Review

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Advances in understanding the effect and mechanism of dehydroepiandrosterone on diminished ovarian reserve

Jing Wang[1,2,3,§], Xinyao Pan[1,2,3,§], Jing Zhou[1,2,3], Xin Li[4], Yan Sun[1,2,3,*], Ling Wang[1,2,3,*]

[1] Laboratory for Reproductive Immunology, Hospital & Institute of Obstetrics and Gynecology, Shanghai Medical College, Fudan University, Shanghai, China;
[2] The Academy of Integrative Medicine of Fudan University, Shanghai, China;
[3] Shanghai Key Laboratory of Female Reproductive Endocrine-related Diseases, Shanghai, China.
[4] Urumqi hospital of traditional Chinese medicine, Urumqi, Xinjiang, China.

SUMMARY Diminished ovarian reserve (DOR) refers to the decline in fertility caused by the loss of normal ovarian function. DOR is associated with adverse reactions to ovarian stimulation during *in vitro* fertilization and embryo transfer (IVF-ET), increasing cycle cancellation rates and reducing pregnancy rates. Although it is well known that dehydroepiandrosterone (DHEA) can be used as a dietary supplement for age-related diseases, its potential has gradually been shown for many diseases. In this review, we focus on the effects of DHEA on DOR, briefly analysing its clinical benefits and limitations and describing the mechanism of function and the clinical trials conducted. Therefore, we summarize the mechanisms and indications of DHEA for DOR.

Keywords dehydroepiandrosterone, diminished ovarian reserve, testosterone, *in vitro* fertilization and embryo transfer

1. Introduction

Decreased ovarian reserve (DOR) refers to the loss of the normal reproductive capacity of the ovary due to a decrease in the numbers and quality of remaining eggs. DOR is present in 10-30% of infertility patients, which is a challenge (*1*). Natural ageing leads to a decrease in ovarian reserve, but genetic defects, aggressive medical treatment, certain surgical procedures and injuries may also cause DOR (*2*). DOR is associated with abnormal reproductive results, such as increased embryonic aneuploidy, fertilization failure, and increased miscarriage rates (*3*). Dehydroepiandrosterone (DHEA), which is the most abundant circulating steroid hormone in humans, plays a critical role in various physiological functions (*4*). Oocytes remain in a static state in the unrecruited primordial follicle and do not truly age. Once recruited, they enter an age-related ovarian environment, the quality of which affects the meiotic segregation processes as women age, resulting in aneuploidy. This result suggests that ovarian ageing may be related to the ovarian environment and not limited to the oocyte itself. DHEA may play a role in altering this ovarian environment, thereby preventing follicle ageing (*5*). The role of DHEA in DOR, mainly in artificial reproduction treatment (ART) and *in vitro* fertilization (IVF), is to improve oocyte quality and quantity and significantly improve anti-Müllerian hormone (AMH) levels (*6*). This review provides a critical assessment of the evidence on the use of DHEA supplementation to improve ovarian function in women with DOR.

2. How can DOR be assessed?

DOR is characterized as a decrease in the quantity or quality of the available oocyte pool, an intermediate situation between normal reproductive biology and premature ovarian failure. A decreasing quantity and quality of oocytes in women, usually around the age of 40 years, is a normal physiological phenomenon (*7*). However, some women experience a much earlier than normal decline in ovarian reserve and premature infertility. The main clinical characteristics of DOR include regular period cycles with abnormal ovarian reserve test results but not at postmenopausal levels (*8*). To define DOR, the antral follicular count (AFC) and AMH and follicle-stimulating hormone (FSH) serum levels are the most estimated and frequently used criteria (*9*).

DOR is defined in the Federal Register Notice based on clinically assessed reduced fertility associated with reduced ovarian function and is usually expressed as

an FSH level > 10 mIU/mL or an AMH level < 1.0 ng/mL (*10*). Research on the relationship between ovarian reserve and follicle quality showed that the FSH levels in DOR patients aged < 35 years were ≥ 10 mIU/mL, and the possibility of obtaining immature oocytes in these patients was 4.4-fold higher than that in normal patients. That is, for each unit increase in basal FSH levels, patients were 23% more likely to have an immature oocyte (*11*). In women under 40 years of age, a single abnormal FSH value may not be predictive of DOR, and repeat testing should be performed promptly. When defining DOR patients according to an AMH level < 1.2 ng/mL, women with DOR have a high number of immature and abnormal oocytes, despite having normal FSH levels, suggesting that FSH itself may not be a good indicator of oocyte quality (*12*).

