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Original article

Impact of Dehydroepiandrosterone on Poor Ovarian Reserve

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Abstract

Background: Ovarian reserve reflecting a woman's reproductive potential, naturally declines with age, impacting fertility. Various biomarkers, including anti-Müllerian hormone (AMH), follicle-stimulating hormone (FSH), estradiol (E2), and antral follicle count (AFC), are used to assess ovarian reserve. Dehydroepiandrosterone (DHEA) supplementation has been proposed to improve ovarian function in women with diminished ovarian reserve. **This study aims to** evaluate the effect of 12 weeks of DHEA supplementation on ovarian reserve markers in women with poor ovarian reserve, comparing it with a placebo group receiving folic acid. **Methods:** This randomized controlled study included 100 women aged 20-40 years with diminished ovarian reserve, diagnosed by low AMH, reduced AFC, and elevated FSH levels. The participants were divided into two equal groups:–cases group receiving DHEA (75 mg/day) and control group receiving folic acid (placebo) 5 mg/day for 12 weeks. Ovarian reserve was assessed by measuring AMH, FSH, LH, E2, AFC, and ovarian volume. **Results**: After 12 weeks, DHEA significantly increased AMH (1.24 ± 0.78 vs 0.85 ± 0.75, $p = 0.012$) and E2 (278.50 ± 135.80 vs 160.67 ± 116.90, $p < 0.001$), while decreasing FSH (9.07 ± 5.53 vs 11.87 ± 5.29, $p = 0.011$). DHEA also significantly increased AFC (4.1 vs 3.47, $p < 0.05$). **Conclusion:** DHEA supplementation significantly improves ovarian reserve markers, including AMH, E2, FSH, and AFC, in women with diminished ovarian reserve, supporting its use as a potential therapeutic option in this population.

Keywords: Dehydroepiandrosterone; Ovarian Reserve; Anti-Müllerian Hormone; Ollicle-Stimulating Hormone; Antral Follicle Count.

Introduction

Ovarian reserve is a critical factor in female reproductive health, signifies a woman's reproductive potential by indicating the quantity and quality of ovarian follicles and oocytes, both of which naturally decline with age (1,2). The process of folliculogenesis, influenced by hormones like follicle-stimulating hormone (FSH) and luteinizing hormone (LH), is essential for oocyte maturation and fertility (3). Multiple screening tests assess ovarian reserve, including basal FSH, anti-Müllerian hormone (AMH), estradiol (E2), antral follicle count (AFC), and inhibin B, with an ideal test showing low variability and high specificity (3). AMH, produced by granulosa cells (GCs) in small follicles, declines first with ovarian aging, followed by inhibin B, while FSH levels rise as AFC decreases (4).

AFC measured on Day 2 of the menstrual cycle through transvaginal ultrasonography, along with serum AMH levels, provide strong predictors of ovarian reserve by indicating both follicle quantity and quality (4). AFC reflects follicles sized 2-10 mm in both ovaries, typically above 12, while AMH, a glycoprotein hormone secreted mainly from GCs in pre-antral and antral follicles, typically ranges from 2-6.8 ng/ml in reproductive-age women, regardless of cycle phase. Oocyte quality declines with age, often due to a deteriorating oocyte environment likely influenced by reduced local androgen levels. Androgen supplementation, such as dehydroepiandrosterone (DHEA), may improve the ovarian environment and enhance oocyte maturation and ovulation (5). However, age remains the best surrogate marker for oocyte quality (6).

Low ovarian response to stimulation, often indicated by fewer than 3-5 developing follicles during an IVF cycle, is associated with poor reproductive outcomes but does not indicate an absolute inability to conceive; thus, it should not be the sole criterion for restricting access to infertility treatment (7). Androgens are crucial in early follicular maturation, as androgen receptors (ARs) are highly concentrated in pre-antral and growing follicles, where their activation supports the transition of dormant primordial follicles into the growing follicle pool (8).

