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Review Article

Clinical application of dehydroepiandrosterone in reproduction: A review of the evidence

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Abstract

The effect of dehydroepiandrosterone (DHEA) therapy on improvement of reproduction outcome is uncertain. Many earlier studies have shown conflicting results. Therefore, a review of the literature is needed to explore the role of DHEA in reproduction. We conducted a literature search of MEDLINE (Ovid) and Pub-Med (2000–June 2014) for all relevant articles that included the terms "dehydroepiandrosterone," "DHEA," and "*in vitro* fertilization." Among the search-identified articles, seven prospective self-controlled studies and four retrospective case–control studies showed DHEA as an adjuvant therapy able to improve *in vitro* fertilization outcomes in poor responders (women with diminished ovarian reserve and/or poor ovarian response). However, four randomized controlled trials did not support the benefit of DHEA therapy for poor responders. By contrast, one prospective randomized study showed that DHEA might be beneficial to reproduction in women without diminished ovarian reserve (normal responders). In summary, a review of the previously published studies does not provide clear evidence that DHEA can be a useful treatment to improve ovarian function in poor responders.

Keywords: dehydroepiandrosterone; diminished ovarian reserve; poor responders; reproduction

1. Introduction

The adrenal prohormone dehydroepiandrosterone (DHEA) and its sulfate conjugate, 3β-hydroxy-5-androsten-17-one, are C19 endogenous steroids, primarily produced by adrenal zona reticularis (50%) and ovarian theca cells (20%), and also derived from circulating DHEAS (30%).[1] DHEA levels steadily decrease with age (by 10% per decade), reaching a nadir after the age of 80 years,[2] suggesting that DHEA might be involved in the aging process. Therefore, many trials were conducted to test the antiaging effect of DHEA. However, nearly all trials failed to provide sufficient evidence to support the antiaging effects of DHEA. It was shown that DHEA supplementation provided minimal improvement of cognitive function.[2–4] Furthermore, DHEA cannot recover the previously declined well-being or promote quality of life.[4,5] Declined physical function also failed to be reversed by DHEA supplementation.[5,6]

Conflicts of interest: The authors declare that there are no conflicts of interest related to the subject matter or materials discussed in this article.

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By contrast, the use of DHEA might be beneficial in women with declined ovarian function, or diminished ovarian reserve (DOR) and/or poor ovarian response (POR), and these women were called poor responders. Since issues of subfertility is still a challenge in medicine, especially for the older population,[7] many strategies have been attempted that seek to ameliorate the problem.[8] Assisted reproductive techniques have advanced significantly in recent years, contributing to a significant improvement in reproduction secondary to female tubal occlusion and/or male infertility factors.[9,10] However, women with DOR or POR, estimated to occur in 5–18% of *in vitro* fertilization (IVF) cycles, present a significant challenge in assisted reproductive techniques.[11] These poor responders have poor IVF outcomes with extremely low pregnancy rates (2–4%), in spite of the use of various stimulation protocols and downregulation strategies.[12] The investigation by Casson et al[13] might be the first to utilize DHEA in the assisted reproductive techniques mediated by augmenting ovarian response. Several years later, Barad and Gleicher[14] described an astonishing case with rapidly increased oocyte production after DHEA supplementation. Thus, scientists were interested in the study of DHEA, since it may function as an antiaging agent to rescue DOR.[13,14] Nevertheless, despite the widespread use of DHEA as an adjuvant to IVF treatment protocols in women with DOR and/or POR worldwide,[14] two major questions still remain unresolved. First, effectiveness of DHEA has remained controversial, because of the lack of a strong evidence to substantiate it. Second, the exact mechanism of DHEA in reproduction remains speculative. Therefore, in our review, we attempted to explore the effect of DHEA on reproduction and also investigated its possible mechanism.

2. Methods

We searched Medline (Ovid) and Pub-Med (2000–June 2014) for case reports, case series, prospective self-controlled studies, retrospective case–control studies, and randomized controlled trials (RCTs). The Medical Subject Headings search terms used included the following: (1) DHEA and dehydroepiandrosterone; (2) poor response, low response, and diminished ovarian reserve; (3) premature ovarian failure and primary ovarian insufficiency; and (4) ovarian response, ovarian stimulation, ovarian reserve, *in vitro* fertilization (IVF), and assisted reproduction techniques.[1,13–68] We included RCTs that compared DHEA with placebo therapy in women, published as full manuscripts in the English language. The primary outcomes of these studies were clinical pregnancy and live birth rates, and the secondary outcomes were ovarian reserve, oocyte/embryo yield and quality, miscarriage rate, and aneuploidy rate. In our search, we analyzed seven prospective self-controlled studies[37–43] for poor responders, four retrospective case–control studies for poor responders,[47–50] four RCTs for poor responders,[32,54–56] one prospective randomized study for normal responders,[57] and one prospective randomized study for primary ovarian insufficiency (POI).[62]

