4 Cases: 75 IU rFSH i.m. twice a day 1 case: purified urinary FSH 75 IU	Peak E_2 concentrations; E_2 /ampoule ratio No. of mature follicles
Barad and Gleicher (2005)	Case report	42.7-year-old patient	1 case	75 mg/day oral micronized DHEA	Norethindrone acetate 10 mg per 10 days (from day 2 of menses)+ 40 µg leuprolide acetate x2/day (3 days later) + 600 IU FSH (Cycle 1) or 450 IU FSH + 150 IU hMG (cycle 2-8) or 300 IU FSH + 150 IU hMG (cycle 9)	Peak E_2 concentrations, No. oocytes retrieved, cryopreservable embryos
Barad and Gleicher (2006)	Case control	Repeated IVF failures; <4 oocytes retrieved; Poor embryo quality; FSH levels >10 mIU/ml; E2 levels > 75 pg/ml	25 cases (self controlled)	75 mg/day oral micronized DHEA for ≥ 16 weeks	Norethindrone acetate 10 mg per 10 days (from day 2 of menses)+ 50 µg leuprolide acetate x2/day (3 days later) + 450 IU rFSH + 150 IU hMG	Peak E_2 concentrations; No. oocytes retrieved; No. of embryos; Oocyte and embryo quality; Embryo transfers;
Barad et al. (2007)	Retrospective case control	b-FSH: ≥7.4 mIU/ml 30-34 years ≥ 8,6mIU/ml ≥35 years;	89 cases; 101 controls	75 mg/day oral micronized DHEA for 4 months	Microdose agonist flare+ 300-450 IU FSH + 150 IU hMG	Clinical Pregnancy R ate
Sönmezer et al. (2009)	Case control	Cycle cancellation due to low E_2 or <4 oocytes retrieved	19 cases (self controlled)	75 mg/day oral micronized DHEA for ≥3 months	rFSH 300 IU/day + hMG 75 or 150 IU + GnRH antagonist	Mean day-3 E_2 , No. of >17 mm follicles, MII oocytes, top quality day-2 and day-3 embryos, reduction of cycle CR and PR
Gleicher et al. (2009)	Retrospective	DHEA supplemented pregnancies	73 cases Control: national USA database	75 mg/day oral micronized DHEA for ≥ 2 months	Not reported	Miscarriage rates
Wiser et al. (2010)	Randomized, prospective, controlled	Retrieval of <5 oocytes, poor-quality embryos or cycle cancellation to COH; <42 years	17 cases 16 controls	75 mg/day oral micronized DHEA for ≥ 6 weeks	Standard long-stimulation protocol: GnRH agonist (triptorelin acetate)+ 450 IU rFSH+ 150 IU rLH	Peak E_2 levels, No. of oocytes retrieved; Embryo quality and No. of embryos transferred; PR, live birth rates.
Gleicher et al. (2010)	Matched case control	Abnormally elevated age-specific bFSH or age-specific AMH	22 cases, 44 controls	75 mg/day oral micronized DHEA for ≥ 4 weeks	Microdose Gn-RH agonist (leuprolide acetate 50 µg) + FSH 300-450 IU daily + hMG 150 IU	Aneuploidy at Pre-implantation Genetic Screening (PGS)

Table 1:

define a patient "poor responder" without advanced maternal age or abnormal ORT. It is important to remember that the term POR refers to ovarian response, so a previous stimulated cycle is essential for the diagnosis. In the case of women over 40 years with an abnormal ORT we are allowed to talk about "expected POR" [4].

Poor responders remain a challenging group of patients to manage in an in vitro fertilization (IVF) program. In fact, poor response often causes cycle cancellation and forces patients to another attempt, trying to obtain a better response in the subsequent cycle.

A variety of different stimulation protocols have been suggested to manage poor responders patients, either using high levels of gonadotropins associated with different dosages and timing of GnRH analogs or antagonists, or trying IVF in a natural cycle or with minimal stimulation. Finally, it was suggested to treat patients with dietary supplements or hormones like Dehydroepiandrosterone (DHEA), growth hormone (GH), oestradiol or androgens.

However, pregnancy rates after in vitro fertilization (IVF) remain disappointingly low.

Present literature on the use of DHEA in POR

Casson and associates, in 2000, firstly suggested an improvement of ovarian function in patients with diminished ovarian reserve from supplementation with DHEA [31]. They presented young women with unexplained infertility and FSH levels <20 mIU/ml treated with a dose of 80 mg of DHEA daily for 2 months. As a result, there were no significant improvements of pregnancy rates, but E_2 levels were tripled in all patients, and the number of follicles retrieved was doubled.