AMH can be considered a major marker of fertility when the ovarian reserve and the pool of growing follicles change (*13,14*). AMH provides a potent marker of the quality of oocytes in young women undergoing controlled ovarian stimulation (COS), as cytoplasmic changes are thought to be the most significant factor in embryo quality and implantation (*15*). Normal perivitelline oocytes were suggested to be associated with a higher fertilization rate and improved embryo development. Some studies were shown that infertile women diagnosed with DOR due to low levels of AMH may also have more follicles in the ovarian cortex than their AMH levels reflect (*16*). Therefore, a low AMH level may not necessarily mean a low number of oocytes (*17*). The linear regression analysis showed that AMH was highly correlated with the cumulative live birth rate in each age group of women, especially with DOR. The inclusion of AMH as a reference indicator will provide more information and personalized prediction of the cumulative live birth rate prior to ART (*18*). However, more supporting research needs to be provided to determine whether AMH can accurately predict follicle numbers.

The AFC refers to the sum of the number of follicles in the two ovaries on Days 2-4 of the menstrual cycle. During *in vitro* fertilization embryo transfer (IVF-ET) treatment, a low AFC predicts a poor ovarian response with high specificity but low sensitivity (*19*). The most commonly reported threshold for predicting adverse reactions is an AFC between 5 and 7 (*20*). AMH levels and the AFC are significant indicators for early identification of DOR before it reaches critical levels (*21,22*). However, the limitations of the AFC lie in the level and judgement of the ultrasound doctor and the tendency of the AFC to overvalue FSH-sensitive follicles and oocyte counts since it inevitably must measure atretic follicles of the same size (*23*).

3. The differences among DOR, POR, and POI

One of the confusing aspects of this topic is that there are several diagnoses and terms associated with DOR. The similarities and differences among concepts related to primary ovarian insufficiency (POI), premature ovarian failure (POF), and poor ovarian response (POR) will be discussed. In clinical diagnosis, POF/POI differs from DOR. DOR is diagnosed by testing for abnormal ovarian reserves in women who have regular menstrual cycles but are not postmenopausal. In contrast, patients diagnosed with POI/POF have postmenopausal FSH levels and no periods for 4 months (*24*). DOR, as a normal physiological process, occurs around the age of 40 years but is pathological if it occurs at a young age. POR refers to a poor ovarian response to IVF stimulation. There is a remarkable overlap between DOR and POR in terms of diagnosis and the corresponding indicators of ovarian reserve. Each specific diagnosis can be found in Table 1.

4. How is DHEA produced and metabolized?

DHEA is a naturally occurring adrenal steroid in mammals. It is synthesized and metabolized from cholesterol to androstenedione and oestrogen (*4*). CYP11A1, a common precursor of all other steroid hormones, transports free cholesterol (FC) to the outer mitochondrial membrane (OMM) through the transport of cytochrome P450 side chain cleavage enzymes (P450scc, CYP11A1) (*25*). Consequent progesterone metabolism produces various bioactive steroids, such as adrenal cortex hormones, ovarian Theca cells, and testicular stromal cells, in a tissue-specific manner (*26*). The synthesis of DHEA is regulated by the hormonal signaling cascade in the hypothalamic-pituitary-adrenal system. Hypothalamus-released corticotropin-releasing hormone stimulates anterior pituitary synthesis and the secretion of adrenocorticotropic hormone (ACTH), partially regulating adrenocortical secretion in adults. Through the ACTH/cAMP/PKA signaling pathway, PKA signals rapidly increase the expression of genes such as STAR, CYP11A1 and CYP17A1 in mitochondria and participate in androgen synthesis and the phosphorylation

