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Androgens and Controlled Ovarian Stimulation Outcomes

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Abstract

Androgens play are an integral part in normal follicular development and in the pathogenesis of conditions such as polycystic ovary syndrome (PCOS), decreased ovarian reserve and poor ovarian response. Besides indirectly mediating the growth of early phases of follicular development, through their actions on FSH (follicle-stimulating hormone) and IGF1(insulin-like growth factor 1), androgens are also the source of estrogens. Hyperandrogenism in PCOS leads to excessive growth of preantral follicles and follicular arrest. Low levels of androgens are responsible for abnormal folliculogenesis and rapid depletion of the ovarian pool. The poor ovarian response is encountered in up to a third of patients undergoing controlled ovarian stimulation, and androgens have been used as a prediction tool and as a treatment intervention. Although the results are not unanimous, serum DHEAS (dehydroepiandrosterone sulfate) appears to anticipate the type of response encountered in controlled ovarian stimulation and the possibility of achieving a live birth after ART (assisted reproduction technique) treatment. Similarly, testosterone could help in the optimization of stimulation protocols. Whether systemically administered androgens could influence the intra-follicular environment is not certain. Still, treatment with both testosterone and DHEA appears to have beneficial effects on both surrogate endpoints, such as embryos quantity and quality, as well as definitive endpoints such as clinical pregnancy rate and live birth rate.

Keywords: androgens; IVF; PCOS.

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1. Introduction

Infertility has become a global problem, and more and more women undergo complicated treatments in the desire to achieve pregnancy. The term poor ovarian response describes the suboptimal ovarian response to gonadotropin stimulation. It is present in up to 30% of IVF (in vitro fertilization) procedures leading to a catastrophic impact on the emotional well-being of patients and substantially increasing the costs of ART procedures. It is now coming to our understanding that androgen's action in the ovary respects the "Goldilocks principle: too much is bad but too little is also bad- just enough makes the difference" [1]. ARKO (androgen receptor knock-out) mice models presenting with decreased fertility, defective follicular development, reduced ovulation, and premature ovarian failure were able to demonstrate not only those androgens were not, in fact, detrimental to reproductive function but that they play a vital role [2].

This review aims to acquaint readers with the present-day knowledge of androgen importance in normal ovarian physiology, the role that androgen determination in serum or follicular fluid has in predicting infertility treatment outcomes and whether adjuvant treatment with androgens could improve the result of ART procedures and in which type of patients it could be applied. We performed a PubMed search using the terms "androgens"/ "testosterone"/" DHEA" and "controlled ovarian stimulation"/" COS" and manually selected articles from the reference lists of relevant publications. We decided on 33 studies and summarized the information.

2. The role of androgens in normal and abnormal follicular development

In addition to being an estrogen precursor, androgens stimulate follicular growth by decreasing apoptotic rates and facilitating FSH-induced follicular development [2]. Through the ARs (androgens receptors), androgens are involved in the growth of preantral follicles, protection against atresia and evolution to antral stages [1]. Follicular atresia is attenuated by androgens through nuclear and extranuclear signaling pathways by enhancing the mRNA expression (micro ribonucleic acid)-125b, which suppresses proapoptotic protein expression. Androgens also enhance FSH receptor expression in a non-genomic fashion, augmenting FSH-mediated follicle growth and development. Paxillin, a molecule involved in both processes, is an essential mediator of extranuclear and nuclear AR signaling [2]. Other proposed implications in follicular development are the recruitment of primordial follicles and the ovulation process, but further studies are needed to establish this [3]. ARs are expressed in granulosa cells, theca cells, and oocytes of the follicles beyond the primordial stage of follicular development. They are most abundant in the early phases of growth. They exert their effect in a paracrine or autocrine manner but give away their place favoring estrogen receptors in later stages [1].