This paper went unnoticed for 5 years, until a 43-year-old infertile woman rediscovered this paper, while looking in literature for a remedy for her poor ovarian response, and took DHEA without notifying her doctors [32]. During 9 months of continued DHEA supplementation, 18 oocytes were retrieved, while before treatment with DHEA only 2 had been retrieved. Following 9 subsequent IVF cycles, a total of 66 embryos were cryopreserved.

Her improvement in ovarian function under DHEA supplementation stimulated Barad and Gleicher, after few months, to publish a case-control study in which 25 women were evaluated in their respective IVF cycle outcomes pre-and post-treatment with DHEA, with the same ovarian protocol stimulation [10]. Most of these women had been advised to become donor oocytes recipients, but they preferred to try DHEA supplementation for approximately 16 weeks, followed by IVF. The patients underwent the same COH protocol for both the cycles before and after DHEA treatment. The supplementation was well tolerated by all patients, demonstrating higher number of fertilized oocytes, transferred embryos, and embryo score per oocyte, besides improved oocytes and embryo quality.

In 2007, the same authors published a case-control study on 190 women aged more than 30 with POR, all receiving the same stimulation protocol [16]. Study group used supplementation with 25 mg DHEA three times daily for up to 4 months, while control group underwent infertility treatment, but did not take DHEA. The DHEA-group reported a lower cancellation rate, but not statistically significant, and a better clinical pregnancy rate (PR), in respect to control group, despite prognostically more favourable controls and higher mean age in the DHEA- group. The miscarriage rate per clinical pregnancy was also found lower in the study group, but these data were not statistically significant.

In a small pilot study of 2007, the same authors presented 8 patients with premature ovarian aging (POA), who received DHEA for at least 1 month (study group), and 19 women with POA who were not treated with DHEA (control group). The study group demonstrated that DHEA may reduce aneuploidy, but unfortunately, the small number of patients in the study awarded to it an insufficient statistical power [33].

This result was confirmed by the study of the same authors published in 2010, where they concluded that the beneficial effects of DHEA supplementation on miscarriage rates were, at least partially, the likely consequence of lower embryo aneuploidy [34].

An interesting study conducted by Gleicher and colleagues in 2009 reported a significantly decreased miscarriage rate after DHEA supplementation, as opposed to total miscarriage rate in the national USA registry, that was attributed by the authors to diminished aneuploid embryo rates, as aneuploidy is a consequence of ovarian aging [35].

A recent study by Mamas and Mamas, in 2009 [11], presented really interesting results: 5 premature ovarian failure (POF) patients conceived after at least 2 months of DHEA supplementation, which led to regular periods and decreased serum FSH concentrations and increased serum oestradiol concentrations.

In the same year, Sönmezer and associates compared the result of a second cycle of 19 patients treated with DHEA 25 mg t.i.d. with the parameters of the previous, failed, cycle of stimulation. They noted statistically significant improvement in number of follicles >17 mm recruited, oocytes retrieved, MII oocytes and a better quality of embryos. Furthermore, there was a statistically significant improvement in pregnancy rate per patients and per transferred embryo, clinical pregnancies and implantation rate.

Interestingly, one study in literature suggests that the treatment with DHEA may influence the sex of the baby, increasing intra-follicular testosterone or other androgens, augmenting the possibility of male offsprings [36,37].

Wiser and associates most recently published the first randomized, prospective, controlled study of supplementation with 75 mg of DHEA orally once a day, at least 6 weeks before starting the first IVF cycle. DHEA patients showed significantly higher live birth rates [38].

Our data

Our still unpublished data show that Dehydroepiandrosterone-sulfate (DHEA-S) administration for three months in poor responders patients can improve the peri-follicular vascularization, enhancing oxygen levels in follicular fluid, which is important in order to develop oocytes and embryo of good quality. The finding of an improved follicular microenvironment in poor responder patients treated with DHEA three months prior to IVF, is in line with the clinical data from Barad et al. [10], reporting that DHEA supplementation leads to an increase in number of good quality oocytes and also good quality embryos.

Thus, the improvement of reproductive parameters after DHEA supplementation in poor responder patients could be explained through the effect that this pro-hormone has on follicular microenvironment (data submitted).

Conclusions

In conclusion, despite a lot of strategies to improve poor responders outcome have been tried, some recent revisions of literature suggest that there is insufficient evidence to support the routine use of DHEA or other androgens in the management of poor responders [39,40].

More strong data from good quality randomized controlled trials (RCTs) with relevant outcomes and follow up are needed [41].

However, despite the limitations of the previous studies, it seems clear that DHEA represents a promising option for the treatment of a large number of women who are -for the time being- really challenging for IVF specialists. In addition to the possible benefits in term of increase of reproductive parameters, DHEA offers the possibility to choose a milder and more cost-effective hormonal protocol. Without supplementation with DHEA, specialists would be forced to use heavy hormonal doses, with minimal response or, as the last resort, egg donation [42].