DHEA enhances steroidogenesis as a precursor of estrogen and testosterone and may also support ovarian follicular growth by increasing IGF-1 levels, which promote granulosa cell proliferation and AMH production, thus aiding hormonal feedback to the pituitary and facilitating normal oocyte maturation and quality (9). DHEA supplementation has shown significant benefits for women with diminished ovarian reserve, enhancing AMH levels and improving ovarian response, particularly in older women and those with poor response to ovarian stimulation (9).

This study aims to evaluate the effect of DHEA administration for 12 weeks on the markers of ovarian reserve including (AMH, FSH, LH, E2 levels,

ovarian volume and AFC) in women with poor ovarian reserve or diminished ovarian response in a comparison with folic acid supplementation as a passive placebo.

Patients and methods

Design and population

This randomized-control study included 100 women aged 20-40 years with poor or diminished ovarian reserve (DOR) who were most likely to seek fertility treatment , it was conducted at Benha Teaching Hospital during the period from March 2017 to May 2023. The study was done after being approved by the Research Ethics Committee, Faculty of Medicine, Benha University. An informed written consent was obtained from the patients. Every patient received an explanation of the purpose of the study and had a secret code number.

DOR diagnostic criteria include low AMH levels below 1.1 ng/mL, indicating a reduced ovarian follicle pool, and a low AFC with fewer than 5 antral follicles visible at the start of the menstrual cycle via ultrasound, both reliable indicators of ovarian reserve. Elevated Day 3 FSH levels above 10 IU/L may also suggest DOR, though FSH levels are less consistently used due to variability. A history of poor ovarian response in prior assisted reproductive technology (ART) cycles, such as fewer than 3 mature eggs retrieved or low estradiol levels during stimulation, further supports DOR diagnosis and may warrant interventions like DHEA.

Exclusion criteria were hormonal disorders like polycystic ovary syndrome (PCOS) or untreated thyroid dysfunction; medical conditions such as active cancer, untreated autoimmune disorders, or severe endometriosis; current use of medications that may affect ovarian function; and participation in other clinical trials, which could confound study outcomes.

Grouping

Women were assigned into two equal groups, **Case group** included women receiving DHEA supplementation, defined by specific dosage and duration criteria, hypothesized to show improvements in ovarian function and fertility outcomes. **Control group** included women with similar baseline characteristics (age, BMI, ovarian reserve) who are not receiving DHEA, allowing comparison while controlling for confounding factors. By matching cases and controls on these variables, the study reduces selection bias, enhancing the accuracy of comparisons between the two groups.

Treatment

Involved administering 75 mg/day of DHEA in three doses over 12 weeks for case group, aiming to enhance ovarian reserve markers and follicular development. Both groups were monitored for ovarian response, with the control receiving a daily placebo of 5 mg folic acid/day for 12 weeks to maintain consistent conditions. Standardized protocols for assessments, monitoring, and follow-up were applied across groups, with

blinding procedures implemented to minimize bias in treatment allocation.

Data collection

Obtaining blood samples in heparinized tubes to prevent clotting, with sampling consistently done on day 3 of the menstrual cycle. For measuring AMH, FDA-approved Roche Elecsys AMH assays were used due to their accuracy and validation against standards. Laboratory processing included centrifuging samples to isolate plasma, storing at -20°C or -80°C until analysis, and strictly following assay instructions. Quality control measures involved regular calibration of equipment, adherence to SOPs, and participation in external quality programs to ensure assay accuracy and reliability through consistent monitoring of assay variation metrics.

Outcomes

The primary outcomes of the study included measuring changes in AMH levels, which serve as a marker of ovarian reserve, as well as assessing fluctuations in FSH, LH, and E2 levels before and after the intervention. Additionally, the AFC was evaluated using transvaginal ultrasound to determine the number of available follicles, which is an indicator of ovarian response to stimulation.

