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OPINION

Is there a role for DHEA supplementation in women with diminished ovarian reserve?

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Abstract
Purpose Poor ovarian reserve and poor ovarian response presents a challenge to IVF centers. Dehydroepiandrosterone (DHEA) supplementation is increasingly being used by many IVF centers around the world in poor responders despite the lack of convincing data. We therefore examined the rationale for the use of DHEA in poor responders, address the relevant studies, present new data, and address its potential mechanisms of action.
Methods All published articles on the role of DHEA in infertile women from 1990 to April 2013 were reviewed.
Results Several studies have suggested an improvement in pregnancy rates with the use of DHEA. Potential mechanisms include improved follicular steroidogenesis, increased IGF-1, acting as a pre-hormone for follicular testosterone, reducing aneuploidy, and increasing AMH and antral follicle count. While the role of DHEA is intriguing, evidence-based recommendations are lacking.
Conclusions While nearly 25 % of IVF programs use DHEA currently, large randomized prospective trials are sorely needed. Until (and if) such trials are conducted, DHEA may be of benefit in suitable, well informed, and consented women with diminished ovarian reserve.

Capsule DHEA use may be of benefit in some patients with diminished ovarian reserve.

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Introduction

Dehydroepiandrosterone (DHEA) is an androgen produced in the zona reticularis of the adrenal gland and in the ovaries. In 1939 a German scientist by the name of Butenandt received the Nobel Prize in Chemistry for identifying and isolating DHEA. DHEA is a weak androgen that is converted to estradiol and testosterone. DHEAS is the sulphate ester of DHEA, and it is synthesized in the adrenal gland. Serum levels of those two sex steroid hormones decline with age [1]. In 1996, DHEA's anti-aging effects were described [2]. This motivated several scientists to study the role of DHEA in reproduction and specifically in diminished ovarian reserve.

Ovarian reserve, generally defined as the size and quantity of the remaining ovarian follicular pool, declines with advancing age. If this pool is smaller than expected at any given age, it is defined as diminished ovarian reserve. Diminished ovarian reserve, also known as age-related infertility, is a major cause of infertility. In brief, the total number of oocytes in any given women is genetically determined and inexorably declines throughout life, from approximately 1–2 million at birth, to about 300,000 at puberty, 25,000 at age 40, and fewer than 1,000 at menopause [3]. Diminished ovarian reserve, whether the result of physiological aging of the ovaries or premature ovarian aging, represents one of the most common challenges in modern infertility management.

This review was triggered by two recent debate articles regarding the use of DHEA in poor responders prior to ART [4, 5]. Both suggested that while the use of DHEA is promising, physicians should not rush into using it in the absence of large randomized placebo controlled trials. We therefore reviewed all the published literature on the use of DHEA in infertile women and specifically in women with diminished ovarian reserve.

Pathophysiology

DHEA and its sulfate ester (DHEAS) are the most common sex steroid in women. Both DHEA and DHEAS work as precursors for the intracellular production of estrogen and androgens. Serum levels of those hormones decline with age resulting in loss of well-being, lowered libido, and lower sexual function in both premenopausal and postmenopausal women [6]. DHEA secretion is primarily adrenal in origin (85 %), and ovarian to a lesser extent (15 %), and as the major source of androgen synthesis in women is converted via androstenedione to testosterone [7]. There is still uncertainty as to whether DHEA has significant physiological actions besides its conversion into androgens and estrogenic compounds [6]. Reviewing competition-binding studies reveals that DHEA has affinity to the androgen receptor and estrogen receptors with preference for estrogen receptor ß over estrogen receptor ∂. The effect on the beta-receptor represents a physiologically meaningful interaction [8]. Sex hormone binding globulin (SHBG) only weakly binds DHEA but not DHEAS, making circulating DHEA highly metabolically active [9].

The production of DHEA and DHEAS increases significantly at the age of 6 to 8 years as the zona reticularis matures [10]. Serum DHEA and DHEAS levels peak between ages 20 and 30 years, then decline by 2 % per year, and by the age of 70 serum levels of both hormones are 20–23 % of their peak values, to nadirs of 10–20 % around age 80 [11, 12].

