Review

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Dehydroepiandrosterone improves the ovarian reserve of women with diminished ovarian reserve and is a potential regulator of the immune response in the ovaries

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Summary **Diminished ovarian reserve (DOR) has a high morbidity rate worldwide and has become a primary cause of infertility. DOR is a daunting obstacle in *in vitro* fertilization (IVF) and leads to poor ovarian response, high cancellation rates, poor IVF outcomes, and low pregnancy rates. Abnormal autoimmune function may also contribute to DOR. Dehydroepiandrosterone (DHEA) is a C19 androgenic steroid. DHEA is secreted mainly by the adrenal gland, and its secretion declines with age. DHEA has a pro-inflammatory immune function that opposes cortisol. The cortisol to DHEA ratio increases with age, which may lead to decreased immune function. DHEA supplementation helps improve this situation. A number of clinical case control studies and several prospective randomized clinical trials have observed a positive effect of DHEA supplementation in women with DOR. However, the underlying mechanism by which DHEA improves ovarian reserve remains unclear. DHEA functions as an immune regulator in many different tissues in mammals and may also play an important role in regulating the immune response in the ovaries. The conversion of DHEA to downstream sex steroids may allow it to regulate the immune response there. DHEA can also enhance the Th1 immune response and regulate the balance of the Th1/Th2 response. DHEA treatment can increase selective T lymphocyte infiltration in mice, resulting in a decline in the CD4+ T lymphocyte population and an upregulation of the CD8+ T lymphocyte population in ovarian tissue, thus regulating the balance of CD4+/CD8+ T cells. This review mainly focuses on how DHEA supplementation affects regulation of the immune response in the ovaries.**

Keywords: Dehydroepiandrosterone (DHEA), diminished ovarian reserve (DOR), immune response, cytokine, lymphocytes, endocrino-immune network

1. Introduction

Ovarian reserve decreases within a certain range as women age. Women with a lower ovarian reserve outside of this range are identified as having diminished ovarian reserve (DOR). Reduced ovarian reserve consists of a decline in the number of primordial follicles, a decrease in the size of the dynamic reserve of small antral follicles, and a deterioration in oocyte quality. These changes are evident as women age. Some genetic mutations and disorders of the endocrine system can accelerate or modulate the rate at which the ovarian reserve is exhausted and cause premature ovarian insufficiency (POI) (*1*). Among the various causes of DOR, abnormal immune function may be a great contributor to this phenomenon (*2*). Patients with DOR often become infertile and have a poor response to *in vitro* fertilization (IVF) (*3,4*). Researchers have developed different protocols to solve this problem, but none of them has proven to be ideal for such patients (*5-7*). Dehydroepiandrosterone (DHEA) is a C19 androgenic steroid that has been found to be effective in many areas. Decades of observational

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studies both in clinical settings and in animals have found that the levels of DHEA(S) are inversely associated with cardiovascular risk, morbidity, and mortality (*8*). In ovariectomized rabbits, DHEA was found to protect against atherosclerosis because it alleviated inflammation in endothelial cells (*9*). DHEA is able to cross the brain-blood barrier. DHEA also has neuroactive characteristics and it has positive effects on human mood, emotions, and behaviors (*10,11*). In 2000, Casson *et al*. were the first to use DHEA supplementation in women with DOR to improve the response to ovarian stimulation (*12*). Many researchers have devoted their attention to the effects of DHEA supplementation in women with DOR. Narkwichean *et al*. conducted a meta-analysis that showed that DHEA administration resulted in a significant increase in the number of oocytes retrieved in women with DOR according to some clinical trials. However, more clinical trials must be performed to verify the results (*13*). In ovariectomized sheep, DHEA supplementation was effective at *in vivo* ovarian folliculogenesis (*14*). Similar results have been observed with Wistar rats in an *in vivo* model (*15*). However, the underlying mechanism by which DHEA improves ovarian reserve remains unclear. DHEA can regulate immune cell function (*16*), and it may regulate the function of many different types of tissue in mammals. Utilizing a human subcutaneous preadipocyte cell line, Chub-S7, McNeils *et al*. found that DHEA inhibition of the amplification of glucocorticoid action was mediated by 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) (*17*). Lazaridis *et al*. performed an *in vitro* study that showed that DHEA also served as a neurosteroid, directly interacting with nerve growth factor (NGF) to prevent neuronal apoptosis (*18*). In ovariectomized rats, DHEA showed the potential to correct oxidative stress-induced endothelial dysfunction (*19*). Thus, DHEA may play an important role in regulating the immune response in the ovaries. DHEA treatment may also modulate the lymphocyte response in both human and animal trials (*20,21*). The current review mainly focuses on how DHEA supplementation affects regulation of the immune response in the ovaries.