Table 1. The diagnostic differences among DOR, POR and POI

DOR	POI	POR	POF
(1).FSH level >10 but nonmenopausal levels (2).AMH level < 1.2 and AFC <10 (3).Failed clomiphene citrate challenge test (4).Regular periods (*10*)	(1).Age < 40 years (2).FSH level > 25 (at least 2 times with an interval of more than 4 weeks) (*63*)	(1).Age ≥ 40 years (2).POR history (3).AMH level < 0.5-1.1 or AFC between 5 and 7 (*64*)	(1).Age < 40 years (2).FSH level > 40 (3).Amenorrhea ≥ 4 months (*65*)

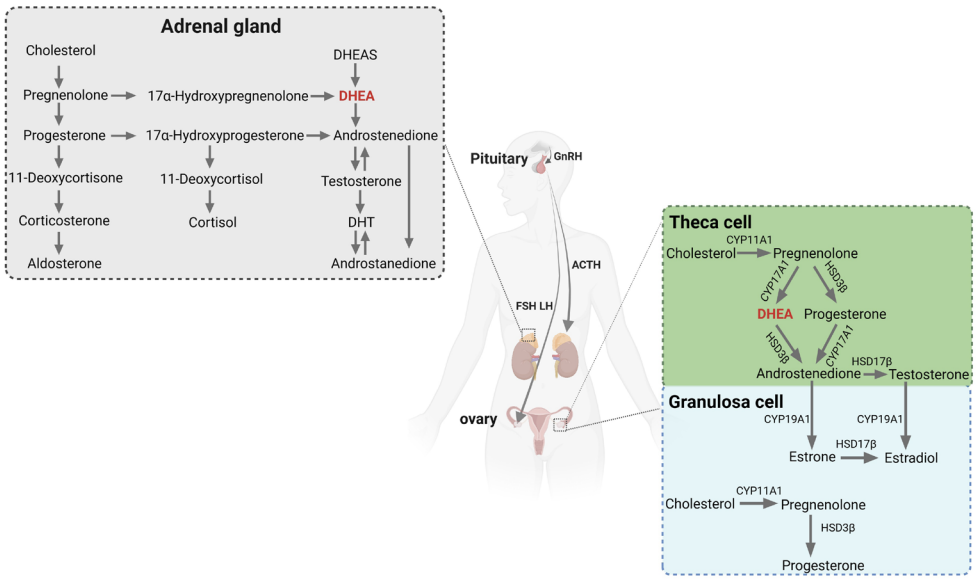

Figure 1. The synthesis and metabolism of DHEA in the adrenal glands and ovaries. The biosynthesis of DHEA involves the secretion of different hormones by the hypothalamus acting on the adrenal glands and ovaries respectively, including ovarian Theca cells, granulosa cells and adrenal cortical cells. Created with BioRender.com.

of transcription factors (*27*). CYP17A1 is an integral membrane protein in the endoplasmic reticulum that transfers electrons from NADPH to CYP17A1 (*28*). DHEA of sulfuric acid can be generated in the adrenal cortex through the 3β′-hydroxyl group. DHEA can be converted to androstenediol by 17β-hydroxyl steroid dehydrogenase (HSD17B) in the adrenal cortex, both of which can eventually be converted to testosterone. Testosterone can transform dihydrotestosterone (DHT) by 5α reductase (SRD5A). The two-cell system cooperates in a specific cycle pattern to stimulate the production of androgens in ovarian Theca cells and oestrogen in granulosa cells (*29*). Testosterone is converted into oestradiol 17β in granulosa cells through the action of CYP19A1 in the theca cells of the ovary (*30*). In short, both the adrenal gland and ovarian tissue can produce T, Δ4A, and DHEA and release them into surrounding tissues for use (Figure 1).

