Archives of Reproductive Medicine and Sexual Health

Volume 1, Issue 1, 2018, PP: 4-13

Immune Regulation: The Possible Mechanism by which Dehydroepiandrosterone Improves Ovarian Reserve in Patients Having Diminished Ovarian Reserve (Dor)

Dr. Kulvinder Kochar Kaur, MD[1]*, Dr. Gautam Allahbadia, MD (Obstt & Gynae), D.N.B[2]
Dr. Mandeep Singh M.D.DM.(Std)(Neurology)[3]

[1]Scientific Director, Dr Kulvinder Kaur Centre for Human Reproduction, Punjab, India.
[2]Scientific Director, Rotunda-A Centre for Human reproduction, Mumbai, India.
[3]Consultant Neurologist, Swami Satyanand Hospital, Jalandhar, Punjab, India.
*kulvinder.dr@gmail.com

***Corresponding Author:** Dr. Kulvinder Kochar Kaur, MD, Scientific Director, Dr Kulvinder Kaur Centre for Human Reproduction, Punjab, India.*

Abstract

Diminished ovarian reserve (DOR) or poor ovarian reserve (POR) is becoming a worldwide problem and becoming an important cause of infertility. There has been concentration on this subject by the laboratories of Gleicher et al and to some extent Solano ME et al who found importance of androgenic steroids in DOR. For the last decade role of DHEA has been studied, be it their secretion getting reduced with age from the adrenal gland or importance of improving results in in vitro fertilization in cases of DOR. It has a proinflammatory effect on immune function which opposes cortisol. It acts as an immune regulator in various tissues including ovaries. In mammals it also improves Th1 immune response. Treatment with DHEA selectively increases T lymphocytes, upregulating CD8+T lymphocyte population in ovaries while down regulating CD4+T lymphocyte population and thus balance of the CD4+/CD8+ population is maintained. Further Gleicher et al studied regarding the disturbed autoimmune status along with studying triple CGG repeats in fragile X mental retardation 1(FXMR1) gene besides role of autoimmune antibodies in case of premature ovarian insufficiency (POI). Still very few studies are available and more work needs to be done regarding the mechanism by which DHEAS is efficacious in improving IVF results in DOR or POI.

Keywords: DHEA; DHEAS; immunefunction; HPA axis;cortisol; Th1/Th2 cytokines; CD4+/CDB+ Balance in ovaries; FXMR1.

Introduction

Ovarian reserve by definition is thequantity and quality of the ovarian primordial follicular pool. Diminished ovarian reserve (DOR) is a decrease in thequantity of ovarian poolin women of reproductive age group, a reduction in the dynamic reserve of small antral follicles and deteriorating oocyte quality. These changes are seen once there is ageing of women. Increasing use of in vitro fertilization (IVF) has unmasked the occurrence of DOR. Roughly 10% of women undergoing IVF will show a poor response to gonadotropin stimulation [1-3]. Various genetic mutations and disorders of the endocrine system can increase or modulate the rate at which ovarian reserve gets exhausted and leads to premature ovarian insufficiency (POI) [4]. Abnormal immune function might be an important cause of DOR [5]. Thus for these patients becoming infertile and showing poor response to in vitro fertilization (IVF) different protocols to solve this problem have been proposed though none has proved to be ideal for these patients [6-8]. Dehydroepiandrosteronesulphate (DHEA) is a C19 androgenic steroid which has been found to be effective in many areas. Years of studies both in clinical setups and in animals have shown that levels of DHEA (S) are inversely correlated with cardiovascular risk, morbidity as wellas mortality [9]. DHEA protected against atherosclerosis in ovariectomized rabbits