Sample size

The sample size was determined using power analysis with the Epi-Info software (version 2002) developed by the World Health Organization and the Centers for Disease Control and Prevention, Atlanta, Georgia, USA. The calculation was based on a 95% confidence level, 80% study power, and ethical considerations.

Approval code : MD 21-1-2018

Statistical analysis

Data will be collected, revised, coded, and imported to the Statistical Package for Social Science (IBM SPSS). The description of data will be in the form of mean ± SD for quantitative data and frequency and proportion for qualitative data. Students t-test and Mann-Whitney U-test will be used for analysis of quantitative data. Persons (X_2) and Fishers exact tests will be used for analysis of qualitative data. The distribution of quantitative data will be tested by Kolmogorov-Smirnov test of normality. The confidence interval will be set to 95% and the margin of error accepted will be set to 5%. So, the p-value will be considered significant as the following: P-value > 0.05: Nonsignificant (NS), P-value < 0.05: Significant (S), P-value < 0.01: Highly significant (HS). (SPSS Inc., Chicago, Illinois, USA)

Results

One hundred patients fulfilled our inclusion criteria of POR. Consent was signed to participate in our research. Fifty patients were exposed to DHEA treatment, and 50 patients were exposed to folic acid treatment for 12 weeks. **Figure 1**

There were no statistically significant differences between the studied groups

regarding age, body mass index, duration of marriage, duration of infertility, basal hormone levels (E2, FSH, LH, AMH), or ovarian reserve indicators (AFC, ovarian volume, presence of mature follicles) with p-values all exceeding 0.05. These results suggest homogeneity between the groups in terms of these factors. **Table 1**

After three months of treatment, DHEA significantly increased mean serum AMH (1.24 ± 0.78 vs 0.85 ± 0.75, $p = 0.012$) and E2 (278.50 ± 135.80 vs 160.67 ± 116.90, $p < 0.001$), while significantly decreasing FSH (9.07 ± 5.53 vs 11.87 ± 5.29, $p = 0.011$). In contrast, the Folic acid group showed a significant decrease in FSH (10.04 ± 5.48 vs 12.93 ± 7.02, $p = 0.02$), but no significant changes in AMH or E2. Additionally, DHEA treatment resulted in a significant increase in antral follicle count (4.1 vs 3.47, $p < 0.05$), while Folic acid showed no significant change (3.5 vs 3.25, $p = 0.091$). No significant differences were observed in ovarian volume for either treatment group. **Table 2**