2. DHEA supplementation has proven effective in women

DHEA (5-androsten-3β-ol-17-one) is a C19 androgenic steroid (Figure 1) that is secreted primarily by the adrenal zona reticularis. DHEA is synthesized by the steroidogenic enzyme P450c17 and partly by the ovary (*22*). The secretion of DHEA has a diurnal rhythm similar to that of cortisol (*23,24*). In humans, the intra-individual concentrations of DHEA and its sulphate, DHEAS, steadily decline with advancing age, unlike those of other androgenic steroids. The concentration peaks during the third decade of life, with a clear sex

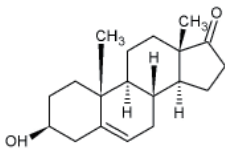

Figure 1. Chemical structure of DHEA.

difference since adult women have lower concentrations of DHEA than men (*25-27*). Given this characteristic of age-related decline, DHEA supplementation may help to improve age-related damage in human beings. To date, no studies have noted an apparent effect of DHEA in healthy males (*28*). Some double-blind placebo-controlled trials have demonstrated that DHEA does not markedly improve well-being or cognitive function in healthy elderly men and women over age 50 (*28,29*). However, DHEA was found to modulate immune function in postmenopausal women (*30*). DHEA is also reported to affect cardiovascular and immunological function differently in women and men (*31*).

2.1. *The effects of DHEA supplementation in women with DOR*

There are no set criteria for DOR thus far, but women with DOR share a poor ovarian response to stimulation as well as high cancellation rates and low pregnancy rates. A poor ovarian response in a previous IVF-embryo transfer (ET) cycle means that fewer oocytes were retrieved or that these oocytes were less mature follicles after high-dose gonadotropin stimulation. Different researchers have defined this process differently. Many studies have investigated the effects of DHEA supplementation on ovarian function. Twelve of those studies were analyzed in the current study (see Table 1). DHEA supplementation is usually oral and administered at 25 mg, three times a day, or 75-90 mg for the entire day, for 6 to 24 weeks. A previous case-control study showed that DHEA improved ovarian reserve and that it significantly increased antral follicle counts (AFCs), anti-Müllerian hormone (AMH) levels (*32-34*), numbers of fertilized oocytes, normal day 3 embryos, embryos transferred, and the average embryo score per oocyte (*35*) while significantly decreasing day 3 follicle-stimulating hormone (FSH) (*33*), fertilized aneuploid embryos (*36*), and miscarriage rates (*37*) (all p-values < 0.05). Estradiol (E2) levels tripled according to two studies (*12,38*) but decreased according to a third (*34*). Several randomized prospective controlled studies investigated the effects of DHEA supplementation but their results were inconsistent. Some researchers obtained the same results as described earlier (*34,38-40*), but the number of oocytes retrieved and the fertilization rate remained inconsistent (*38,40,41*), whereas others failed to show that DHEA was effective at improving IVF outcomes (*40,41*). These studies,

Table 1. Efficacy of DHEA supplementation prior to IVF cycle

(Table continued on next page)