3. Possible mechanisms

Although the underlying mechanisms of DHEA-induced improvement of reproductive outcomes remain uncertain, it is speculated that the effect of DHEA may be mediated by androgen and insulin-like growth factor-1 (IGF-1).

DHEA, an essential substrate for steroidogenesis, is a precursor of estradiol and testosterone[15] and serves as a prohormone of follicular fluid testosterone during ovarian induction with exogenous gonadotrophins.[16] Androgen receptors (ARs) were detected in the ovarian stroma and granulosa cells of the primordial follicles, and were more clearly seen in primary follicles and more advanced-stage follicles.[17–24] Perhaps, through ARs or metabolic pathways, androgens are believed to promote recruitment and initiation of primordial follicle growth; stimulate development of primary, preantral, and antral follicles[18]; rescue follicles from atresia[19]; suppress apoptosis[17]; and upregulate follicle-stimulating hormone (FSH) receptor expression[20,21,23] as well as IGF-1 expression.[22] In granulosa cell-specific AR knockout mice, a loss of classical genomic AR signaling in the granulosa cell brings about subfertility, dysfunctional late follicle development, increased follicular atresia, reduced cumulus cell (CC) expansion, as well as ovary viability.[25,26] Clinically, it has been indicated that the androgen level decreases with advancing female age and is lower in women with DOR, POR, or POI.[27,28] Two meta-analysis studies demonstrated that pretreatment with transdermal testosterone was associated with an increase in clinical pregnancy and live birth rates in poor responders undergoing ovarian stimulation for IVF.[29,30]

Besides, in an experimental model of sheep ovary, DHEA could stimulate early follicular growth during the preantral and early antral stages, possibly mediated through modulation of the anti-Müllerian hormone (AMH) expression and promotion of granulosa cell proliferation.[31] AMH was reported as a good marker of ovarian reserve.[69,70] In a clinical analysis, it was proposed that DHEA supplementation may enhance the follicular microenvironment by significantly decreasing the follicular fluid levels of hypoxic inducible factor 1, which represents a key molecule in the reaction of cells to hypoxia.[32,71]

By contrast, in a preliminary study, oral administration of DHEA led to a marked enhancement of serum IGF-1 concentrations.[33] The ratio of IGF-1/insulin-like growth factor binding protein-3 in serum or in the follicular fluid may be indicative of oocyte quality and maturity.[34] Furthermore, IGF-1 had positive effects on embryo quality and development.[35,36]

4. Poor responders or women with DOR and/or POR

In 2000, Casson et al[13] first postulated that using adjuvant DHEA in poor responders would lead to an enhanced ovarian response. A small series of five poor responders were administered DHEA 80 mg daily for 2 months prior to entering into their next intrauterine insemination cycle. The peak estradiol (E2) concentrations and E2/ampoule ratio increased in all six cycles. One of the cycles resulted in a

delivered twin pregnancy.[13] In 2005, Barad and Gleicher[14] reported the case of an older female (43 years) with DOR who received serial ovulation induction with concomitant daily self-administration of DHEA and weekly acupuncture treatment. After nine ovulation cycles, her peak E2 was 9178 pmol/mL, leading to the retrieval of 17 oocytes, which seemed to be a dramatic improvement.[14] Later on, a number of studies were conducted to better elucidate the effects of DHEA supplementation in poor responders.[37–45]