Since the US Dietary Supplement Health and Education Act in 1994, DHEA became available over the counter. The FDA considers DHEA a nutritional supplement, while a prescription is required in most European countries. The commercial DHEA products currently available are manufactured from yams, however the purity and potency of the commercially available products are not known, with content ranging from 0 % to 150 % of the labeled amount [13, 14].

Published studies

Casson et al. were the first to describe the therapeutic benefits of DHEA supplementation in women with diminished ovarian reserve [15]. They described five subjects, all of who were below 41 of age with normal FSH concentrations who had poor response to ovarian stimulation with gonadotropins in ovulation induction followed by intra uterine insemination cycles. After oral supplementation with 80 mg of micronized DHEA for two months, their peak estradiol level tripled and their response to stimulation increased by two folds and concluded that DHEA supplementation might be a novel way to maximize ovarian response in poor responders [15]. The mechanism by which DHEA exerts its effects is uncertain; however, the authors speculated it may have a role in increasing the serum concentrations of IGF-1, which in turn may improve the response to gonadotropins [15]. Previously, Casson et al. studied the effect of DHEA supplementation on IGF-1 and High Density lipoprotein in postmenopausal women [16]. DHEA resulted in an increased IGF-1 at 3 months and a decreased high density lipoprotein and apolipoprotein A1 at 6 months [16]. A prior study investigated the expression of IGF-1 in a DHEA-induced rat polycystic ovarian model: using In situ hybridization technique, the expression of IGF-1 in prenatral and small antral follicles in the DHEA-treated rats was increased (but not in large antral follicles), as was IGF-1 expression in granulosa cells in a cell-culture system [17]. However, Casson's paper was appropriately criticized for methodological errors, such as the bias introduced with changing the stimulation regimen, as well as the choice and type of gonadotrophins used [18].

There was no follow up studies to Casson's original paper until 2005, when a 43 year old female patient was undergoing her first IVF cycle at a New York City fertility clinic, and produced one egg and one embryo. After her first cycle, she was advised to consider the option of egg donation. However, she declined and after reviewing the medical literature, she decided to start oral DHEA supplementation. Following nine consecutive all freeze IVF cycles, her oocyte and embryo yields increased from cycle to cycle. Her use of DHEA was unknown to her treating physician until the 6th cycle. This change in her ovarian function resulted in the initiation of a prospective investigation of the role of DHEA in patients with diminished ovarian reserve [19].

Barad et al. then studied the role of DHEA in twenty five patients with diminished ovarian reserve. They noted a significant increase in oocyte and embryo numbers, better embryo grades, and improved average embryo scores [20]. In a subsequent study by the same group, eighty nine patients with poor ovarian reserve were supplemented with DHEA for 4 months. DHEA improved all the studied outcome parameters, i.e. time to pregnancy, pregnancy rate, and number of embryo transferred [21]. Also, DHEA resulted in a similar improvement in patients with age-dependent diminished ovarian reserve and patients with premature ovarian insufficiency. Similar outcomes were suggested by another group [22], who studied forty seven patients with prior clomiphene citrate failures and were supplemented with 75 mg of DHEA daily for at least 60 days prior to stimulation with either letrozole or clomiphene citrate in combination with FSH [22]. Another study evaluated the outcome of nineteen poor responder patients undergoing IVF supplemented with DHEA for at least 3 months. Those patients demonstrated a significant decrease in day 3 estradiol level, reduced cycle cancellations, improved embryo transfer, and higher pregnancy

rates [23]. Mamas reported on five women with premature ovarian failure that achieved pregnancies after DHEA supplementation. Three patients had a spontaneous pregnancy and the fourth had clomiphene citrate with IUI after 3–6 months of DHEA supplementation [24]. In a later follow up, they reported a total of 14 women with POF and FSH levels between 62 and 98 mIU/ml with 8 achieving natural conception within 3–7 months of DHEA supplementation and only one miscarriage [25].