since it alleviates inflammation in endothelial cells [10]. It can crossthe blood brain barrier (BBB), it has neuro active characteristics and positively influences mood, emotions and behavior in man [11, 12]. DHEA supplementation was used to improve the response to ovarian supplementation by Casson et al to begin with [13]. Since then a lot of workers have paid attention to improve DOR using DHEA. A meta-analysis was conducted by Narwechian et al, which revealed that DHEA administration caused a significant increase in the number of oocytes retrieved in women with DOR, based on some clinical trials. But they concluded that more trials were needed for verifying these results [14]. Also in ovariectomized sheep DHEA addition was found to be effective in increasing ovarian folliculogenesis [15]. Similarly in Wistar rats used as an in vivo model the responses were found [16]. Still the basic mechanism by which DHEA improves this ovarian reserve remains unclear. It has been found that DHEA can regulate immune function [17], and that it might regulate immune cellfunction of many tissues in mammals. Utililizing a human subcutaneous preadipocyte cell line, Chub -67, it was found by McNeils et al that DHEA inhibits the amplification of (11β-HSD1) [18]. Also DHEA served as a neurosteroid directly by directly interacting with nerve growth factor (NGF) as shown by Lazardis etalin an in vitro study for preventing neuronal apoptosis [19]. DHEA also improves oxidative stress induced endothelial dysfunction in ovariectomized rats [20]. Also DHEA treatment may also modulate the lymphocyte responses based on both human and animal trials [21, 22]. Thus DHEA may have an important rolein regulating the immune response in ovaries, which is the main aim of this review.

DHEAS in DOR

Structure and Biochemistry

Structurally DHEAS is 5-androsten-3β-ol-17-one which is a C19 androgenic steroid, which is mainly secreted by the adrenal zonareticularis. It gets synthesized by the steroidogenic enzyme P450c 17 and also partly by ovary (fig1) [23]. Its secretion has a diurnal rhythm, which is similar to that of cortisol [24, 25]. With increasing age both DHEA and its sulphate gradually declines, which is unlike that of other androgenic steroids. DHEA concentrations peak during the 3rd decade of life, having a clear sex difference because adult women have lower concentrations as compared to men [25-27]. Because of this age related fall supplementation of DHEA might be of helpin improving age related damage in human beings.

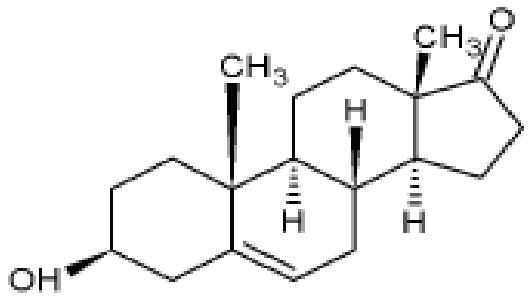

Figure 1. *Chemical structure of DHEA*

DHEA Supplementation & DOR

No set criteria for DOR exist. Following the consensus meeting of ESHRE working group on DOR held in 2011 [28], Bologna criteria were introduced, which recommends at least 2 of the following 3 feautures be present for labeling POR or DOR

i) Advanced maternal age (>=40years) or any other risk factor for POR

ii) A previous DOR (<=3oocytes with a conventional stimulation protocol).

iii) An abnormalovarian response test (ORT) (i.e antral follicle count (AFC), 5-7 follicles, or antimullerian hormone (AMH), 0.5-1.1ng/ml).

Although despite these guidelines different researchers have used different criteria besides these Bologna criteria.

Many studies have examined the effect of DHEA supplementation on ovarian hormones. Analyzing 12 of those studies Zhang et al analyzed that DHEA supplementation is usually given orally t.i.d, or 75-90mg for the full day over 6-24 weeks [29]. It was shown in a previous case controlled studythat DHEA improved ovarian reserve (OR), and it significantly increased AFC and AMH levels [30-32], numbers of fertilized oocytes, normal day3 embryos, embryo transferred as well as the average embryoscore per oocyte [33]. Also they significantly decreased day3 follicle stimulating hormone (FSH) [31], fertilized aneuploid embryos [34], and miscarriage rates [35] (withallp values<0.05). Estradiol (E2) levels increased three times as per 2 studies [13, 36], but decreased according to another

one [32]. A lot of randomized prospective controlled studies investigated the effects regarding DHEA supplementation but with inconsistent results. As per some same results as described before [32, 36-38], but total oocytes retrieved and the fertilization rate was not consistent. Also IVF outcomes were not improved by DHEA in others [38, 39]. One can not compare these studies statistically however as there was no set criteria regarding defining DOR. DOR was defined as abnormally increased age-specific baseline FSH levels and/or abnormally low AMH levels [40-42], increased inhibin levels and AFC<4-5 [31, 32, 36, 39].