Androgens may induce ovarian follicular and thecal interstitial growth via the action of IGF-1(insulin growth factor 1) and its receptor. It was demonstrated that androgen treatment (testosterone, DHT-dihydrotestosterone) increased IGF1, mRNA concentration and IGF-1 receptor mRNA in granulosa, thecal and interstitial compartments of developing follicles of primates up to the small antral stage [4].

Also, androgens increase levels of FSHR (follicle stimulating hormone receptor) and sensitivity of pre-antral follicles to FSH, potentiating FSH actions in the ovary. In addition, androgens stimulate steroidogenesis and act

as estradiol precursors. All these actions lead to the growth of smaller follicles and transition to the antral stage [1]. In humans and other primates, ovulation is generally mono-follicular. Except for the follicle that will undergo ovulation, other follicles that have experienced increased growth secondary to the rise in FSH early in folliculogenesis will become atretic. Although it seems paradoxical, androgens stimulate growth in early-stage follicles, but they inhibit proliferation and induce apoptosis [5].

Dewailly and his colleagues proposed the model of "the two triangles" to explain the interactions between androgens, FSH, anti-Mullerian hormone and estradiol during folliculogenesis [6]. The two triangles-oriented base-to-base are four vertices-androgens, estrogens, FSH and AMH, with FSH and AMH forming the joint base in both triangles. This design incorporates six sides that can explain the relationships between its components during the gonadotropin-independent follicular growth phase and gonadotropin-dependent follicular growth phase, respectively [7].As the name “gonadotropin-independent” implies, in the early phases of follicular development, gonadotrophins are not supposed to play a role. Despite this, studies have concluded that FSH plays an effect of follicular growth alongside other stimulating factors such as androgens and intra-ovarian molecules, and in its absence the growth process would be accomplished, although less effectively [7].

During the gonadotropin-independent phase, androgens enhance FSH-R expression, and in turn, FSH stimulates follicular growth and AMH production in the absence of estradiol [7]. AMH expression is up regulated by cAMP (cyclic adenosine monophosphate**)** and FSH in human granulosa cells and LH has an additive effect, which appears more important in PCOS [8].

AMH acts to counterbalance the effect of FSH and protect against precocious exhaustion of the follicular pool and premature selection by FSH. Thus, authors challenge the concept that AMH is directly regulated by androgens and propose rather an indirect effect through the amplification of FSH effect by androgens [7].

During the gonadotropin-dependent phase, the triangle is formed by FSH, AMH and estradiol. At this follicular phase, the effects of androgens on GCs(granulosa cells) appear to wane in favor of estradiol. Initially, AMH inhibits aromatase activity induced by FSH. Still, later, the inhibitory influence subsides, allowing aromatase-induction by FSH and synthesis of estradiol that gradually increases until it reaches a threshold that will suppress the AMH secretion in large antral follicles [7]. The model of the "two triangles" does not exclude the previous theory of "2 cells, two gonadotrophins", the latter being involved in the final phases of follicular growth. According to the "2 cells, two gonadotrophins" theory, androgens (mainly testosterone and androstenedione) synthesized in theca cells under LH control diffuse across the basal lamina of the follicle, where they are converted to estrogens via CYP19 (aromatase) action, whose activity is influenced by FSH [5]. Thus, the function of aromatase is to convert androgens to estrogens. It was demonstrated that follicular hyperandrogenism in PCOS women could downregulate aromatase in luteinized granulosa cells. Therefore, when its activity is suppressed, androgens accumulate in the follicular fluid [6].

Shaw and his colleagues [9] demonstrated the mechanism of preserved estrogen secretion in women in the early menopausal transition. They observed an up-regulation in aromatase activity that counteracts decreasing androgen concentration with age. So, it appears that ovaries have an adaptation capability to fluctuating

androgen concentrations [10].

