Dehydroepiandrosterone as an adjunct to gonadotropins in infertile Indian women with premature ovarian aging: A pilot study

ABSTRACT

BACKGROUND: Dehydroepiandrosterone (DHEA) supplementation is a relatively recent development that augments ovarian responsiveness in patients with poor ovarian reserve and premature ovarian aging (POA). AIMS: To evaluate the efficacy of DHEA supplementation prior to gonadotropins for ovulation induction in women with POA. DESIGN: Prospective randomized controlled study. METHODS: Fifty infertile women with POA were randomized into two groups of 25 each. Group 1 received tablet DHEA 25 mg while group 2 received placebo thrice daily for 6 months. After 3 months, gonadotropin induction with intrauterine insemination was done. STATISTICAL ANALYSIS: Groups were compared using t-test and Mann–Whitney U-test as appropriate. Pre- and post-parameters were compared using t-test -paired and Wilcoxon signed-rank tests as appropriate. RESULTS: Of 50 patients, 62% (31/50) presented with primary and 38% (19/50) with secondary infertility. The mean age was 32.1 ± 4.7 years. Serum antimullerian hormone levels (1.5 ± 0.6–1.9 ± 0.4 ng/ml vs. 1.4 ± 0.5–1.5 ± 0.6 ng/ml) and antral follicle count (3.2 ± 1.0–9.3 ± 3.1 vs. 3.3 ± 1.1–3.4 ± 1.4) improved significantly in DHEA group after 3 months. Serum follicular stimulating hormone and estradiol levels though showed significant intra-group improvement (16.9 ± 5.5 mIU/ml to 14.7 ± 6.2 mIU/ml and 86.6 ± 57.5 pg/ml to 105.6 ± 54.3 pg/ml, respectively) with DHEA, the inter group difference was not significant. Ovulation increased from 48% to 86.3% in DHEA group versus 44–66% in placebo group. Six women (24%) conceived after DHEA in comparison to none in the placebo group. CONCLUSIONS: DHEA supplementation may have a beneficial role as an adjunct to gonadotropins in the treatment of infertility with POA, but further evidence is required.

KEY WORDS: Antimullerian hormone, dehydroepiandrosterone, premature ovarian aging

INTRODUCTION

Ovarian failure is a natural consequence of the aging process. Approximately 10% of women deviate from age-specific standards and before reaching menopause, suffer from premature ovarian aging (POA), also called occult primary ovarian insufficiency.[1,2] POA represents a milder precursor stage to premature ovarian failure (POF). Diminished ovarian reserve (DOR) is defined by elevated age-specific baseline follicular stimulating hormone (FSH) levels and/or decreased antimullerian hormone (AMH) levels <1.5 ng/ml, indicative of DOR at all ages.[2,3] The levels of FSH may vary in different women but the fertility potential decreases significantly when levels are >12–15 mIU/ml.[4,5] Those women with FSH ≥12 but <40 mIU/ml with age under 40 years come under the definition of POA.[5,6] Either in vitro fertilization (IVF) with donor oocytes or adoption is often advised as a last resort to treatment for such women with DOR.

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Dehydroepiandrosterone (DHEA) supplementation is a relatively recent development in the armamentarium for the management of female infertility, used primarily in women with DOR. DHEA has been found to exert its effect in DOR in a number of ways like increased follicular insulin-like growth factor-I or inducing a polycystic ovarian syndrome (PCOS) like environment.[6,7] In assisted reproductive technology cycles, DHEA has also been reported to reduce aneuploidy and thus improves oocyte and embryo numbers as well quality.[8] Various studies in IVF have shown the role of DHEA in poor responders in augmenting ovarian responsiveness. Thus, a study was planned to evaluate the effect of DHEA as an adjunct to gonadotropins on ovulation and pregnancy rate in intrauterine insemination cycles (IUI) cycles in infertile patients of POA.