Immune Functions of DHEA

DHEA exerts an effect on human neuroendocrine cells along with playing an important role in immune regulation, mainly by balancing proinflammatoryand anti-inflammatory signals. Inflammation develops in humans with age, that involves up regulation of some proinflammatory cytokines like interleukin (IL)-1, IL-6, tumour necrosis factor (TNF)-α, IL-12, interferon (IFN)-α and IFN-β. These cytokines negatively impact in old age on various systems of the body [43-45]. Hence an imbalanced relationship develops between proinflammatory cytokines and anti-inflammatory cytokines like IL-4, IL-6, IL-13 and IL-10 [46]. This is a part of hypothalamo-pituitary-adrenal (HPA)-axis. If HPA Axis is activated, both cortisol along with DHEA get released. Although cortisol has an anti-inflammatory effect, DHEA seems to have an opposite effect. With decreasing levels of DHEA with age there is an increase of cortisol: DHEA ratio which might interact with a weakened immune function [47, 48]. Increased cortisol: DHEAS ratio was seen in bereaved elderly participants, who showed decreased production of neutrophil reactive species [11]. A positive effect on immunity was seen with DHEA supplementation in the elderly. 20mg/day DHEA treatment for 8weeks reversed antioxidant parameters like decreased superoxide dismutase activityin the brain and heart, reduced inducible nitric oxide synthase mRNA levels and increased haemoxygenasem RNA levels in aged rats [49]. Cortisol acted in a dose related manner, both in vitro and vivo as shown by Buoso et al on human guanine nucleotide binding protein and the beta polypeptide 2 like1 (GNB2L1) promoter repressor, that decreased receptor for activated C kinase (RACK1)m RNA and protein expression. Using prolonged DHEA exposure counteracted the effect of cortisol and restored RACK1 levels and cytokine production as assessed by lipopolydaccharide (LPS) Induced TNF-α release, which most likely occurred due to interfering with glucocorticoid receptor binding to the glucorticoid response element (GRE) sequence [50]. Other diseases and improved organ function and survival has been seen by use of DHEA supplementation. Still there mechanisms are not clearly understood. In past decades reasearchers have tried to study these effects in nonhumanmammals. In aged baboons, they found an increased C- Re active protein and increased cytokine release from unstimulated peripheral blood mononuclear cells (PBMC). Outcomes in amurine polymicrobial sepsis and trauma model by restoring TNFα in the liver and lungs occurred 48h after supplementation with DHEA and attenuated it in the liver after 96h, much like atime and organ dependent modulator [51]. Also restoration of splenocyte proliferation, decrease in rate of cellular apoptosis of splenocytes,

besides an attenuation of increased IL-6 levels is caused by DHEA addition [52]. DHEA also reduced PBMC's function and increased the ability of human PBMC patients with depressed response to release proinflammatory cytokines-IL-1β, IL-6 and TNF-α, following abdominal surgery [53].

DHEA-Immune Response in Ovaries

Level of ovarian response in the ovaries changes with age along with ovarian reserve. Lot of interaction between immune systemand the ovaries occurs as the immune cells are associated with regulation of every step of the H-P-O Axis by regulating growth and regression of both follicles and corpus luteum (CL) [54-56]. In an adult ovary activated myeloid dendritic cells (MDC) also play a role in follicular development and atresia along with differentiation of the corpus luteum. There is massive infiltration of MDC and Tcells in the corpus luteum, which results in parenchymal and vascular regression of the CL [57]. OR of women with age related DOR is improved by DHEA in POI, even though POI is more closely related toovarian immune disorders. Young women having a history or family history of autoimmunity are at risk for POI [58, 59]. Many types of autoimmune ovarian autoimmune insufficiency abnormalities exist. Three different types of ovarian autoimmune insufficiency, autoimmune ovarian insufficiency associated with adrenal autoimmunity,

autoimmune ovarian insufficiency associated with nonadrenal autoimmunity and isolated idiopathic POI [60]. Most prevalent is adrenal autoimmunity [4, 61]. Testing for triple CGG repeats on both alleles of the fragile X mental retardation1 (FMR1) gene and assessed autoimmune status including an antiphospholipid antibody panel,an antinuclear antibody panel, total immunoglobulin levels, the thyroid antibodiesand antiadrenal antibodies then these researchers (group from lab of Gleicher et al) found that abnormal autoimmune function ,including expansion of triple CGG repeats on the FMR1 gene increased the risk of POI [62, 63].