Ref.	Definition of DOR	Study type	Methods			Result (P value)	Conclusion
			Study object	Route of medication	Dose		
Casson *et al.* (*12*)	Poor response to high-dose gonadotropin stimulation (peak E2 < 500 pg/mL and mature follicle ≤ 2)	A series of case studies	5 women with unexplained infertility (under age 41, FSH < 20 mIU/mL)	Oral, twice a day for 2 months, prior to IUI	80 mg	↑ DHEAs, testosterone, responsiveness, peak E2, and E2/ampoule ratio (0.012). One achieved twin pregnancy. The E2 level tripled in all five cases. The number of oocytes doubled	It improves the response to ovarian stimulation after controlling for gonadotropin dose
Barad *et al.* (*35*)	FSH > 10 mIU/mL or E2 >75 pq/mL (275.3 pmol/L)	Case-control study	25 women with DOR and repeated IVF failure	Oral, three times a day, for 17 ± 2.13 weeks	25 mg	↑ fertilized oocytes (< 0.001), normal day3 embryos (< 0.001), embryos transferred (0.005) and average embryo score per oocyte (< 0.001)	Confirms the previously reported beneficial effects of DHEA supplementation on ovarian function in women with DOR
Gleicher *et al.* (*37*)	FSH > 10 mIU/ml or E2 > 75 pq/mL (275.3 pmol/L)	Case-control study	22 consecutive patients with DOR	Oral, three times a day	25 mg	↓ miscarriage rate at all ages, but most pronounced above age 35	Miscarriage rates after DHEA were not only lower in an average IVF population but were comparable with rates reported in normal fertile populations
Gleicher *et al.* (*36*)	abnormally elevated age-specific baseline FSH or abnormally low age-specific AMH	1:2 matched case control study	120 women with DOR	Oral, three times a day, for at least 4 weeks	25 mg	↓ number (= 0.029) and percentage (< 0.001) of aneuploid embryos	Beneficial DHEA effects on DOR patients are the likely consequence of lower embryo aneuploidy
Gleicher *et al.* (*32*)	AMH concentrations were evaluated as a reflection of ovarian reserve	Retrospective cross-sectional and longitudinal analysis	15 women with DOR	Oral, three times a day, for 73 ± 27 days	25 mg	↑ AMH concentrations (= 0.002) and women age < 38 responded more than women who were older. AMH improved pregnancy rates longitudinally by 60% (< 0.0002), and IVF, by 23.64%, compared with those not treated (= 0.001)	DHEA supplementation significantly improved ovarian reserve in parallel with longer DHEA use and improvement was more pronounced in younger women
Weissman *et al.* (*89*)	Poor ovarian response in previous IVF-ET cycles (high-dose gonadotropin stimulation: < 5 oocytes retrieved, ≤ 3 follicles of 16 mm or larger each on the day of cycle cancellation, serum E2 level < 500 pg/mL on the day of hCG administration)	Case-control study	41 women (age ≤ 40 years) with DOR were divided into two groups: age < 35 or ≥ 35	Oral, once a day during the follicular phase in IVF	75 mg	↑ progesterone on day 5 of stimulation (< 0.0001); increased progesterone on the day of hCG administration (< 0.0001); Similar number of retrieved and fertilized oocytes	DHEA administration during IVF cycles in women with DOR causes a significant elevation of progesterone levels without an apparent deleterious effect on cycle outcome
Yilmaz *et al.* (*33*)	AFC < 5 or AMH < 1.1 ng/mL and a previous poor ovarian response	Case-sectional study	280 women (mean age 30.97 ± 5.76 years) were divided randomly into two groups: 104 women in the DHEA group and 104 women in the control group	Oral, three times a day prior to assisted reproductive technology for at least 6 weeks	25 mg	Significant differences were seen in both groups after DHEA supplementation: ↑ AFC (0.001), AMH (0.002) and inhibin B (0.001), ↓ day 3 FSH (0.001) and estradiol (0.001).	DHEA supplementation is an effective option for patients with DOR as an alternative to oocyte donation prior to assisted reproduction