The first prospectively randomized clinical trial was published by Wiser et al. in 2010, who concluded that DHEA patients demonstrated improved embryo quality over time and higher live birth rates with increasing length of DHEA supplementation [26]. However, this paper should be interpreted cautiously because it suffers from significant shortcomings such as the low number of subjects (N=33; 17 used DHEA and 16 did not) and cycles (N=51) in the trial, lack of power analysis before starting the trial, the short duration of DHEA use, inability to compare appropriately the groups (6 weeks for the initial group, and 16–18 weeks for those who did not conceive and underwent a second IVF cycle; 17 completed one cycle and 9 completed a second cycle), and whether there was indeed a significant difference among women who used DHEA [27]. Wiser et al. also counted one patient who spontaneously conceived in the study group rather than excluding her [26]. Excluding this one patient would have resulted in a non-significant difference between the two groups. In addition, Kolibianakis reported that the statistical test used by Wiser et al. (Fisher's Exact Test) is not the appropriate test to use since this test requires that the observations are independent from each other [28].

Most recently, Moawad and Shaeer published the second and largest prospective randomized controlled study [29]. They studied the effect of DHEA on patients with poor ovarian reserve undergoing IVF. The study included 133 patients with prior poor response to ovarian stimulation in IVF. Poor response was defined by the production of less than five follicles in prior cycle or whenever the gonadotropins dose was at least 300 IU/day. Patients with AMH level above 1.7 μg/L were excluded. It was not clear how randomization was performed (the authors note that patients were "divided without prejudice into two groups"). The study group included 67 patients who received 25 mg of DHEA three times daily for at least 12 weeks prior to IVF. Sample size was calculated for 80 % power and 5 % level of significance to detect a 30 % increase in oocyte yield in the DHEA arm (it is not clear why the authors chose oocyte yield rather than clinical or ongoing pregnancy rates as studies using oocyte yield are notoriously erroneous secondary to cycle to cycle variability even without any change in stimulation protocol [30]. The amount of recFSH used was significantly lower, and peak estradiol level and endometrial thickness were significantly higher in the DHEA group. Also, the numbers of retrieved oocytes (but not the number of mature oocytes or fertilization rate) and the number of embryos transferred in the DHEA group were higher than the control group, and the cancellation rate was significantly lower in the DHEA group. In addition, the pregnancy rate per cycle was significantly higher in the DHEA group (20.9 % compared to 15.2 %, P=0.048). There were no differences in miscarriage rates between the two groups (5.2 % and 6.4 %, respectively). The study suggested that DHEA improves IVF outcomes in poor responders [31]. Table 1 reviews the published literature in women using DHEA.

How long DHEA supplementation should be initiated before IVF is currently unknown but Barad et al. reported that positive DHEA effects occur within 2 months and peak after 4 to 5 months of supplementation, and therefore suggested DHEA supplementation for at least 6 weeks prior to in vitro fertilization [21]. In addition, they noted a significant numbers of spontaneously conceived pregnancies during this waiting period [21]. Therefore, DHEA alone can raise the spontaneous fecundity rate.

Mechanism(s) of action

The exact mechanism(s) by which DHEA improves ovarian reserve, pregnancy rate, IVF parameters as well as the decreased miscarriage rate is still under investigation, and some have been alluded to above (Table 2). The apparent improvement in miscarriage rate and IVF pregnancy rate may be explained by improving embryo ploidy [22, 23]. The risk of age related aneuploidy is explained by major disturbances in chromosomes alignments on the meiotic spindle of oocytes which is primarily caused from the complex interplay of inter and intracellular signals regulating follicular development. Thus, meiotic chromosomal segregation has a crucial role in age-related aneuploidy. Hodges et al. suggested that changes in oocytes growth would influence meiotic chromosome segregation [32]. DHEA supplementation results in an increased ovarian IGF-1 expression, which is reduced in poor responders [15]. The role of androgens in follicular development was described in multiple studies [33–37]. Increasing intra follicular androgens results in an increased AMH expression by the granulosa cells and inhibin-B production [35]. Androgen receptors have been described in the following: ovarian stroma, theca and granulosa cells, and primary follicles [34]. Fratterelli et al. suggested that a day three-testosterone levels below 20 ng/dl are associated with poorer IVF pregnancy rate [35]. In a follow up study from the same group, there was an association with IVF parameters but not with increased pregnancy [36]. The most recent study investigating the role of androgen and specifically testosterone suggested that transdermal testosterone gel supplementation results in an improved ovarian response to IVF stimulation and IVF outcomes in poor responders [33]. Androgen Receptor