PCOS is the staple condition where excess androgens lead to enhanced development of follicles and dysfunctional formation of antral follicles leading to the aspect of polycystic ovaries and infertility. Low concentrations of androgens are also detrimental to reproduction and are described in conditions such as LFOR (low functional ovarian reserve) and POI (premature ovarian insufficiency) [1]. The concept of the two triangles can also be applied in the pathophysiology of PCOS, suggesting that PCOS is the effect of an exaggeration of physiologic processes. Thus, epigenetic and/or genetic intrinsic overactivity of theca cells causes hyperandrogenism, which in turn induces excessive pre-antral follicle growth by hypersensitization of granulosa cells to FSH and induces increased AMH expression. Elevated AMH in the microfollicular environment might be responsible for the follicular arrest observed in PCOS. Later in follicular development, increased levels of AMH abnormally inhibit FSH effects on aromatase and lead to disturbed growth and differentiation of antral follicles. Ovarian hyperstimulation syndrome (OHSS) is more frequently encountered in PCOS patients. It can be explained by the increased sensitivity of GCs to FSH due to the increased number of FSHR on these cells and, subsequently, overproduction of estrogens [7].

Testosterone levels correlate mildly and positively with AMH. Elevated testosterone levels are associated with an increased risk of PCOS, and decreased risk of DOR. AMH and testosterone appear to mutually reinforce each other. On the one hand, increased testosterone levels stimulate follicular FSHR expression and promote follicular growth leading to increased AMH levels. On the other hand, AMH leads to increased testosterone levels through stimulating LH secretion from GnRH neurons and inhibition of aromatase activity in granulosa cells. At the other end of the spectrum, in DOR, decreased testosterone levels cannot sustain steroidogenesis, and reduced levels of AMH lead to a more rapid depletion of the ovarian pool [9].

3. Link between responder type and androgen levels

To standardize the definition of POR (poor ovarian response), ESHRE published 2011 the Bologna criteria, which consider the patient's age and other risk factors for POR, ovarian reserve tests, and outcomes of previous stimulation cycles [11].

Due to the heterogeneity of POR patients classified using the Bologna criteria and the lack of individualized management strategies, a new classification was proposed. Poseidon criteria divide patients with the poor ovarian response into four categories– the first two categories, "unexpected poor responders", represent the patients with good ovarian reserve markers but decreased response to stimulation and are further subdivided based on age: group 1 <35 years and group 2 ≥35 years. The last two categories, "expected POR," is represented by females with a decreased ovarian reserve and aged <35 years (group 3) or > 35 years (group 4). Also, because Poseidon subgroups differ in the pathophysiological mechanism implicated and the number of oocytes needed to obtain a viable blastocyst for transfer point out to fact that individualized treatment protocols are needed [12]. Whether or not androgen levels in serum could predict the type of response observed during COS is still a matter of debate.

In a pilot study performed by Fuentes and his colleagues [4], androgen levels in serum and follicular fluid in women with POR (poor ovarian response) undergoing controlled ovarian stimulation (COH) were compared with those of normal ovarian response. By dividing the infertile women into four categories using POSEIDON (Patient-Oriented Strategies Encompassing Individualized Oocyte Number) stratification (based on age, ovarian reserve, and response to stimulation), they observed that all POR women were hypo androgenic compared to controls. Still, women under <35 years of age with ovarian markers indicative of low ovarian reserve (group 3) had decreased levels of all androgens and especially DHEAS in both serum and follicular fluid. Although the number of patients in this group was very low, the question arising is whether androgen supplementation in some patients, in this case using DHEAS, could achieve better COH outcomes. Also, DHEAS may exert its role independent of the synthesis of ovarian steroids because estrogen and testosterone concentrations didn't differ from controls [13]. In support of these findings, another study found that In the subset of young women with diminished ovarian reserve appreciated using AMH, where low pregnancy and live birth rates are expected, DHEAS appears to have a predictive value for live birth after the first GnRH (gonadotropin-releasing hormone) antagonist IVF cycle. Women with a DHEAS concentration of >5.4 mmol/l had a five times higher probability of clinical pregnancy and live birth rates compared with those who had DHEAS levels less than 5.4 mmol/l. However, the groups were similar regarding the number of oocytes retrieved and the number of embryos obtained and transferred, suggesting DHEAS could be of value in anticipating oocyte/embryo quality due to his hypothetic role in improving oocyte maturation if present in sufficient amounts for proper androgen conversion and maintenance of a favourable ovarian microenvironment [14].

