Supplementation with Dehydroepiandrosterone as a Promising Treatment for Poor Responders

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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 patient to patient. 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-I 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,
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 E2 concentration <300–500 pg/ml) after the use of a standard stimulation protocol, with a small number of follicles and oocytes retrieved [24]. However, measuring E2 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:

1. Advanced maternal age (≥ 40 years) or any other risk factor for POR;
2. A previous POR (<3 oocytes) with a conventional stimulation protocol;
3. 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                                                                               |                           | 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 E2 concentrations, E/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                                                   | Norcethindione 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 E2 concentrations, No. of 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 2 months                                      | Norcethindione acetate 10 mg per 10 days (from day 2 of menses) + 50 µg leuprolide acetate x2/day (3 days later) + 450 IU FSH + 150 IU hMG | Peak E2 concentrations, No. of oocytes retrieved, No. of embryos; Oocyte and embryo quality; Embryo transfers; |
| Barad et al. (2007)  | Retrospective case control | b-FSH; ≥ 4 mIU/ml or 30-34 years ≥ 8.6 mIU/ml or ≤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 Rate; |
| Sönmezser et al. (2009) | Case control        | Cycle cancellation due to low E2 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 E2, No. of >17 mm follicles, Mill 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 FSH + 150 IU LH | Peak E2, 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 FSH 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 Dehydroepiandrostosterone (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 E2 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, Sönmez 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 patient 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 intrafollicular 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 Dehydroepiandrosteronesulfate (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].

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