5. Mechanism of DHEA for DOR

The most exclusive function of DHEA is that it can be metabolized to potent androgens and oestrogens (*31*). Supplementation with DHEA appears to produce more precise results and cause fewer adverse side effects than supplementation with testosterone (*32,33*). DHEA converts intracellularly to androgens with no significant active testosterone released into the blood (*33,34*). In addition, DHEA enhances the ovarian response to the androgen pathway and may serve as a ligand for androgen receptor (AR) along with FSH to promote follicle formation through increased numbers of primary, preantral and antral follicles (*35*). With DHEA supplementation, the expression of FSH receptor (FSHR) is enhanced in granulosa cells (*36*) (Figure 2). Studies have also demonstrated that DHEA upregulates serum AMH and inhibin B (INHB) levels as well as paracrine insulin-like growth factor-1 (IGF-1), which contributes to the recruitment of follicles to improve the ovarian response (*37*). However, some studies have reported that AMH or INHB levels did not increase significantly, while a noticeable increase in AFC was observable. Thus, an increased AFC suggests that preventing atresia of the small antral follicles may be one of the potential mechanisms by which DHEA exerts its effect. Zhang *et al.* (*38*) published a meta-analysis of changes in AMH levels and the AFC after DHEA supplementation, which showed that DHEA treatments increased the AFC. In another self-control study, the results showed a significant improvement in AMH levels in the DHEA self-control group (*39*). However, when comparing AMH levels between the DHEA and placebo groups, there were no significant differences observed between pre- and post-supplementation. Therefore, the impact of DHEA supplementation on ovarian reserve markers remains controversial. Further trials are required to investigate the potential effects of DHEA on ovarian reserve markers and pregnancy hormones. DHEA regulates many genes involved in molecular mitochondrial morphological changes. DHEA significantly increases the gene expression of the outer mitochondrial membrane protein mitofusin-1 (MFN1) and regulates optic atrophy 1 (Opa1) fusion of the inner mitochondrial membrane. Although DHEA had difficulty improving the expression of fusion genes, the expression of the split genes DNM1L and mitochondrial fission factor (Mff) was significantly reduced. This also shows that DHEA supplementation greatly reduces the expression of fission genes (*40*). DHEA can increase the function and activity of mitochondria, reduce the apoptosis and

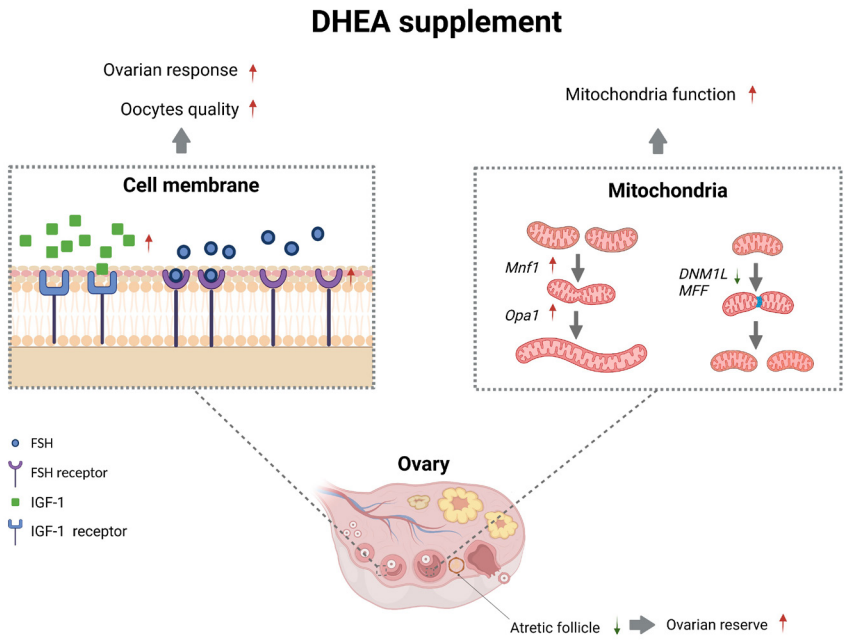

Figure 2. The mechanisms of DHEA for DOR. DHEA increases the expression of FSHR through the AR signal pathway, promotes the growth of preantral follicles, and reduces follicular atresia. DHEA reduces the expression of fission genes DNMIL and MFF genes and enhances the mitochondrial function. Elevated IGF-1 expression can promote follicle maturation and steroid production. Created with BioRender.com.

cell necrosis of cumulus cells (CCs) and human granular cell lines, and delay the ageing of CCs. In addition, DHEA also reduces mitochondrial division and increases the clearance of poorly mitotic mitochondria (*41*). Dr. Narkwichean (*42*) showed that DHEA may slightly alter the microenvironment of the primate ovary by reducing damage to DNA and apoptosis and increasing the mass of mitochondria, the activity of mitochondrial dehydrogenase and the expression of mitochondrial transcription Factor A (TFAM) in CCs (*43*).