Several prospective self-controlled studies declared that beneficial effects on reproductive outcomes[37–40] and ovarian reserve markers[41–45] were found following DHEA supplementation in poor responders or women with DOR and/or POR (Table 1)[37–43]. Barad and Gleicher[37] proclaimed that paired analysis of IVF cycle outcomes in 25 patients with DOR, who underwent both pre- and post-DHEA cycles, demonstrated significant increases in retrieval oocytes ($p < 0.05$), fertilized oocytes ($p < 0.001$), normal Day 3 embryos ($p = 0.001$), transferred embryos ($p = 0.005$), and average embryo scores per oocyte ($p < 0.001$) following DHEA supplementation. The study of Sönmezer et al[38] enrolled 19 poor responders, who experienced IVF cycles both prior to and after DHEA treatment.[35] An increased number of retrieved oocytes (4.9 ± 2.3 vs. 2.5 ± 1.6; $p < 0.05$), metaphase II oocytes (4 ± 1.8 vs. 2.1 ± 1.8; $p < 0.05$), and top-quality Day 3 embryos (1.9 ± 0.8 vs. 0.7 ± 0.6; $p < 0.05$) were achieved in DHEA-treated cycles compared with those in the preceding cycles without DHEA treatment.[35] Pregnancy rates per patient and per embryo transfer (47.4% vs. 10.5%; $p < 0.01$ and 50.0% vs. 18.2%; $p < 0.05$) were also significantly superior in DHEA-supplemented cycles. In a recent study, Zangmo and colleagues[39] presented a prospective cohort study of 50 poor responders, who were treated with oral micronized DHEA daily for 4 months prior to entry into their next IVF cycles. After treatment with DHEA, there were significant increases in the numbers of retrieval oocytes, metaphase II oocytes, fertilized oocytes, Grade I embryos, and transferred embryos compared to non-DHEA treatment cycles in both age groups ($\leq$ 35 years and $\geq$ 36 years).[39] Moreover, Yilmaz et al[41] demonstrated that when they compared the evaluation of ovarian reserve markers in 41 DOR patients who underwent IVF cycles both prior to and after DHEA supplementation, significant improvement was observed in Day 3 FSH level, estradiol level, antral follicle count (AFC), AMH level, and inhibin B level ($p = 0.001$, 0.001, 0.002, 0.001, and 0.001, respectively,) following DHEA supplementation, without age-related difference. Additionally, Gleicher et al[46] performed a retrospective cross-sectional and longitudinal analysis of 120 consecutive women with DOR. Fifty-five patients in a longitudinal follow-up showed a significant improvement in AMH concentrations after DHEA supplementation over time ($p = 0.002$).[46] Among 55 women who had undergone IVF, those who conceived demonstrated a significantly better AMH response following DHEA supplementation than unsuccessful patients ($p = 0.001$).[46] Nonetheless, data from the self-controlled studies should be interpreted with caution due to potential bias.

In addition, some retrospective case–control studies showed that DHEA supplementation was able to improve the pregnancy rate,[47,48] reduce the miscarriage rate,[49] and lessen embryo aneuploidy[50] (Table 2). Barad et al[47] undertook a retrospective case–control study of 190 women with DOR who were divided into a study group ($n = 89$; supplied with DHEA prior to entry into their next IVF cycles) and a control group ($n = 101$; receiving IVF cycles without DHEA). The cumulative clinical pregnancy rates were significantly higher in the DHEA group than in the control group (28.4% vs. 11.9%; $p < 0.05$).[47] Remarkably, almost half of all the pregnancies in the study group occurred spontaneously prior to the initiation of IVF; however, even within the patients who proceeded with IVF, there was a strong trend towards higher pregnancy rates (20.6 vs. 11.9%).[47] The retrospective study of Fusi et al[48] included 38 women with DOR who received DHEA supplementation and 24 comparable women who had not been treated with DHEA prior to the IVF cycle, to evaluate the spontaneous pregnancy rate during preparation for IVF. Amazingly, the pregnancy rates (21.05% vs. 4.1%; $p < 0.05$) and ongoing pregnancy rates (13.15% vs. 0%; $p < 0.01$) measured prior to starting the IVF cycle were significantly higher in the DHEA group than in the control group.[48] Gleicher et al[49] retroactively compared miscarriage rates in 73 DHEA-supplemented pregnancies at two independent North American infertility centers, age-stratified, with miscarriages reported in a national United State IVF database.[46] Miscarriage rates after DHEA therapy were significantly lower at all ages, especially above the age of 35 years [odds

Table 1
Prospective self-controlled studies on the use of DHEA in poor responders.