Table 1 Published data on DHEA use in infertile women

Author (Reference)	Number of subjects	Intervention	Study design	Dose of DHEA	Duration
Casson [15]	5	OI/IUI	Case series	80 mg/day	2 months
Barad [19]	1 (Index Patient)	IVF	Case report	75 mg /day	11 months
Barad [20]	25 (1 IVF cycle before and 1 IVF cycle after DHEA)	IVF	Retrospective	75 mg/ day	17.6±2.13 weeks
Barad [21]	89	IVF	Case control	75 mg/day	4 months
Mamas [26]	5 (POF)	4 natural conceptions and 1 clomid + IUI	Case report	50–75 mg/day	3–6 months
Bedaiwy [24]	47 (prior CC failure)	CC/IUI	Case control	75 mg/day	2 months
Sönmezer [25]	19 (poor responders)	IVF/ICSI	Case control	75 mg/day	90–180 days
Wiser [31]	33 (51 IVF cycles)	IVF	Prospective Randomized	75 mg/day	6 weeks
Gleicher [42]	120 (DOR)	AMH measurement	Retrospective	75 mg/day	30–120 days (mean 73±27)
Moawad [29]	133 (poor responders)	IVF	Prospective Randomized	75 mg/day	12 weeks

OI ovulation induction; *IUI* intra uterine insemination; *POF* premature ovarian failure; *CC* clomiphene citrate; *DOR* diminished ovarian reserve

Knock Out female mice have been studied extensively and revealed a reduced androgen signaling, subfertility, defective folliculogenesis, decreased antral follicular count, higher granulosa cell apoptosis and increased resistance to ovarian stimulation with gonadotropins. The granulosa cell specific androgen receptors are critical regulators of normal ovarian development and function [38]. Using the previously mentioned mouse model, Sen et al. concluded that all reproductive phenotypes including decreased antral follicular count, defective folliculogenesis, granulosa cell apoptosis and increased resistance to ovarian stimulation, can be explained by the lack of androgen expression in granulosa cells and those receptors appear to promote pre-antral follicle count and prevent follicular atresia. Therefore, androgen receptors are essential for normal follicular development and female fertility [38].

Gleicher et al. published a review article on the role of androgens in follicle maturation and ovulation induction. Recent data, based on the mouse model, convincingly prove essential contribution of androgens to normal follicle maturation and, therefore, female fertility [39]. Androgens appear most engaged at preantral and antral stages, primarily affect granulosa cells, and exert effects via androgen receptors through transcriptional regulation, with ligand-activated androgen receptor modulating FSH activity in granulosa cells. Therefore, androgens demonstrate a significant effect on the stages of early follicle maturation, and represent a new class in ovulation induction [40]. It is important to note that about 50 % of follicular fluid testosterone during ovarian stimulation comes from circulating DHEAS [41], and DHEA could therefore act as a precursor for testosterone in the follicular fluid. Current studies are ongoing on the mechanism(s) of DHEA's action. Preliminary data suggest that DHEA also increases the antral follicle count, which in turn results in the increase in AMH noted above [42].

Table 2 Potential mechanisms of action of DHEA in infertile women

Potential mechanisms of DHEA action
1- Improves steroidogenesis as a precursor for estradiol and testosterone
2- Influences ovarian follicular growth by acting as a ligand for androgen receptors
3- Increases IGF-1
4- Creation of PCOS-like characteristics and increasing LH
5- Acts as the pre-hormone for follicular fluid testosterone
6- Reduces age-related aneuploidy by affecting meiotic chromosome segregation
7- Increases small antral follicles and AMH levels

Anti Mullerian Hormone (AMH) levels were found to predict treatment outcomes in women on DHEA supplementation [42]. When AMH levels were above 1.05 ng/ml, clinical pregnancy rate, live birth rate, and miscarriage rate were significantly improved with DHEA utilization. Thus, AMH level of at least 1.05 ng/ml was found to be a distinct level for better results [42]. AMH levels were found to increase in parallel with the duration of DHEA supplementation, and this improvement is more pronounced in young patients with primary ovarian insufficiency compared to patients with age-related diminished ovarian reserve [42].