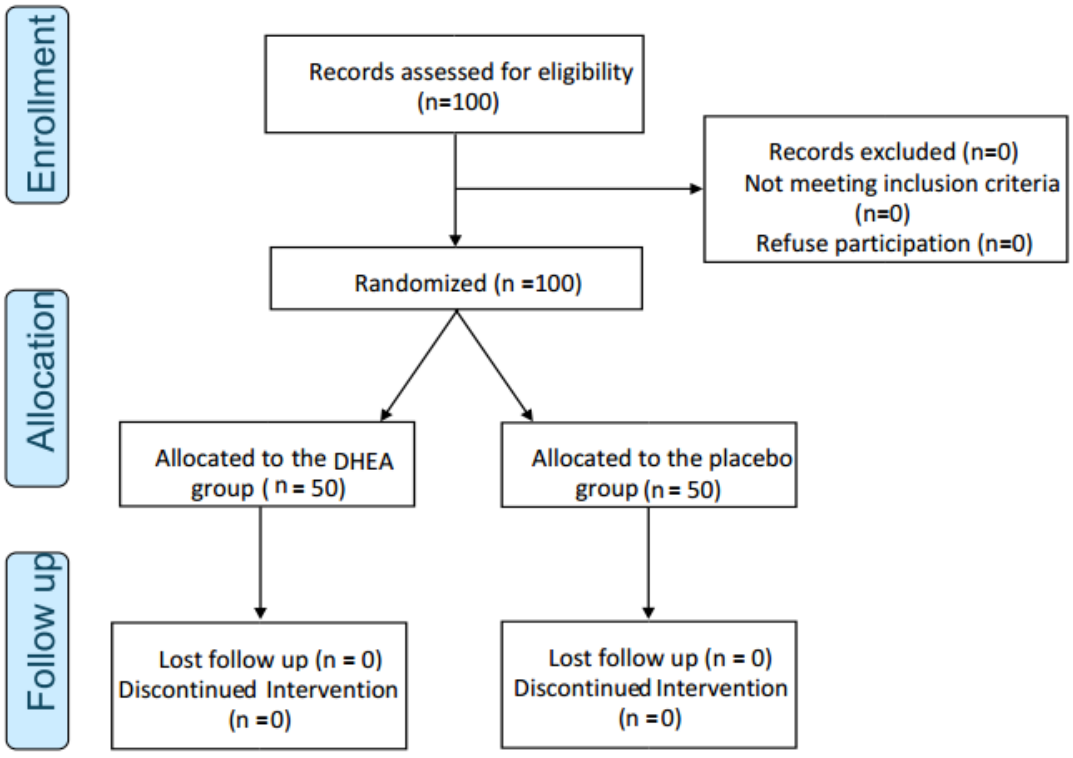

Figure 1: CONSORT flowchart of the enrolled patients

Table 1: Comparison between the studied groups regarding the demographic and anthropometric data, and baseline ovarian reserve markers (AMH, FSH, LH, E2)

Parameter	Groups				Test	p value
	DHEA treatment group (n= 50)		Folic acid treatment (n= 50)			
	Median	IQR	Median	IQR		
Age (year)	37.15	5.80	37.06	5.06	U= 4.44	0.358
BMI (kg/m2)	22.39	2.48	22.18	2.73	U= 2.15	0.611
Duration of marriage (years)	9.5	2.79	8.36	4.53	U= 3.985	0.274
Duration of infertility (years)	6.23	2.48	6.54	4.23	U= 2.368	0.407
	Mean	**SD**	**Mean**	**SD**		
AMH (ng/mL)	0.85	0.75	0.97	0.73	t= -3.981	0.464
Basal FSH (mIU/L)	11.87	5.29	12.93	7.02	t=-5.517	0.345
Basal LH (mIU/L)	4.85	2.33	4.41	2.54	t=-0.014	0.711
Basal E2 (pg/L)	160.67	116.9	181.56	137.2	t=-2.188	0.051
AFC (mm)	3.47	1.95	3.25	2.07	t=-1.352	0.058
Ovarian volume (cm3)	1.49	0.24	1.51	0.32	t=-1.254	0.413
Mature Follicles ≥10mm	N/A	N/A	N/A	N/A	--	--

BMI: Body Mass Index, AMH: Anti-Müllerian Hormone, FSH: Follicle Stimulating Hormone, LH: Luteinizing Hormone, E2: Estradiol, AFC: Antral Follicle Count, IQR: Interquartile Range, SD: Standard Deviation, U: Mann-Whitney U-test, t: Student t-test, DHEA: Dehydroepiandrosterone.

Table 2: Comparison between the studied groups regarding ovarian reserve markers (AMH, FSH, E2), and ovarian volume and AFC pre- & post-treatment in each group.

Parameter	Groups DHEA treatment group (n= 50) Pre treatment	Post treatment	P value	Folic acid treatment group (n= 50) Pre treatment	Post treatment	P value
AMH (ng/mL)	0.85 ± 0.75	1.24 ± 0.78	0.012*	0.97 ± 0.73	1.15 ± 1.07	0.328
FSH (mIU/L)	11.87 ± 5.29	9.07 ± 5.53	0.011*	12.93 ± 7.02	10.04 ± 5.48	0.02*
E2 (pg/L)	160.67 ± 116.9	278.50 ± 135.80	<0.001*	181.56± 137.2	213.95 ± 70.8	0.145
volume AFC (mm)	3.47 ± 1.95	4.1 ± 1.2	<0.05*	3.25 ± 2.07	3.5 ± 2.41	0.091
Ovarian (cm3)	1.49 ± 0.24	1.9 ± 0.31	0.069	1.51 ± 0.32	1.62 ± 0.14	0.127