Gleicher [2] and his colleagues in their study, provided evidence of hypoandrogenism in patients with diminished functional ovarian reserve (DFOR) of all ages. Still, there was a difference in the proposed mechanism implicated based on the patients' age. While decreased total testosterone concentrations were readily apparent in the more youthful patients with DFOR (females classified as having premature ovarian ageing/occult primary ovarian insufficiency POA/OPOI = abnormally high FSH levels and abnormally low AMH), suggesting a primary androgen deficiency condition of adrenal origin, females aged >40 classified as having physiologic diminished ovarian reserve presented with increased DHEAS concentrations in association with low serum testosterone possibly secondarily to a defect in androgen conversion caused by defects in ovarian theca cell function and number. Based on these findings, the authors also questioned the current uniform treatment of infertile patients with DHEA regardless of age and whether women with DOR >40 years couldn't benefit more from supplementation with testosterone than DHEA [15].

On the contrary, in a retrospective study performed on 459 women with a usual ovarian reserve who were undergoing their first ICSI (intracytoplasmic sperm injection), DHEAS serum concentration did not appear of value in predicting clinical pregnancy and could not be incorporated in a more complex model for predicting IVF outcomes along with AMH and age [16]

Ovarian androgens appear more critical than adrenal androgens during IVF. Although in a prospective cohort study, they correlate with many IVF parameters such as peak estradiol levels, follicle number, and oocyte number, ovarian androgens failed to predict pregnancy outcomes [17].

A study examining the role of serum androgen concentrations in predicting POR using the Bologna criteria suggested that testosterone, instead of DHEAS concentration, can expect POR, although limited. But when basal testosterone was incorporated in a multivariate model encompassing age, AFC, basal FSH, basal FSH/LH and basal testosterone, it was superior in predicting POR and clinical pregnancy than AFC alone [18]. In women with decreased ovarian reserve, basal testosterone levels are a good predictor of pregnancy outcomes, and several large follicles are achieved on the day of hCG administration. Because basal testosterone(T) levels correlate with the dose of gonadotropins used and the number of stimulation days, lower T levels might predict poor ovarian response. In other words, T levels could help optimize stimulation protocols, identifying patients in need of an increase in gonadotropin dose and more stimulation days [19] .

In his study, de Los Santos did not find an impairment in follicular androgen secretion and response to LH in low responder women and proposed that other mechanisms such as a decrease in the number of FSHR or aromatase activity lead to an impairment in the response to controlled ovarian stimulation protocols. Authors also suggest that if used, androgen treatment should be administered for a more extended period to increase the recruitment of smaller follicles, rather than simply administering them only briefly to increase intraovarian androgen levels of the current cycle [20].

Treatment

In a comprehensive systematic review and network meta-analysis of RCTs analyzing ten adjuvant treatment strategies for ovarian stimulation in patients with POR undergoing IVF, among whom DHEA and testosterone were included, authors concluded that all adjuvant treatments led to the usage of a lower dose of gonadotropins, thus protecting from the detrimental effects of higher FSH dosage on egg and oocyte quality that lead to a decrease in live birth rates in subfertile patients and a more rapid depletion of the already low oocyte pool in POR patients. Supplementation with adjuvant agents may provide better outcomes in COS protocols rather than increasing FSH dosage alone [21].