Abbreviations: ↑, increased; ↓, decreased; DHEA, dehydroepiandrosterone; DOR, diminished ovarian reserve; POR, poor ovarian reserve; E2, estradiol; AMH, anti-Müllerian hormone; FSH, follicle stimulating hormone; LH, luteinizing hormone; IVF, *in vitro* fertilization; IUI, intrauterine insemination; IVF-ET, *in vitro* fertilization-embryo transfer; AFC, antral follicle count; POI, premature ovarian insufficiency; IVF-ICSI, *in vitro* fertilization-intracytoplasmic sperm injection; BMP-15, bone morphogenetic protein-15.

Table 1. Efficacy of DHEA supplementation prior to IVF cycle

(Table continued)

Ref.	Definition of DOR	Study type	Methods			Result (P value)	Conclusion
			Study object	Route of medication	Dose		
Kara *et al.* (*41*)	POR: serum AMH < 1 ng/mL or serum FSH > 15 IU/L and AFC < 4 on day 2 of the menstrual cycle.	Randomized, prospective controlled study	280 women (mean age 30.97 ± 5.76 years) were divided randomly into two groups: 104 women in the DHEA group and 104 women in the control group	Oral, once a day prior to IVF-ICSI	75 mg	The number of oocytes retrieved and the fertilization rate are slightly higher in the study group. The pregnancy rate is higher in the control group. No significant difference can be observed	Failed to show that DHEA supplementation enhances IVF-ICSI outcomes in women with poor ovarian reserve
Zhang *et al.* (*38*)	Fulfills any of the following: (1) day 3 FSH level ≥ 10 nIU/L or FSH/LH > 3:2; (2) AFC < 5; or (3) a previous poor ovarian response to ovarian stimulation: retrieval of fewer than five oocytes or cycle cancellation due to poor response to ovarian stimulation	Randomized, prospective controlled study	95 women with DOR were divided randomly into two groups: 42 in the DHEA group and 53 in the control group.	Oral, once a day for 3 consecutive menstrual cycles before entering IVF cycle	75 mg	The DHEA group had a significant increase in the serum level of AMH (0.015), FSH (0.036) and E2 (0.002), BMP-15 in follicular fluid samples (0.000), and the accumulated score of embryos (0.033)	Confirms the beneficial effect of DHEA for infertility patients with DOR
Poli *et al.* (*40*)		Experimental prospective, pre-post study	29 women with DOR or a poor response in a prior IVF cycle	Oral, once a day for 8 weeks before stimulation with FSH in IVF cycle.	75 mg	Significant increase in the number of the retrieved oocytes (< 0.01) and the oocyte quality (0.002). Significant decrease in cancelled IVF cycles (0.003)	Confirmed the beneficial effect of DHEA in patients who were poor responders to IVF treatments. DHEA appears to be an effective treatment for age related sub-fertility.
Tsui *et al.* (*34*)	POR: Individuals to whom the following apply: (1) FSH > 15 nIU/L or AMH < 1 ng/mL; (2) abnormally low AFC < 4 on day2 of their menstrual cycle; (3) an unsuccessful flexible daily GnRH antagonist in the first IVF cycle	Prospective study	10 women with POR	Oral, three times a day prior to next IVF cycle for 3 months (mean: 12.2 weeks)	30 mg	Significant increase in AFC (< 0.05), AMH (< 0.001), numbers of retrieved oocytes (< 0.01), fertilized oocytes (< 0.001), day 3 embryos (< 0.001), and transferred embryos (< 0.01). Significant decrease in Day 3 FSH and E2 (both < 0.001)	The potential benefits of DHEA supplementation in women with POR were suggested by biochemical parameters and IVF outcomes.
Tartagni *et al.* (*39*)	Out of the normal range: (1) Day 3 FSH < 10 IU/L; (2) AMH:2.8~6.8 ng/L; (3) inhibin > 45 pg/mL	Double blind, randomized, placebo-controlled study	109 infertile patients (ages 36-40 and failed in the first IVF cycle) were divided into 2 groups: (1) DHEA group and (2) control group.	Oral, once a day, from 8 weeks before next IVF cycle	75 mg	Significantly higher live birth rate (< 0.05) in the DHEA group and significantly higher miscarriage rate in the control group (< 0.05).	DHEA may significantly improve IVF outcomes in infertile women with advanced reproductive age and normal ovarian reserve.