6. ART results of DHEA supplementation for DOR

Women with DOR usually respond poorly to COS in ART cycles, and approximately 5-18% of IVF cycles conclude with POR, yielding successful pregnancy rates as low as 2% to 4%. There may be a poor response to COS, which means that fewer oocytes can be obtained according to the standard IVF protocol and that not enough good-quality embryos can be transferred, which leads to a poor reproductive prognosis. Shiqiao Hu (*44*) compared the birth rates of non-DOR patients and DOR patients undergoing ART fresh embryo transfer (ET) cycles. Dr. Yeung (*45*) randomly assigned 32 women to receive DHEA supplementation before IVF treatment. The results showed that pretreatment with DHEA in women undergoing IVF for DOR did not improve their prognosis, while no differences were found in the number of oocytes retrieved, IVF cycle cancellation rates or miscarriage rates (*29,45-47*). However, some retrospective studies revealed the opposite conclusion. Dr. Sonmezer reported that DHEA-treated DOR patients had not only increased numbers of > 17 mm follicles and MII oocytes but also high-quality 2-3 day embryos (*48*). Another report also showed an increased number of > 15 mm follicles, MII oocytes and embryos after DHEA supplementation (*49*). Dr. Kotb MM (*50*) started a study with 140 women with POR who were undergoing ART. Regarding the oocyte count and fertilization rate, the DHEA group had significantly higher clinical pregnancy rates and sustained pregnancy rates. Dr. Yeung's experiments showed a similarity in the size and numbers of oocytes in the two groups, while the fertility rates and numbers of high-quality embryos were higher in the DHEA group (*51*). In a meta-analysis, the clinical pregnancy rates were significantly increased in patients with DOR who received DHEA pretreatment; however, when the data were restricted to randomized controlled trials, there was no statistically insignificant difference in the clinical pregnancy rates (*52*). Regarding the abortion rate, there was no difference between women who received pretreatment with DHEA and those who did not (*46*). A meta-analysis by Xu L (*53*), including 9 prospective randomized controlled trials (RCTs) and 833 patients, showed that patients treated with DHEA had improved oocyte retrieval, clinical pregnancy and live birth rates compared to controls. During the 12 weeks before IVF, subjects received three doses of 25 mg DHEA or placebo daily (*54*).

The POSEIDON classification, which combines ovarian reserve markers with age, COS and other risk factors targeted to treatment, has positive results in predicting adverse effects. Some studies have demonstrated improved oocyte and embryo production and cumulative pregnancy rates in women classified in POSEIDON Group 4 who receive DHEA supplements.

Table 2. Summary of clinical studies on IVF in DOR patients with DHEA treatment

First author/Year	Group	Dosage	Conclusion
MD Ozcil, 2020 (*6*)	DHEA (*n* = 34)	50 mg	DHEA improves ovarian reserve and pregnancy rates in women with POR
Qiaofei H, 2017 (*66*)	DHEA (*n* = 53) Control (*n* = 50)	25 mg	DHEA increased the expression of AR in granulosa cells
Agarwal R, 2017 (*39*)	DHEA (*n* = 20) Control (*n* = 20)	25 mg	DHEA increased AMH expression
Zhang H, 2016 (*67*)	DHEA (*n* = 64) DHEA + climen (*n* = 60)	25 mg	DOR with low FSH levels may benefit more from DHEA and climen supplementation
Haydardedeoğlu B, 2015 (*68*)	DHEA (*n* = 44) Control (*n* = 22)	25 mg	DHEA may reduce aneuploidy in the embryos of women with DOR
Gleicher N, 2013 (*69*)	DHEA (*n* = 44) Control (*n*= 213)	75 mg	DHEA significantly improves ovarian reserve, especially in young women
Weissman A, 2011 (*70*)	DHEA (*n* = 15) Control (*n* = 15)	75 mg	DHEA increases circulating progesterone concentrations
Gleicher N, 2009 (*71*)	DHEA (*n* = 73)	25 mg	DHEA significantly reduces the miscarriage rate in DOR patients over 35 years old
Casson PR, 2000 (*72*)	DHEA (*n* = 5)	80 mg	DHEA improves the ovarian response and reduces the gonadotropin dosage