AMH: Anti-Müllerian Hormone, FSH: Follicle Stimulating Hormone, LH: Luteinizing Hormone, E2: Estradiol, AFC: Antral Follicle Count, IQR: Interquartile Range, SD: Standard Deviation, U: Mann-Whitney U-test, t: Student t-test, DHEA: Dehydroepiandrosterone, * p-value (significance level <0.05).

Discussion

Ovarian reserve reflecting a woman's reproductive potential, naturally declines with age, impacting fertility. Various biomarkers, including AMH, FSH, E2, and AFC, are used to assess ovarian reserve. DHEA supplementation has been proposed to improve ovarian function in women with diminished ovarian reserve. The aim of the study is to evaluate the effect of 12 weeks of DHEA supplementation on ovarian reserve markers in women with poor ovarian reserve, comparing it with a placebo group receiving folic acid.

The study ensured baseline comparability between treatment groups in age, BMI, and ovarian reserve markers (AMH, FSH, E2, AFC, and ovarian volume) to minimize confounding. After 12 weeks of DHEA supplementation, significant improvements in ovarian reserve

markers were observed, including increased AMH and E2 levels and decreased FSH levels, indicating enhanced follicular development and ovarian function.

Over the study period, comprising three months, a total of 100 patients meeting the inclusion criteria for POR were enrolled, with 50 patients allocated to the DHEA treatment group and another 50 to the folic acid treatment group.

Following 12 weeks of DHEA supplementation, significant improvements in ovarian reserve markers were observed. Specifically, there was a notable increase in mean serum AMH levels and a concurrent decrease in FSH levels compared to pre-treatment levels. These findings suggest that DHEA supplementation may enhance ovarian reserve by promoting follicular development and inhibiting the negative feedback loop mediated by FSH. The observed increase in E2 levels post-treatment further supports the notion of improved ovarian function and hormone production in response to DHEA supplementation.

Some authors evaluated the effects of DHEA supplementation on AMH levels and AFC in women with diminished ovarian reserve undergoing IVF, finding increased AFC in six self-controlled studies and higher AMH levels in two studies across all age groups (10). However, the RCT by other authors reported no significant differences in AFC or hormone levels between DHEA and placebo groups, though women with higher follicular DHEA levels exhibited better-quality embryos (11). Similarly, (12) found no significant changes in estradiol levels with DHEA use. Overall, the evidence on DHEA's impact on ovarian reserve markers remains inconclusive, necessitating further research.

A study reported that daily DHEA supplementation did not increase the number of oocytes retrieved among poor IVF responders (13). In contrast, some authors found significant increases in retrieved oocytes in women under 36 years and older women (10). Some authors also observed significantly higher implantation rates in DHEA-treated patients across various case-control trials, RCTs, and prospective cohort studies, supported by other studies, who reported notable implantation rate improvements in the DHEA group (10, 14).

Some authors evaluated the effects of DHEA therapy on ovarian response and pregnancy outcomes in women with diminished ovarian reserve, finding mixed results (14). While some studies reported no significant differences in retrieved oocytes between DHEA and control groups, a published study demonstrated that DHEA supplementation improved oocyte retrieval, fertilization rates, reduced gonadotropin doses, and shortened controlled ovarian hyperstimulation duration, though parameters like metaphase II oocyte counts and total embryos remained unaffected (15).

A meta-analysis conducted that DHEA supplementation significantly increased clinical pregnancy rates in poor responders undergoing IVF, though this effect was not evident in RCTs due to concerns about statistical robustness (12). Conversely, it was reported that a significant increase in both clinical pregnancy and live birth rates among DHEA-treated patients based on a broader analysis of RCTs, cohort, and case-control studies, although only one study showed statistically reliable higher live birth rates (10).