Abbreviations: ↑, increased; ↓, decreased; DHEA, dehydroepiandrosterone; DOR, diminished ovarian reserve; POR, poor ovarian reserve; E2, estradiol; AMH, anti-Müllerian hormone; FSH, follicle stimulating hormone; LH, luteinizing hormone; IVF, *in vitro* fertilization; IUI, intrauterine insemination; IVF-ET, *in vitro* fertilization-embryo transfer; AFC, antral follicle count; POI, premature ovarian insufficiency; IVF-ICSI, *in vitro* fertilization-intracytoplasmic sperm injection; BMP-15, bone morphogenetic protein-15.

however, cannot be compared statistically since there were no set criteria to define DOR. Usually, DOR was defined as abnormally elevated age-specific baseline FSH levels and/or abnormally low AMH levels (*42-44*), elevated inhibin-B levels, and AFCs less than 4 to 5 (*33,34,38,41*).

2.2. *Immune function of DHEA*

Use of DHEA has been described in many areas and is mainly considered because of its immunoregulatory function. DHEA has an effect on human neuroendocrine cells and plays an important role in immune regulation, especially by balancing pro-inflammatory and anti-inflammatory signals. Humans develop inflammation with age, which involves the up-regulation of certain pro-inflammatory cytokines, such as interleukin (IL)-1, IL-6, tumor necrosis factor (TNF)-α, IL-12, interferon (IFN)-α, and IFN-β. In old age, these cytokines negatively impact various systems in the body (*45-47*). This leads to an unbalanced relationship between pro-inflammatory cytokines and anti-inflammatory cytokines (IL-4, IL-6, IL-13, IL-10) (*48*). DHEA is part of the hypothalamus-pituitary-adrenal (HPA) axis. When the HPA axis is activated, both cortisol and DHEA are released. Cortisol has an anti-inflammatory effect, whereas DHEA appears to have an opposing effect. As DHEA levels decline with age, the molar ratio of cortisol to DHEAS increases and may interact with weakened immune function (*49,50*). Elderly bereaved participants showed decreased production of neutrophil reactive oxygen species and an increased cortisol to DHEAS ratio (*10*). DHEA supplementation has a positive effect on immunity in the elderly. Treatment with 20 mg/kg DHEA for 8 weeks reversed antioxidant parameters, such as decreased superoxide dismutase activity in the brain and heart, decreased inducible nitric oxide synthase mRNA levels, and increased heme oxygenase mRNA levels, in aged rats (*51*). Buoso *et al*. found that cortisol acted in a dose-related manner *in vitro* and *in vivo* on human guanine nucleotide binding protein and the beta polypeptide 2 like 1 (GNB2 L1) promoter repressor, which reduced receptor for Activated C Kinase 1(RACK-1) mRNA and protein expression. Prolonged DHEA exposure counteracted the effects of cortisol and restored RACK-1 levels and cytokine production (assessed with lipopolysaccharide (LPS)-induced TNF-α release); this most likely occurred as a result of interfering with glucocorticoid receptor binding to the glucocorticoid responsive element (GRE) sequence (*52*). Furthermore, DHEA supplementation has been proven to be effective in treating other diseases and improving organ function and survival. However, these mechanisms are not yet fully understood. Over the past few years, an increasing number of researchers have turned their attention to the effects of DHEA on regulation of the immune response, but these effects have been produced in non-human mammals. In aged baboons, researchers found increased serum C-reactive protein and increased cytokine release from unstimulated peripheral blood mononuclear cells. Supplementary DHEA improved outcomes in a murine polymicrobial sepsis and trauma model by restoring TNF-α in the liver and lungs after 48 hours and attenuating it in the liver after 96 hours, much like a time- and organ-dependent modulator (*53*). DHEA supplementation also leads to a restoration of splenocyte proliferation, a decrease in the rate of cellular apoptosis of splenocytes, and an attenuation of increased IL-6 levels (*54*). DHEA also restored peripheral blood mononuclear cell (PBMC) function and increased the ability of human PBMCs patients with depressed immune function to release pro-inflammatory cytokines (IL-1β, IL-6, and TNF-α) following major abdominal surgery (*55*).