Authors	Number	Period[a]	Findings
Barad and Gleicher[37]	25	≥4 mo	Benefits in retrieval oocytes, fertilized oocytes, normal Day 3 embryos, Day 3 embryo grade, and transferred embryos
Sönmezer et al[38]	19	≥3 mo	Benefits in retrieval oocytes, MII oocytes, embryo grade, and pregnancy rate
Yilmaz et al[41]	41	≥6 wk	Benefits in ovarian reserve markers (FSH, estradiol, AFC, AMH, and inhibin B)
Singh et al[42]	30	4 mo	Benefits in ovarian reserve markers (FSH and AMH)
Hyman et al[43]	32	≥3 mo	Benefits in AFC, retrieval oocytes, MII oocytes, and transferred embryos
Zangmo et al[39]	50	4 mo	Benefits in retrieval oocytes, MII oocytes, fertilized oocytes, Grade I embryos, and transferred embryos
Poli et al[40]	29	≥8 wk	Benefits in retrieval oocytes and oocyte quality

AFC = antral follicle count; AMH = anti-Müllerian hormone; DHEA = dehydroepiandrosterone; FSH = follicle-stimulating hormone; MII = metaphase II.
[a] Period represents the duration for which the women received 75 mg DHEA daily.

Table 2
Retrospective case–control studies of DHEA in poor responders.

Authors	Number	Period[a]	Findings
Barad et al[47]	89 DHEA vs. 101 controls	≥4 mo	Benefit in cumulative pregnancy rate
Gleicher et al[49]	73 DHEA vs. IVF data base[b]	≥2 mo	Reduction in miscarriage rate
Gleicher et al[50]	22 DHEA vs. 44 controls	4–12 wk	Reduction in aneuploid embryos
Fusi et al[48]	38 DHEA vs. 24 controls	≥12 wk	Benefit in spontaneous pregnancy

DHEA = dehydroepiandrosterone; IVF = *in vitro* fertilization.
[a] Period represents the duration for which the women received 75 mg DHEA daily.
[b] Compared to miscarriages reported in a national United States IVF database.

ratio = 0.49; 95% confidence interval (CI) 0.25–0.94; $p = 0.04$].[49] Furthermore, miscarriage rates after DHEA supplementation were not only lower than those in an average national IVF population but also comparable to the rates reported in general populations.[49] In a 1:2 matched case–control study, 22 women with DOR, supplemented with DHEA, and 44 control patients underwent preimplantation genetic screening of embryos during IVF cycles. DHEA supplementation was proved to have a significant reduction in the number (2.8 ± 2.5 vs. 4.5 ± 3.1; $p = 0.029$) and percentages (38.2 ± 24.4% vs. 61.0 ± 22.4%; $p < 0.001$) of aneuploid embryos.[50] Nevertheless, the results of retrospective case–control studies were also not free from bias.

According to the abovementioned studies, some people considered DHEA as a potential intervention to rejuvenate ovarian reserve and improve IVF outcomes for poor responders or women with DOR, but some people discounted those results because of the lack of a strong evidence from prospective RCTs.[51,52] A meta-analysis with only three eligible controlled studies was conducted to investigate the efficacy of DHEA as an adjuvant to improve IVF outcomes in women with DOR. There was no significant difference in the clinical pregnancy rate and miscarriage rates between women pretreated with DHEA and those without DHEA pretreatment (relative risk 1.87, 95% CI 0.96–3.64; $p = 0.07$ and relative risk 0.59, 95% CI 0.21–1.65; $p = 0.32$, respectively).[53] Therefore, the authors concluded that there remain insufficient data to support a beneficial role of DHEA as an adjuvant to IVF cycle, and well-designed RCTs are imperative to support the use of DHEA in standard practice for poor responders.[53] Unfortunately, such studies are, practically speaking, difficult to perform, since patients with DOR always have limited time to conceive and are unwilling to join a randomized trial in which they may be assigned to a placebo group. Indeed, two registered prospective, placebo RCTs, one in the United States and the other in Europe, had to be abandoned because of insufficient enrollment of women, willing to be randomized to placebo (Gleicher et al, unpublished data, 2006; Barad et al, unpublished data, 2007).

Encouragingly, the first prospective RCT was published by Wiser et al.[54] Their trial enrolled 33 women with significant DOR, 17 in the DHEA group and 16 in the control group.[54] In the DHEA group, 17 patients completed the first IVF cycle and nine completed a second cycle, for a total of 26 cycles; among the control group, 16 patients completed the first cycle and nine completed the second cycle, for a total of 25 cycles.[54] In the DHEA group, embryo quality improved significantly in the second cycle, compared to the first cycle. A significantly higher live birth rate was found in the total cycles in the DHEA group than in the control group (23.1% vs. 4.0%; $p = 0.05$), but not in the first cycle (17.6% vs. 6%; $p = 0.2$).[54] Unfortunately, Wiser et al's[54] study was criticized for severe methodological and statistical problems as well as many limitations and weaknesses,[51,52] leading us to discredit the data. Recently, three updated, randomized, prospective, controlled studies were published, but failed to confirm the benefits of DHEA in poor responders or DOR patients[31,55,56] (Table 3).[32,54–57,62] Artini et al[32] selected 24 patients diagnosed as poor responders, with 12 in the DHEA group and 12 in the control group in the RCT. The total numbers of retrieval oocytes, fertilized oocytes, good-quality embryos, transferred embryos, and clinical pregnancies per cycle were comparable between the two groups.[32] A randomized, double-blind, placebo-controlled study by Yeung et al[55] included 32 women