**METHODS**

Women with age <40 years presenting with infertility in the outpatient department and infertility clinic from April 2010 to March 2012 were assessed and 50 women with POA were recruited. POA was documented with FSH levels ≥12 mIU/ml but <40 mIU/ml measured on 2nd day of the unstimulated cycle. Those women with POA who were not willing for IVF due to nonaffordability were included in the study. The patients with a history of any hormonal intake/ovulation induction within 3 months or those with other causes of infertility like tubal or male factor were excluded from the study. A written informed consent was obtained from each participant after a detailed explanation and information about the study. The study was done in accordance with the ethical standards of the Institutional Ethical Committee.

To best of our knowledge, there has been no previous study from India in which DHEA was given in patients of POA in a non IVF setting. As this is the first such study, it can be considered a pilot study in India. Randomization was done according to computerized randomization table by a research nurse not involved in patients’ further clinical management and patients were divided into two groups of 25 each. Group 1 received tablet DHEA (Tab Eema-D, Corona Remedies Pvt Ltd., Ahmedabad, Gujarat, India) 25 mg 3 times daily for 6 cycles while the women in group 2 were given tablet containing inert lactulose as placebo. The placebo tablets were identically same as DHEA tablet with respect to size, shape, and color. After 3 months of pretreatment, ovulation was induced with gonadotropins from day 3 of the cycle followed by IUI for 3 cycles. Starting dose of gonadotropin was 75 IU of human menopausal gonadotropin intramuscular (injection GMH, INCA Lifesciences, Sunpharma Laboratories Ltd., Mumbai), which was incremented according to the response and maximum dose given per day was 300 IU. Serial follicular monitoring by transvaginal ultrasound (TVS) was done. Ovulation was triggered with human chorionic gonadotropin (injection HUCOG, 5000 IU/ml Intramuscular, Bharat Serums Ltd., Ambernath) when at least one follicle reached a mean diameter of 18 mm followed by IUI after 36 h. Ovulation was confirmed on TVS by noticing the presence of free fluid in the pouch of douglas and crumpled follicle.

Baseline FSH, luteinizing hormone (LH), thyroid stimulating hormone (TSH), prolactin, testosterone, estradiol, and DHEA-S (DHEA sulfate) were done on day 2–3 of cycle by the chemiluminescent immunoassay using Access 2 Immunoassay system (Beckman Coulter) while AMH was done by enzyme-linked immunosorbent assay (ELISA). Antral follicle count (AFC) was measured on day 2–3 of cycle by counting number of antral follicles (2–10 mm) in transverse axial section of the ovaries on GE LOGIQ 3 PRO ultrasound machine. AFC was measured in both ovaries and the sum of both counts was taken as AFC. Hormone profile including FSH, LH, testosterone, DHEA-S, and estradiol was repeated at 3 months and 6 months interval in both the groups while AMH was repeated only once after 3 months of therapy by ELISA due to limited availability of kits. The subjects were followed up for a period of 6 months. During statistical analysis, changes within the group were analyzed by paired t-test/Wilcoxon signed-rank/repeated measured ANOVA/Friedman test for continuous parameters. The difference between the groups was analyzed by Wilcoxon rank-sum/t-test. P < 0.05 was taken as statistically significant.

The primary outcome measured was the increase in AFC defined by the total number of antral follicles (2–10 mm) on day 2, ovulation rate measured by the number of patients in which ovulation was documented and change in hormonal profile while the secondary outcome was documentation of pregnancy.

**RESULTS**

Of the total 50 women, 62% (n = 31) presented with primary infertility and 38% (n = 19) with secondary infertility. The mean age of women was 32.1 ± 4.7 years with a range of 22–39 years. The two groups were comparable regarding baseline characteristics and hormone profile as shown in Table 1.