Table 2. Types of autoimmune abnormalities

Type of auto-antibody	Containing
Antinuclear antibody	–
Anti-phospholipid antibody	lupus anticoagulant, anti-phosphatidylserine, anti-cardiolipin, β2-glycoprotein (IgG, IgM, IgA)
Anti-thyroid antibodies	anti-thyroglobulin, anti-thyroid peroxidase
Anti-adrenal antibodies	anti-21-hydroxylase
Anti-ovarian antibodies	non-specific
Total immunoglobulins	IgG, IgM, IgA, IgE

3. DHEA and the immune response in the ovaries

The level of the immune response in the ovaries changes with age along with the ovarian reserve. There is substantial interaction between the immune system and the ovaries as immune cells are associated with regulation at every level of the hypothalamus-pituitary-ovarian axis by regulating growth and regression of both follicles and the corpus luteum (*56-58*). In adult ovaries, activated myeloid dendritic cells (MDC) also play a role in follicular development and atresia, as well as differentiation of the corpus luteum. MDC and T cells massively infiltrate the corpus luteum, resulting in parenchymal and vascular regression, which then leads to the demise of the corpus luteum (*59*). DHEA improves the ovarian reserve of women with age-related DOR women with POI even though POI is more closely related to ovarian immune disorders. Young women who have a history or family history of autoimmunity are at risk for POI (*60,61*). There are many types of autoimmune abnormalities (Table 2). There are three different types of autoimmune ovarian insufficiency: autoimmune ovarian insufficiency associated with adrenal autoimmunity, autoimmune

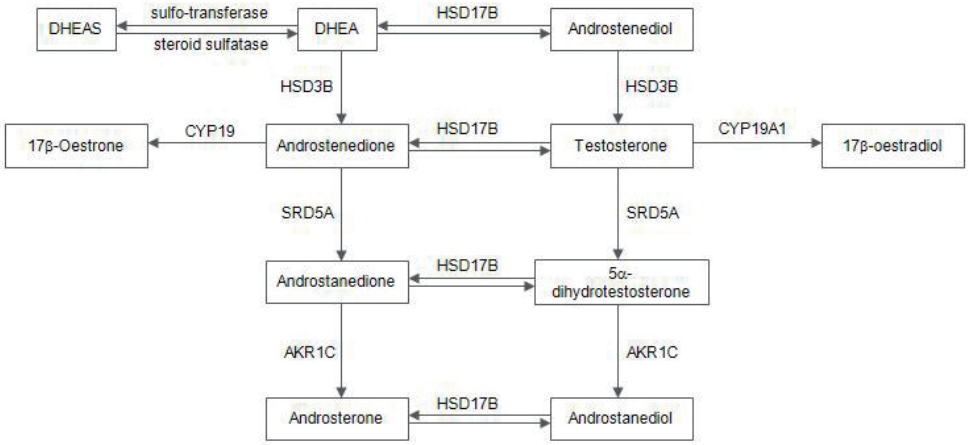

Figure 2. Path for conversion of DHEA to other downstream steroids. Abbreviations: DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone sulphate; HSD17B,17β-hydroxysteroid dehydrogenase isoenzymes; HSD3B, 3β-hydrogenase isoenzymes; CYP19A1, P450 aromatase; SRD5A, 5α-reductase isoenzymes; AKR1C, 3α-hydroxysteroid dehydrogenase isoenzymes.