Table 3
Randomized controlled trials of DHEA on reproduction.

Authors	Number	Period[a]	Findings
Poor responders			
Wiser et al[b,54]	33	≥6 wk	Benefits in embryo quality and live birth rate
Artini et al[32]	24	3 mo	No benefits in IVF outcomes
Yeung et al[55]	32	≥12 wk	No benefits in ovarian response markers, ovarian response, or IVF outcomes
Kara et al[56]	208	12 wk	No benefits in IVF outcomes
Normal responders			
Tartagni et al[57]	52	8 wk	Benefits in IVF outcomes
Primary ovarian insufficiency or premature ovarian failure			
Yeung et al[62]	22	16 wk	Benefits in higher AFC and ovarian volume, but no benefits in serum AMH and FSH levels

AFC = antral follicle count; AMH = anti-Müllerian hormone; DHEA = dehydroepiandrosterone; FSH = follicle-stimulating hormone; IVF = *in vitro* fertilization.
[a] Period represents the duration for which the women received 75 mg DHEA daily.
[b] The study had been criticized because of severe methodological and statistical problems.

with POR, randomized to the DHEA group ($n = 16$) or placebo group ($n = 16$). DHEA supplementation indeed resulted in statistically significantly higher serum DHEAS level, free androgen index, and follicular DHEAS level, but no statistically significant differences in the ovarian response markers (AFC, AMH, or FSH) and IVF outcomes (pregnancy and live birth rates) were found between the two groups.[55] Kara et al[56] presented a randomized, prospective controlled trial that enrolled 208 DOR women, 104 cases in the DHEA group and 104 in the control group. The results failed to show that DHEA as an adjuvant enhances IVF outcomes (retrieval oocytes, metaphase II oocytes, fertilization rate, and clinical pregnancy rate) in women with DOR.[56]

In summary, our review of case reports, case series, prospective self-controlled studies, and retrospective case–control studies reported potential beneficial effects of DHEA supplementation on reproductive outcomes and ovarian reserve in poor responders or women with DOR and/or POR; however, a meta-analysis and seven prospective RCTs failed to verify the benefit. The role of DHEA in poor responders or women with DOR and/or POR seemed to be inconclusive and questionable after extensive reviews. Consequently, well-designed large-scale prospective RCTs are necessary to clarify whether or not DHEA has any beneficial effect on reproduction.

5. Normal responder

Casson et al[13] deemed that DHEA treatment, applied for normal patients, can decrease the dose of gonadotrophin. Gleicher et al[49] suggested that DHEA supplementation may be used in a normal fertile population above 35 years of age to diminish the miscarriage rate. However, there were no related published data until recently. Tartagni et al[57] submitted a double-blind, randomized, placebo-controlled study of 52 infertile patients with normal ovarian reserve, divided into the DHEA and control groups. Patients in the DHEA group had a significantly higher live birth rate ($p < 0.05$) and a lower miscarriage rate than those in the control group ($p < 0.05$)[57] (Table 3). Further research is essential to reinforce the result.

6. POI or premature ovarian failure

POI is a situation that represents impaired ovarian function on a continuum with intermittent ovulation; its diagnosis should be confirmed by obtaining two FSH levels in the menopausal range at least 1 month apart as well as amenorrhea for at least 4 months prior to the age of 40 years.[58] Up to 50% of women with POI have varying degrees of residual ovarian function, and it is estimated that approximately 5–10% can conceive spontaneously.[59] Nonetheless, POI usually gives rise to eventual premature ovarian failure, characterized by permanent loss of ovarian function.[55]