Various methods have been used to improve outcomes in such patients, among which DHEA supplementation has been helpful in some, but not all, POR patients. Because of the lack of randomized trials, consensus on androgen supplementation in women with LFOR has not been reached. Whether orally administered androgens could influence the ovarian hormonal milieu. The analysis of serum and follicular fluid testosterone concentrations of patients undergoing natural cycle IVF, performed by von Wolff and his colleagues [17], failed to show any correlation, and serum testosterone did not correlate with follicular fluid DHEA, estradiol and AMH. Although serum testosterone appeared to decrease slightly (non-significantly) in women of advancing age, follicular testosterone did not. Therefore, the authors concluded that the stable intrafollicular androgens concentrations could not be modified by external supplementation. Still, the authors draw attention to some possible drawbacks. First, the study's conclusions cannot be generalized to patients who, for IVF protocols, receive gonadotropins. Secondly, patients in this group had, by default, lower testosterone concentration. Also, because only the final stages of oocyte development were analyzed in this study, an early effect of androgens reflected in the number of oocytes could not be excluded. Finally, the nature of the survey only allows indirect evidence to be drawn on the effects or lack thereof of androgen supplementation on the endocrine milieu. Only

randomized controlled studies that compare follicular androgen concentration with or without exogenous androgen administration would be able to address the problem [22] concisely. In different studies, DHEAS supplementation improved oocyte number, egg and embryo quality and increased pregnancy rates of IVF. Positive effects appear secondary to the conversion of DHEA to testosterone and are mediated through the AR [3]. DHEA supplementation may upregulate the expression of AR and FSHR on GCs cells of DOR women. Impaired conversion of DHEAS to testosterone, secondarily to age or mutations in the FMR1 gene, could explain why some women are non-responders [1].

DHEA act as an anti-cell death agent through mitochondrial protective effects in human granulosa cells [20]. DHEA may prevent mitochondrial dysfunction by regulating mitochondrial homeostasis and mitophagy. Mitochondrias generate ATP, which is important in the normal developmental process of the embryos and adequate mitochondrial function is needed to assure proper oocyte quality. As such, mitochondrial disturbances caused by various causes such as oxidative stress, hypoxia, genetic factors can lead to impaired oocyte maturation, fertilization failure and compromised embryo development. Cumulus cells are the somatic cells surrounding the oocyte and their prime function is to offer protection and nutrition of the oocyte. Therefore, by improving mitochondrial biogenesis in cumulus cells increased number of oocytes and better-quality embryos could be obtained. In POR patients, DHEA enhances the function and quality of cumulus cell mitochondria. [17]

It was determined that IGF-1 and IGFBP-1 determination has the potential to be used at the start of IVF cycles to predict the likelihood of achieving a live birth [9]. A recent meta-analysis of randomized controlled studies concluded that DHEA supplementation could be clinically helpful to boost IGF-1 levels, especially in women. The increase in IGF-1 levels was observed with a dose of 50 mg DHEA for a period longer than 12 weeks [23]

Finally, DHEA supplementation induces significant elevation of progesterone levels during the follicular phase of IVF cycles, likely mirroring larger-scale changes in the hormonal milieu, and especially steroids induced by DHEA. Also, progesterone elevation in the follicular phase did not have a detrimental impact on implantation rate and endometrial receptivity [24].

Concerning primary outcomes, the retrospective cohort study performed by Chern and his colleagues concluded that DHEA supplementation for three months before stimulation improved IVF outcomes in POR women, such as clinical pregnancy rate, ongoing pregnancy rate and live birth rate [25]. In a recent meta-analysis comparing various adjuvant treatments, DHEA treatment ranked the top modality to achieve a higher clinical pregnancy rate [25]. These results are supported by another meta-analysis encompassing six RCTs which concluded that DHEA supplementation was associated with significantly increased clinical pregnancy, live birth rate, endometrial thickness but had no influence on E2 on hCG (human chorionic gonadotropin) day and miscarriage rate in patients with in vitro fertilization [26]. In a meta-analysis issued in 2016 of more than 21 publications and over 1000 patients, Zhang concluded that DHEA supplementation increases ovarian response and outcomes in women undergoing IVF/ICSI. DHEA had a positive influence on implantation rate, clinical pregnancy, and live birth rates while decreasing the number of miscarriages in women with POR and patients with normal ovarian response who pursued ART treatments. Oocyte numbers and ovarian reserve markers (AFC and AMH) increased following DHEA administration [27]. In a systematic review and meta-analysis published in 2016,