DHEA dose and duration of use

There is no consensus on the optimal or the maximal dose of DHEA, nor the duration of use, though most studies did not exceed 6 months, and to our knowledge, no published data has evaluated the plasma levels of DHEA after supplementation at various time intervals in women with diminished

ovarian reserve. Wiser et al. have used DHEA 25 mg TID in their randomized controlled study [31], the same dose used in Gleicher's and Barad's articles. There are no studies suggesting the different advantages of different forms of DHEA or routes versus others; however, Casson et al. suggested distinct advantages from micronized and oral DHEA [15]. The side effects of such low dosage are minimal and related to its androgenic effects, which include hair loss, oily skin, and acne vulgaris. Other reported effects include better energy and sex drive. The safety of DHEA supplementation was studied by Panjari et al., who suggested that supplementing DHEA in postmenopausal women for 52 weeks was safe [43]. A case report documented a post traumatic seizure after 4 weeks of DHEA supplementation; however, the patient who is 30 years old, had a history of severe head injury at the age of 25 [44]. She had contusions in the left frontal lobe as a result of the accident with a sequel of short memory loss and learning disability [44]. However, Gleicher and Barad in their review paper did not encounter a single complication of clinical significance in over 1,000 patients, and we also did not encounter any significant side effects in over 150 women treated to date [42]. If anything, in agreement with Gleicher and Barad many of our patients felt improved energy and a better libido. In an interesting abstract that has not been published as far as we know, Ryan et al. suggested a higher prevalence of males born with DHEA supplementation after spontaneous conception, Femara with timed intercourse, or ovulation induction with IUI [45], however to our knowledge, this data has not been published in a peer-review journal (other than in an abstract form), and no such data is available for women conceiving with ART.

Conclusions

In the US and Western Europe, women above the age of 38 years and young women with premature ovarian aging and diminished ovarian reserve represent currently a sizable group of infertile patients. A low cost and potentially effective clinical approach such as DHEA supplementation is quite attractive as an adjuvant before ART, with an increase in spontaneous conceptions. In a recent online survey by IVF Worldwide, 25.8 % of respondents (representing 196 centers in 45 countries performing 124,700 ART cycles) used DHEA in their poor responder patients, 97 % of them about 3 months before stimulation start [46]. As mentioned above, DHEA assumes a role in improving the pregnancy rate in young women with premature diminished ovarian reserve as well as decreasing the age related aneuploidy and eventually miscarriage rate in older women with age related diminished ovarian reserve. It is important to note however that all the above studies suffer from improper design, low number of enrolled subjects, and lack of truly randomized trials. Of note, Gleicher and Barad attempted to do two randomized trials but the trials had to be terminated for poor recruitment as prospective women refused to be randomized to the placebo arm. We believe that DHEA supplementation is an emerging concept in improving oocyte/ embryo yields and possibly oocyte quality by affecting the follicular environment. Much remains to be answered however, such as who does and who does not benefit from DHEA supplementation, what is the appropriate (and maximal) dose and duration, best delivery system, whether an altered sex ratio is present, and whether DHEA is of any use in women with undetectable AMH levels (<0.16 ng/ml).

Based on the above studies, DHEA supplementation seems to improve the ovarian environment where follicle maturation takes place, and appears to function by acting on the androgen receptors that are expressed on the granulosa cells and ovarian stroma, resulting in increasing antral follicle counts and AMH levels, and therefore ovarian reserve. While the criticism of the dearth of studies and lack of adequately powered randomized prospective placebo-controlled trials is valid [4, 5, 47], we agree with Gleicher and Barad that these studies will be extremely hard if not impossible to perform [48]. While DHEA's use is considered experimental, until (and if) such studies are published, and considering the absence of significant side effects, the low cost, and the increase in spontaneous pregnancies, we suggest that utilization of DHEA in suitable, consented, and well informed patients may improve ovarian reserve, response to ovarian stimulation, and potentially pregnancy outcome.

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