(16) found that DHEA supplementation was associated with higher clinical pregnancy rates, but no significant difference was observed in RCTs alone. Some authors reported significant benefits from DHEA, including increased clinical and ongoing pregnancy rates (15). In contrast, a study found no significant differences in clinical pregnancy, ongoing pregnancy, live birth, or miscarriage rates between DHEA and control groups (11). Similarly, (12) reported higher clinical pregnancy and live birth rates in the DHEA group, though these differences were not statistically significant. Overall, while trends suggest potential benefits of DHEA on clinical pregnancy and live birth rates, the statistical significance varies across studies.

Patients with Premature Ovarian Failure (POF) experience significant reproductive challenges, with limited therapeutic options that require further research (17). High FSH levels in these individuals lead to the downregulation of granulosa-cell FSH receptors, making follicles resistant to stimulation. A study suggests that estrogen can increase FSH receptor numbers on GCs, enhancing FSH binding (18) Additionally, in cases of premature ovarian failure (POF), pretreatment with estrogen reduced FSH levels and accelerated ovulation induction, with some patients successfully conceiving following treatment with progesterone and estrogen.

In that study, in patients suffering from premature ovarian failure (POF), pretreatment with estrogens decreased FSH levels and increased the pace at which ovulation was induced. The folic acid group saw unsignificant effects with a significant drop in FSH and a slight insignificant increase in AMH.

Although this conclusion is not consistent with other research, a recent RCT found no significant differences in serum FSH and AMH levels between the DHEA group and the folic acid group over the trial period. The DHEA group showed a considerable increase in E2, while the folic acid group's patients had a significantly lower level of E2 .

DHEA plays a crucial role in follicular development as androgens are essential for proper follicle maturation, primarily through ARs on GCs. DHEA, a key precursor in human sex steroid synthesis, may enhance steroidogenesis in the ovary, supporting the two-cell/two-gonadotropin theory (19). In peripheral tissues, DHEA is converted to E2 and

testosterone, with testosterone and its metabolite 5α-dihydrotestosterone (DHT) being the most potent AR agonists. Increased AR expression influences follicle development and FSH activity, suggesting a feedback loop between androgens and FSH that regulates follicular maturation (20,21). Short-term DHEA exposure has been shown to increase oocyte yield, indicating potential synergy between DHEA and FSH for patients with POR.

This study assessed the impact of DHEA on ovarian reserve by measuring serum levels of AMH, FSH, and E2. DHEA treatment resulted in significantly lower FSH levels and higher AMH levels compared to the folic acid group, aligning with previous research. AMH is a reliable predictor of ovarian response and live-birth outcomes, particularly in women with reduced OR. Despite similar changes in FSH and AMH between the DHEA and folic acid groups, a recent RCT showed no significant differences in these levels. Additionally, DHEA treatment significantly increased E2 levels compared to folic acid. Notably, patients with low FSH levels showed a rise in AMH, but no significant changes in FSH were observed. The effect of DHEA was more pronounced in patients with high FSH levels, who showed a notable decrease in FSH and an increase in AMH. Although the study group was small, the results highlighted notable differences between the DHEA and folic acid groups.

While the findings of this study are promising, several limitations should be acknowledged. These include the relatively short duration of treatment and follow-up, the lack of a placebo-controlled design, and the absence of pregnancy outcomes as a measure of treatment success.

Conclusion

DHEA supplementation significantly improves ovarian reserve markers, including increased AMH and E2 levels, and enhances ovarian response, as evidenced by a higher antral follicle count, in women with diminished ovarian reserve. In contrast, folic acid supplementation showed no significant impact on these parameters. This suggests that DHEA could be a promising therapeutic option for improving fertility outcomes in women with poor ovarian reserve.

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