References

1. Lashen H, Ledger W, Lopez-Bernal A, Barlow D (1999) Poor responders to ovulation induction: is proceeding to *in-vitro* fertilization worthwhile? *Hum Reprod* 14:964-969.
2. Kyrou D, Kolibianakis EM, Venetis CA, Papanikolaou EG, Bontis J, et al. (2009) How to improve the probability of pregnancy in poor responders undergoing in vitro fertilization: a systematic review and meta-analysis. *Fertil Steril* 91:749-766.
3. Fasouliotis SJ, Simon A, Laufer N (2000) Evaluation and treatment of low responders in assisted reproductive technology: a challenge to meet. *J Assist Reprod Genet* 17:357-373.
4. Ferraretti AP, La Marca A, Fauser BC, Tarlatzis B, Nargund G, et al. (2011) ESHRE consensus on the definition of 'poor response' to ovarian stimulation for in vitro fertilization: the Bologna criteria. *Hum Reprod* 26:1616-1624.
5. Burger HG (2002)Androgen production in women. *Fertility and sterility* 77:3-5.
6. Walker ML, Anderson DC, Herndon JG, Walker LC (2009) Ovarian aging in squirrel monkeys (Saimiri sciureus). Reproduction 138:793-799.
7. Casson PR, Carson SA, Buster JE (1998) Testosterone Delivery Systems for Women: Present Status and Future Promise. *Semin Reprod Endocrinol* 16:153-159.
8. Orvieto R, Bar-Hava I, Yoeli R, Ashkenazi J, Bar J, et al. (2004) Results of in vitrofertilization cycles in women aged 43–45 years. *Gynecol Endocrinol* 18:75-78.
9. Patrizio P, Milton L Poor responders: How to define, diagnose and treat?
10. Barad D, Gleicher N (2006) Effect of dehydroepiandrosterone on oocyte and embryo yields, embryo grade and cell number in IVF. *Hum Reprod* 21:2845-2849.
11. Mamas L, Mamas E (2009) Premature ovarian failure and dehydroepiandrosterone. *Fertil Steril* 91:644-646.
12. Hillier SG, Whitelaw PF, Smyth CD (1994) Follicular oestrogen synthesis: the 'two-cell, two-gonadotrophin' model revisited. *Mol Cell Endocrinol* 100:51-54.
13. Casson PR, Santoro N, Elkind-Hirsch K, Carson SA, Hornsby PJ, et al. (1998) Postmenopausal dehydroepiandrosterone administration increases free insulin-like growth factor-I and decreases high-density lipoprotein: a six-month trial. *Fertil Steril* 70:107-110.
14. Morales AJ, Nolan JJ, Nelson JC, Yen SS (1994) Effects of replacement dose of dehydroepiandrosterone in men and women of advancing age. *J Clin Endocrinol Metab* 78:1360-1367.
15. Vendola K, Zhou J, Wang J, Famuyiwa OA, Bievre M, et al. (1999) Androgens Promote Oocyte Insulin-Like Growth Factor I Expression and Initiation of Follicle Development in the Primate Ovary. *Biol Reprod* 61:353-357.
16. Barad D, Brill H, Gleicher N (2007) Update on the use of dehydroepiandrosterone supplementation among women with diminished ovarian function. *J Assist Reprod Genet* 24:629-634.
17. Weil S, Vendola K, Zhou J, Bondy CA (1999) Androgen and follicle-stimulating hormone interactions in primate ovarian follicle development. *J Clin Endocrinol Metab* 84:2951-2956.
18. Feigenberg T, Simon A, Ben-Meir A, Gielchinsky Y, Laufer N (2009) Role of androgens in the treatment of patients with low ovarian response. *Reprod Biomed Online* 19:888-898.
19. Liu D, Iruthayanathan M, Homan LL, Wang Y, Yang L, et al. (2008) Dehydroepiandrosterone stimulates endothelial proliferation and angiogenesis through extracellular signal-regulated kinase 1/2-mediated mechanisms. *Endocrinology* 149:889-898.
20. Kroboth P, Salek F, Pittenger A, Fabian T, Frye R (1999) DHEA and DHEA-S: a review. *J Clin Pharmacol* 39:327-348.
21. Gleicher N, Barad DH (2011) Dehydroepiandrosterone (DHEA) supplementation in diminished ovarian reserve (DOR). *Reprod Biol Endocrinol* 9:67.
22. Karp G, Bentov Y, Masalha R, Ifergane G (2009) Onset of late posttraumatic seizure after dehydroepiandrosterone treatment. *Fertil Steril* 91: e931-932.
23. Kaaks R, Berrino F, Key T, Rinaldi S, Dossus L, et al. (2005) Serum Sex Steroids in Premenopausal Women and Breast Cancer Risk Within the European Prospective Investigation into Cancer and Nutrition (EPIC). *J Natl Cancer Inst* 97:755-765.