A case series of five patients with premature ovarian failure (mean FSH of 65.8 mIU/mL and mean E2 of 26.4 pg/mL), receiving 50–75 mg DHEA supplementation for 2–6 months, revealed dramatic improvement of ovarian reserve (mean FSH of 15.28 mIU/mL and mean E2 of 56.6 pg/mL), and all achieved pregnancy spontaneously or after intrauterine tuboperitoneal insemination.[60] Gleicher et al[61] performed a retrospective case–control study of 27 consecutive IVF cycles in women with POI, eight cases in the DHEA group and 19 in the control group, undergoing preimplantation genetic diagnosis. The results suggest that DHEA treatment increases the number of euploid embryos available for embryo transfer in women with POI.[61] A randomized, double-blinded, placebo-controlled study by Yeung et al[62] enrolled 22 women with unexplained POI, randomized into a DHEA group ($n = 10$) and a placebo group ($n = 12$). The AFC ($p = 0.034$) and total ovarian volume ($p = 0.033$) were significantly higher in the DHEA group than in the control group, but no significant change in serum AMH and FSH levels had been detected throughout the study[62] (Table 3). Further studies are needed to confirm this result.

7. Side effects

Women with DHEA supplementation may experience possible androgenic effects such as oily skin, acne, deepening of the voice, mild hair loss, and facial or body hair growth[47,63]; however, some feel energized, and report increased libido and an improved sense of well-being.[37,46,47] In published studies, the adverse effects of DHEA appear to be minimal with the therapeutic dose of 75 mg per day.[63] However, the long-term effects of DHEA supplementation remain unknown. Now that first-trimester placenta is capable of converting cholesterol to pregnenolone to DHEA,[64] exposure to DHEA in early pregnancy should be assured. Nevertheless, another safety issue of substantial concern is that DHEA may increase the risk of estrogen- or androgen-dependent malignancies. It has been substantiated that circulating estrogens and androgens are positively associated with the risk for breast cancer in premenopausal women.[65,66]

8. Further work

Of significant importance is the need for well-designed and large-scale prospective RCTs. Currently, several trials are under way to explore the potential effects of DHEA on ovarian response and reproductive outcomes in poor responders undergoing IVF cycles and in patients with POI (see http://clinicaltrials.gov). Moreover, the optimal dose and duration of DHEA supplementation were still uncertain, although the majority of the published studies used DHEA at a dose of 75 mg daily for 6–16 weeks. In an experimental model of rats, Ikeda et al[67] found that medium-term DHEA administration increases the number of follicles and enhances production of AMH, which may provide local negative feedback to folliculogenesis and interfere with growth of early follicle. Accordingly, long-term DHEA administration leads to a decrease in healthy follicles and an increase in atretic follicles. Further investigation is necessary to establish a standard dose and duration of DHEA administration, as well as ascertaining the maximal dose and duration.

By contrast, various definitions of poor response or DOR were noted in different studies, bringing about comparison difficulties since there was no standard definition of DOR or poor response prior to the Bologna criteria.[68] In 2011, the European Society of Human Reproduction and Embryology campus workshop in Bologna standardized the definition of abnormal ovarian reserve and poor response.[68] Hence, further research is suggested to enroll patients according to the Bologna criteria.

Furthermore, in recent years, analysis of gene expression in CCs is considered a noninvasive approach to identify oocytes with a high potential, to achieve better IVF outcomes. Recent studies have reported that the expression of candidate genes in CCs have the potential to serve as a marker of oocyte maturation and competence, embryo development and quality, pregnancy outcome, and live birth.[72−74] Thus, investigation of the effect of DHEA on gene expression of CCs may be a good idea to identify the exact mechanisms of DHEA in follicular microenvironment.[45] In our previous study, we found that DHEA supplementation might influence gene expression of CCs in women with POR, and these genes were involved in extracellular matrix formation, cell development, differentiation, and apoptosis regulation. Additionally, changes of the abovementioned genes favored the oocyte maturation.[45]

In conclusion, based on previous research, the effect of DHEA is believed to be mediated by androgen and IGF-1, although the exact mechanisms remain elusive. However, the effect of DHEA on gene changes of CCs may be a promising research field to explore the molecular mechanisms of DHEA on reproduction. A number of prospective self-controlled studies and retrospective case−control analyses favored the use of DHEA supplementation in poor responders or women with DOR and/or POR, but very few prospective RCTs supported its benefit, contributing to insufficient evidence for the usefulness of DHEA treatment in improving ovarian function in poor responders. Therefore, the effect of DHEA on reproduction appears to be inconclusive and dubious, and large-scale prospective RCTs are mandatory to clarify this doubt.

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