testosterone supplementation had a positive effect on clinical pregnancy rates and live birth rates in infertile women with poor ovarian response undergoing IVF. Still, DHEA supplementation failed to improve ART outcomes [28]. A Cochrane database systematic review found that both testosterone and DHEA were associated with a higher yield of live births than placebo or no treatment intervention in women identified as poor responders undergoing ART. Still, after excluding studies with an increased risk of performance bias, the statistical significance was no longer achieved. As such, the authors restrain from drawing a definitive conclusion regarding the role of androgen therapy in improving ART outcomes [29]. Secondary outcomes regarding oocytes and embryos numbers also seem to improve after androgen supplementation. In a meta-analysis published in 2016, oocyte numbers and ovarian reserve markers (AFC and AMH) increased following DHEA administration [26]. In the study performed by Chern, women treated with DHEA had a higher number of retrieved oocytes, metaphase II oocytes, fertilized oocytes, day three embryos, and top-quality embryos on day 3 [25]. These results partially agreed with the findings from Liu's meta-analysis on the number of received oocytes but not on the numbers of embryos transferred [26]. Testosterone produced the highest number of embryos in the 2020 Zhang meta-analysis [29]. hCG and rLH used as adjuvant agents are presumed to increase the production of endogenous intraovarian androgens. Zhang and his colleagues meta-analysis found that hCG obtained the highest number of retrieved oocytes. Still, neither hCG nor rLH (recombinant luteinizing hormone) was associated with better clinical outcomes [29].

Regarding the category that would most likely benefit from treatment, Chern and his colleagues found that women with hypoadrenalism of adrenal origin, reflected by decreased serum concentration of DHEAS, were more likely to improve after treatment [21]. In group 2 of Poseidon classification, the review developed by Abu-Musa recommends pre-treatment with DHEAS before OS to counteract age-related decreased androgen production and diminished theca function and obtain a higher pregnancy rate [30]. Testosterone administration in categories 3 and 4 may also evolve to be of service as an adjuvant treatment [12] because androgens increase the number of FSH receptors on granulosa cells and increase recruit ability and growth of preantral follicles and antral follicles via IGF-1 [31,32,33].

Despite the favourable results, the authors draw attention to the few high-quality studies on this subject and point out the need for further studies to reach a firm conclusion.

5. Conclusion

We are currently at the forefront of understanding the role of androgens in normal ovarian physiology and their involvement in follicular growth. Hypo androgenic and hyperandrogenic states appear to profoundly influence female Reproduction and ovarian physiology. Although not all mechanisms involved have been elucidated, and the quality of evidence regarding their role in predicting responder type during controlled ovarian stimulation is modest, it is implied that their determination could be of interest in predicting outcomes of ART and help clinicians and their infertile patients choose the best treatment modality. In the future, a more concise characterization of POR women could lead us to targeted treatments for these patients. Androgens are already being given on a large scale by professionals in human reproduction facilities hoping for better outcomes. If more randomized, large-scale controlled trials are to be designed, the next period could further our knowledge

about the same subtypes of females that could benefit from androgen treatment and the best duration and dose needed to assure proper outcomes. This review summarizes current data on how androgens are involved in follicular physiology and the applicability of serum and follicular determinations. Also, it conveys an overview of ART outcomes and caveats of usage of androgens as adjuvant therapy.

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