Though the effects of DHEA supplementation in women with DOR are clearly evident the mechanism behind these effects still are not clear. With the complexiммune function of DHEA in women with DOR, some researchers have started studying the immune function of DHEA in women with DOR. Still limited research reports on this topic are available till date. Summary of the these limited studies is presented.

Conversion to other Steroids

There are no specific receptors for DHEA found till date, some theories suggest that DHEA might functiononce steroidogenic enzymes convert it to other downstream steroids, specially sex steroidslike estrogen and androgens (fig2) Small structural changes in androgens =>markedly different biological effects. There are tissue specific expressions of steroidogenicenymes, and hence DHEA may have a specific function. These steroids interact critically with immune function. Estrone can shift the female immune system to a Th2-type response in the luteal phase, while postmenopausal women exhibit increased Th1 cytokines [64]. Also DHEA can restore PBMC function and increase the ability of human PBMC's torelease proinflammtory cytokines after surgery via the estrogen receptor; thus this immunomodulatory effect of DHEA appears to be connected to estrogen receptors – [53]. Though total androgen concentrations are not associated with pregnancy during DHEA supplementation with POI, interaction between DHEA and total and free testosterone also significantly affect pregnancy rate at the start of an IVF cycle [65]. There is significantly lower total testosterone in women with POI or anormal FMR1 genotypes [66]. Efficiency of androgen conversion from DHEA to testosterone(T) and the amplitude of Tgain are related to pregnancy rates. The conversion Is more pronounced in young women and women with selected FMR1 genotypes /subgenotypes [67]. DHEA and T also suppress concavalin A(Con A)-induced proliferation of thymocytesin vitro and DHEA is less potent than T, which means that the balance between the 2 steroids can alter immune homeostasis [68]. T and E2 vary widely following DHEA administration,and T:E2 ratio increased significantly in 7 nonobesepostmenopausal women [69].

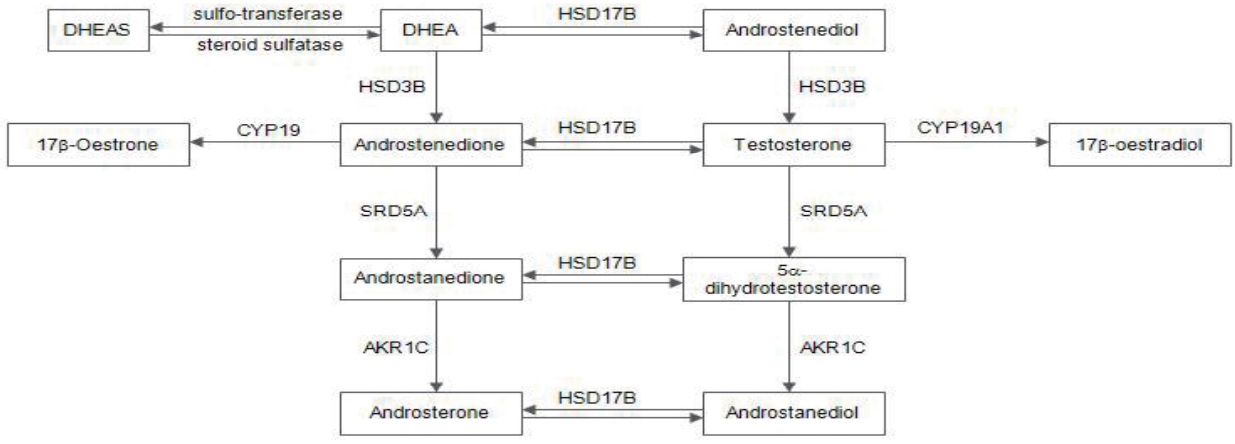

Figure 2. *The regulatory pathway by which DHEA Conversion occurs to other downstream steroids courtesy ref 38.*

Abbreviations

DHEA, dehydroepiandrosterone; DHEAS, dehydro epiandrosterone sulfate; HSD 17β, 17β-hydroxy steroid dehyrogenase isoenzymes; CYP19A1, P450 aromatase; SRD 5A, 5α reductase isoenzymes; AKR1C, 3α-hydroxy steroid dehyrogenaseisoenzymes.