24. Garcia JE, Jones GS, Acosta AA, Wright G Jr (1983) Human menopausal gonadotropin/human chorionic gonadotropin follicular maturation for oocyte aspiration: phase II, 1981. *Fertil Steril* 39:174-179.
25. Tarlatzis BC, Zepiridis L, Grimbizis G, Bontis J (2003) Clinical management of low ovarian response to stimulation for IVF: a systematic review. *Hum Reprod Update* 9:61-76.
26. Serafini P, Stone B, Kerin J, Batzofin J, Quinn P, et al. (1988) An alternate approach to controlled ovarian hyperstimulation in "poor responders": pretreatment with a gonadotropin-releasing hormone analog. *Fertil Steril* 49:90-95.
27. Fridstrom M, Akerlof E, Sjoblom P, Hillensjo T (1997) Serum levels of luteinizing and follicle-stimulating hormones in normal and poor-responding patients undergoing ovarian stimulation with urofollitropin after pituitary downregulation. *Gynecol Endocrinol* 11:25-28.
28. Raga F, Bonilla-Musoles F, Casañ EM, Bonilla F (1999). Recombinant follicle stimulating hormone stimulation in poor responders with normal basal concentrations of follicle stimulating hormone and oestradiol: improved reproductive outcome. *Hum Reprod* 14:1431-1434.
29. Chong AP, Rafael RW, Forte CC (1986) Influence of weight in the induction of ovulation with human menopausal gonadotropin and human chorionic-gonadotropin. *Fertil steril* 46:599-603.
30. Surrey ES, Schoolcraft WB (2000) Evaluating strategies for improving ovarian response of the poor responder undergoing assisted reproductive techniques. *Fertil steril* 73:667-676.
31. Casson PR, Lindsay MS, Pisarska MD, Carson SA, Buster JE (2000) Dehydroepiandrosterone supplementation augments ovarian stimulation in poor responders: a case series. *Hum Reprod* 15: 2129-2132.
32. Barad DH, Gleicher N (2005) Increased oocyte production after treatment with dehydroepiandrosterone. *Fertil Steril* 84:756.
33. Gleicher N, Weghofer A, Barad D (2007) Increased euploid embryos after supplementation with dehydroepiandrosterone (DHEA) in women with premature ovarian aging. *Fertility and sterility* 88:S232.
34. Gleicher N, Weghofer A, Barad DH (2010) Dehydroepiandrosterone (DHEA) reduces embryo aneuploidy: direct evidence from preimplantation genetic screening (PGS). *Reprod Biol Endocrinol* 8:140.
35. Gleicher N, Ryan E, Weghofer A, Blanco-Mejia S, Barad DH (2009) Miscarriage rates after dehydroepiandrosterone (DHEA) supplementation in women with diminished ovarian reserve: a case control study. *Reprod Biol Endocrinol* 7:108.
36. Sönmezer M, Ozmen B, Cil AP, Ozkavukçu S, Taşçi T (2009) Dehydroepiandrosterone supplementation improves ovarian response and cycle outcome in poor responders. Reprod Biomed Online 19: 508-513.
37. Ryan EAJ, Claessens EA, Blanco Mejia S (2008) The sex ratio of offspring born to women, using dehydroepiandrosterone (DHEA) to improve ovarian response. *Fertility and sterility* 90:S116-S117.
38. Wiser A, Gonen O, Ghetler Y, Shavit T, Berkovitz A, et al. (2010) Addition of dehydroepiandrosterone (DHEA) for poor-responder patients before and during IVF treatment improves the pregnancy rate: a randomized prospective study. *Hum Reprod* 25: 2496-2500.
39. Yakin K, Urman B (2011) DHEA as a miracle drug in the treatment of poor responders; hype or hope? *Hum Reprod* 26:1941-1944.

40. Sunkara SK, Pundir J, Khalaf Y (2011) Effect of androgen supplementation or modulation on ovarian stimulation outcome in poor responders: a meta-analysis. *Reprod Biomed Online* 22:545-555.

41. Pandian Z, McTavish AR, Aucott L, Hamilton MP, Bhattacharya S (2010) Interventions for 'poor responders' to controlled ovarian hyper stimulation (COH) in in-vitro fertilisation (IVF). *Cochrane Database Syst Rev* CD004379.

42. Mamas L, Mamas E (2009) Dehydroepiandrosterone supplementation in assisted reproduction: rationale and results. *Curr Opin Obstet Gynecol* 21:306-308.