ovarian insufficiency associated with non-adrenal autoimmunity, and isolated idiopathic POI (iPOI) (*62*); adrenal autoimmunity is the most prevalent (*2,63*). Researchers tested for triple CGG repeats on both alleles of the fragile X mental retardation 1 (FMR1) gene and assessed autoimmune status (including an antiphospholipid antibody panel, an antinuclear antibody panel, total immunoglobulin levels, thyroid antibodies, and antiadrenal antibodies), and then they found that abnormal autoimmune function, including expansions in triple CGG repeats on the FMR1 gene, increased the risk for POI (*64,65*).

Although the effects of DHEA supplementation in women with DOR are readily evident, the mechanism behind these effects remains unclear. Given the complex immune function of DHEA and ovarian immune disorders in women with DOR, some researchers have begun to explore the immune function of DHEA in women with DOR. However, the research reports to date on this topic are extremely limited. Only a few studies have been conducted and their results are summarized below.

3.1. *Conversion to other steroids*

No certain specific receptor for DHEA has been found to date, and some theories suggest that DHEA may function once steroidogenic enzymes convert it to other downstream steroids, especially sex steroids such as estrone and androgens (Figure 2). Small structural changes in androgens result in markedly different biological effects. Steroidogenic enzymes have tissue-specific patterns of expression; thus, DHEA may have a special function. These steroids interact critically with immune function. Estrone can shift the female immune system to a Th2-type response in the luteal phase, whereas postmenopausal women often exhibit enhanced Th1 cytokines (*66*). As mentioned previously, DHEA can restore PBMC function and increase the ability of human PBMCs to release pro-inflammatory cytokines after surgery *via* the estrogen receptor; this immunomodulatory effect of DHEA appears to be connected to estrogen receptors (*55*). Although total androgen concentrations were not associated with pregnancy during DHEA supplementation in women with POI, interaction between DHEA and total and free testosterone also significantly affected pregnancy rates at the start of an IVF cycle (*67*). Total testosterone is significantly lower in women with POI or abnormal FMR1 genotypes (*68*). The efficiency of androgen conversion from DHEA to testosterone and the amplitude of testosterone gain are related to pregnancy rates. Conversion is usually more pronounced in young women and women with selected FMR1 genotypes/subgenotypes (*69*). DHEA and testosterone also suppressed canavalin A (Con A)-induced proliferation of thymocytes *in vitro*, and DHEA is less potent than testosterone, which means that the balance between the two steroids can alter immune homeostasis (*70*). Testosterone and estradiol levels vary widely after DHEA administration, and the testosterone to estradiol ratio increased significantly in seven healthy nonobese postmenopausal women (*71*).

When steroidogenic enzymes convert DHEA to other steroids, those enzymes have a substantial effect on the immune response. Although women with POI have a poor ovarian follicle pool compared to healthy fertile women, women with POI and steroidogenic cell autoimmunity (SCA-POI), which involves circulating autoantibodies directed against steroidogenic enzymes such as 21-α-hydroxylase, 17-β-hydroxylase, and side-chain cleavage enzyme (P450sccAb) (*72-76*), have a better ovarian reserve than women with iPOI and postmenopausal women. Steroid sulphatase is controlled by an x-linked gene. Women have twice the amount of steroid sulphatase in macrophages. The

macrophages enter peripheral lymphoid organs through afferent lymphatic drainage (*77,78*). IL-4, which is a typical Th2 cytokine, increases the expression of 3-beta-hydroxysteroid dehydrogenase type 2 (HSD3B2) mRNA, and thus may lead to the increased production of estrogen from DHEA (*79*).