In addition, DHEA supplementation in patients over 40 years of age may improve cumulative pregnancy rates (*55*). A lack of uniform evidence-based methodology and inclusion criteria exists for clinical studies, as well as heterogeneity in IVF treatment protocols, so there is conclusive evidence on clinical data (Table 2).

7. The dosage, duration and side effects of DHEA supplementation

A meta-analysis included patients with DOR who were treated with DHEA at a dose of 75 mg per day in RCTs (*53*). Another study also showed that most people tolerated a DHEA dose of 75 mg/day well (*56*). The dose of DHEA varies from 50 to 90 mg/day, and the treatment duration ranges from 1 to 12 months. For patients with adrenal insufficiency, the initial dosage of DHEA is 25-50 mg per day orally, with symptomatic improvement and an expected treatment duration of at least 4-6 months. Because DHEA may have side effects similar to those of androgens, lower doses (25-30 mg/day) may be better for long-term treatment (*57*). However, no pharmacological studies have been conducted to determine the optimal dose, duration, or timing of DHEA supplementation in patients with DOR (*58*). As dietary supplements, DHEA formulations are not regulated by the Food and Drug Administration (FDA) for pharmaceutical quality. Therefore, there is no guarantee of standardization of the formulations used (*59*).

Dr. Karp (*60*) demonstrated that DHEA could cause seizures. Furthermore, DHEA may also cause oily skin, acne and unnecessary female- or male-pattern hair growth (hirsutism) (*61*). DHEA should not be taken for seizures by women with liver dysfunction, hypertension, acute manic symptoms, convulsions and palpitations (*60,62*). Further studies are needed to provide more evidence of side effects and to optimize DHEA supplementation for the best efficacy.

8. Conclusion

DHEA is an important steroid in a variety of physiological processes and its therapeutic effects are gradually being shown in research. The exact underlying mechanism by which DHEA affects the ovaries and embryos has not been fully demonstrated, so further evidence of the effects of DHEA pretreatment in patients with DOR and its role in IVF-ET needs to be verified. The differences in the results of different studies may lie in differences in the definition of DOR, the use of COS, the dosage of DHEA and the duration of DHEA treatment. The role of DHEA on DOR needs to be supported by more data.

Further DHEA research has shown DHEA to have great potential for dealing with multiple physiological processes and sheds light on the treatment of several gynaecological diseases. Supplementation with DHEA in women with DOR who are planning to undergo IVF/ICSI remains controversial, and more experiments are needed to prove its effectiveness. A variety of trials including women selected by Bologna criteria have analysed serum levels as well as clinical pregnancy rates as major outcomes to evaluate the effect of DHEA. DHEA achieves its action in DOR patients by multiple mechanisms, which may result in the complex evaluation of the outcomes. However, some of the trials have proven that DHEA does exert an influence on the results, and some have hardly reached statistical significance. Through various randomized and double-blind prospective clinical trials, a standard evaluation system should be built to measure the outcomes more scientifically.

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[§]These authors contributed equally to this work.
**Address correspondence to:*
Ling Wang, Obstetrics & Gynecology Hospital of Fudan University, 419 Fangxie Road, Shanghai, China 200011.
E-mail: dr.wangling@fudan.edu.cn

Yan Sun, Hospital & Institute of Obstetrics and Gynecology, Fudan University, 128 Shenyang Road, Yangpu, Shanghai, China 200081.
E-mail: ysunsh@126.com

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