Once steroidogenic enzymes convert DHEA to other steroids, these enzymes have a substantial effect on the immune response. Though women with POI have a poor ovarian follicle pool as compared to healthy volunteer fertile controls, women with POI and steroidogenic cell autoimmunity (SCA-POI) that involves autoantibodies directed against steroidogenic enzymes like 21 –α-hydroxylase, 17-β-hydroxylase, and side chain cleavage enzyme (P450 sec Ab) [70-74], have a better OR than women with iPOI and postmenopausal women. Steroidsulphatase 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 [75,76]. IL-4 which is a typical Th2 cytokine increases the expression of 3-beta-hydroxy steroid dehydeogenase (HSD3B2) m RNA and thus might lead to the increased production of estrogen from DHEA [77].

Control of Th1 and Th2 Response

Normally cytokines play important role by influencing communication between T cells, macrophages and other immune cells. It has been deduced from studies in mice along with humans that there is presence of helper T (Th) cells which is based on the profile of cytokine secretion. The Th1-type immune response is believed to be associated with IgG2 a production that is driven by cytokines like IFN-γ, IL-2, TNF-α, and IL-12, while Th2-type immune response involves IgE production which is driven by specific cytokines like IL-4, IL-5, IL-10 and IL-13 [78, 79]. Restoration of cell mediated immune response of proinflammatory cytokines like IL-1, IL-6, TNF-α and IL-18 is brought about by DHEA. Treatment of mice with DHEA showed elevated production of cytokines like serum TNF –α, IL-6, IL-12 p70 and IFN-γ [80, 831]. It also raised vascular cell adhesion molecules (VCAM1) and intercellular celladhesion molecule 1(ICAM-1) in the granulosa cell layer cysts and the theca cell layer of all follicles and cysts when DHEA androgenization causes the cyst formation [81]. There might be improvement of ovarian reserve by DHEA in patients having DOR by stimulating antiapoptotic processes in cumulus cells. Upregulation of genes related to extracellular matrix (ECM) formation is probably involved in these processes along with down regulation of genes which are related to cell development, differentiation, and apoptosis [82]. Also DHEA supplementation has been shown to have an effect on Th1/Th2 response. Asthmatic female mice that are ovalbumin –sensitized show inhibition of Th2-associated cytokines and chemokines following administration of DHEA which possibly led to hyporesponsiveness [83]. Release of anti-inflammatory cytokines like IL-2 and IL-10 was also decreased by DHEA, that are Th2 –associated cytokines, along with reduction in the expression of activation marker CD69 on CD4+T cells [21]. Summing up these effects might be associated with an increased Th1 response along with weakening of Th2 response.

Effect on Interaction between CD4+/CD8+T Cells

Further DHEA improves immune function by regulating the multiplication of and balance between various kinds of lymphocytes. While culturing T Lymphocytes from BALB c mice in vitro, there was no change in viability of T Lymphocytes, although DHEA did increase the oxidative stress by decreasing antioxidant molecules, like glutathione (GSH) [84]. Orally when DHEA was given to young pigs DHEAS increased in vitro proliferation following immunization and it increased the in vivo response of immunization against keyhole limpet haemocyanin (KLH), thus increasing the neutrophil : lymphocyte ratio and increasing the concentration of IgG as shown by Burdick et al [22]. Effects of DHEAS are just opposite to that of cortisol : hencecortisol : DHEA ratiomight influence the differentiation of Tcells. There is a positive correlation of extrathymic (DP)CD4+/CD8+ Tcells with circulating levels of TNF-α and with cortisol/DHEA ratio [85]. Flow cytometry showed that DHEA treatment in mice markedly increased the CD4+Lymphocytepopulation while reducing CD8+ lymphocyte population and hence modulating the CD4+/CD8+ lymphocyte balance in both ovarian tissue as wellas retroperitoneal lymph nodes [80]. Probably it is related to the selective T Lymphocyte infiltration of the ovarian tissue [86].

Conclusions

Thus DHEAS has been found to be effective in patients of DOR, helping getting bettet outcomes in IVF cycles. It might be regulating ovarian immunity via its conversion to other downstream steroids.ii) by balancing Th1/Th2 immune responses or kulvinder modulating types and balance of lymphocytes. Still the mechanism underlying immune effects of DHEA on ovarian tissue requires further clarification along with more number of studies.

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Citation: **Dr. Kulvinder Kochar Kaur, Dr. Gautam Allahbadia, Dr. Mandeep Singh.** *Acceptance of Contraception after Illegal Abortion in Antananarivo, Madagascar. Archives of Reproductive Medicine and Sexual Health. 2018; 1(1): 4-13.*