3.2. *Balance of the Th1 and Th2 immune response*

Cytokines have an extremely important place in the immune response. They can influence communication between T cells, macrophages, and other immune cells. Numerous studies in mice and humans have deduced the presence of T helper (Th) cells based on the profile of cytokine secretion. The Th1-type immune response is thought to be associated with IgG2a production, which is driven by cytokines such as IFN-γ, IL-2, TNF-α, and IL-12, whereas the Th2-type immune response involves IgE production driven by specific cytokines (IL-4, IL-5, IL-10, and IL-13) (*80,81*). DHEA restores the cell-mediated immune response of pro-inflammatory cytokines (IL-1, IL-6, TNF-α, and IL-18). Mice treated with DHEA exhibited increased production of cytokines such as serum TNF-α, IL-6, IL-12p70, and IFN-γ (*82,83*). DHEA supplementation also increases vascular cell adhesion molecule 1 (VCAM-1) and intercellular cell adhesion molecule 1 (ICAM-1) in the granulosa cell layer of cysts and the theca cell layer of all follicles and cysts when DHEA androgenization induces the formation of cysts (*83*). DHEA may improve ovarian function in women with poor ovarian response by activating anti-apoptotic processes in cumulus cells. These processes most likely involve the upregulation of genes related to extracellular matrix (ECM) formation and downregulating genes related to cell development, differentiation, and apoptosis (*84*). In other areas, DHEA supplementation has been reported to have an effect on regulation of the Th1/Th2 response. In ovalbumin-sensitized asthmatic female mice, Th2-associated cytokines and chemokines were inhibited after DHEA administration, which led to hyper-responsiveness (*85*). DHEA decreased the release of anti-inflammatory cytokines (IL-2 and IL-10, which are also Th2-associated cytokines) and it reduced the expression of the activation marker CD69 on CD4+ T cells (*20*). All of these effects may bring about an enhanced Th1 response and a weakened Th2 response and lead to a new balance in the Th1/Th2 response.

3.3. *Balance between CD4+/CD8+ T cells*

DHEA also improves immune function by regulating the proliferation of and balance between different types of lymphocytes. During the culturing of T lymphocytes from BALB/c mice *in vitro*, DHEA did not change the viability of T lymphocytes, but it did increase oxidative stress by reducing antioxidant molecules, such as glutathione (GSH) (*86*). Burdick *et al*. conducted a study and found that oral administration of DHEAs in young pigs increased *in vitro* lymphocyte proliferation following immunization and that it increased the *in vivo* response of immunization against keyhole limpet haemocyanin (KLH), thus increasing the neutrophil to lymphocyte ratio and increasing the concentration of IgG (*21*). DHEA effects opposite those of cortisol; thus, the cortisol to DHEA ratio may influence the differentiation of T cells. Extrathymic (DP) CD4+/CD8+ T cells positively correlated with circulating levels of TNF-α and with the cortisol/DHEAs ratio (*87*). Flow cytometry showed that DHEA treatment in mice significantly increased the CD4+ lymphocyte population and decreased the CD8+ lymphocyte population, thus modulating the CD4+/CD8+ lymphocyte balance in both ovarian tissue and retroperitoneal lymph nodes (*82*). This may be due to the selective T lymphocyte infiltration of ovarian tissue (*88*).

4. Conclusion

DHEA attenuates diminished ovarian reserve and helps to obtain better results in IVF cycles. DHEA may modulate ovarian immunity through its conversion to other downstream steroids, by balancing the Th1/Th2 immune response, or by modulating the types and behavior of T lymphocytes. The mechanism underlying the immune effects of DHEA on ovarian tissue needs to be studied further.

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