With DHEA supplementation, serum FSH decreased significantly from 16.9 ± 5.5 mIU/ml to 14.7 ± 6.2 mIU/ml at 6 months as compared to placebo group (17.1 ± 7.2–18.4 ± 10 mIU/ml) though it did not reach statistical significance (P = 0.29). A steep fall in FSH levels was seen in the first 3 months followed by a gradual fall as shown in Figure 1. As a result, serum estradiol levels increased...
from 86.6 ± 57.5 to 105.6 ± 54.3 pg/ml in intervention group as compared to control group (85.1 ± 40.5-87.2 ± 40.6 pg/ml, \(P = 0.6\)). Serum LH levels also showed a fall in DHEA group as compared to placebo while there was no change in serum testosterone levels as shown in Table 2. DHEA supplementation improved serum AMH levels significantly from 1.5 ± 0.6 to 1.9 ± 0.4 ng/ml after 3 months as compared to placebo as shown in Figure 2. Similarly, AFC showed a significant increase from 3.2 ± 1.0 to 9.3 ± 3.1 after 6 months of DHEA in comparison to placebo (3.3 ± 1.1-3.4 ± 1.4) as shown in Figure 3. In DHEA pretreated group ovulation rate increased from 48% to 86.3% after 6 months to placebo group (44-66.6%; \(P = 0.16\)) as shown in Table 3. DHEA supplementation prior to gonadotropin induction reduced the dose (1 ampoule = 75 IU) and the duration at the start of induction and it decreased subsequently in last cycle while no significant difference observed between 4 and 6 months in group 2 [Table 4a and b].

Of 25 subjects in DHEA pretreated group, 24% (\(n = 6\)) conceived in comparison to none in the placebo group. One patient conceived spontaneously after 3 months of DHEA alone. Three patients conceived during induction with DHEA plus gonadotropins, one in the 5th cycle and two during the 6th cycle and the remaining 2 patients conceived spontaneously during 1st and 3rd month follow-up period. Of the total 6 pregnancies, three ended in early pregnancy loss; two with missed abortion and one was a molar pregnancy while the remaining three continued pregnancy till term and delivered one female and two male baby by cesarean section (one due to fetal distress and two due to malpresentation).

None of our patients reported any adverse effect except mild acne in 2/25 (8%) women receiving DHEA. None of the patients had androgenic side effects of DHEA such as weight gain, hirsutism, or voice change. Of 25 patients in group B, 3/25 (12%) had complained of nausea, 5/25 (20%) had loose stools, and the other 3 (12%) had bloating. No such side effects were seen in DHEA group. None of the patients withdrew from DHEA therapy because of the side effects.

**DISCUSSION**

As the prevalence of infertile population with DOR is increasing, the treatment of POA assumes increasing clinical importance. Our study showed that DHEA results in an improvement in hormone profile, that is, decrease in serum FSH and an increase in serum estradiol and AMH levels. There was also a significant increase in AFC and ovulation rate after DHEA suggesting a primary effect on the ovarian

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**Table 1: Comparison of baseline characteristics of subjects in two groups**

| Baseline characteristics | Mean±SD (minimum-maximum) | \(P\) |
|--------------------------|---------------------------|------|
| Age (years)              | 32.9±4.7 (23-39)           | 0.16 |
| Weight (kg)              | 56.5±5.3 (44-66)           | 0.13 |
| BMI (kg/m\(^2\))         | 22.9±2.6 (21.8-24.0)       | 0.24 |
| Duration of infertility (years) | 6.08±4.7 (1-16)     | 0.6  |
| FSH (mIU/ml)             | 16.9±5.5 (12.2-27.6)       | 0.5  |
| LH (mIU/ml)              | 7.8±5.3 (2.7-23.1)         | 0.6  |
| Estradiol (pg/ml)        | 86.6±57.5 (62.9-110.4)     | 0.4  |
| DHEA-S (µg/dl)           | 220.2±103.4 (98-380)       | 0.1  |
| Testosterone (ng/ml)     | 0.86±1.09 (0.1-1.3)        | 0.4  |
| Prolactin (ng/ml)        | 19.0±5.4 (5.43-23.6)       | 0.6  |
| TSH (mIU/ml)             | 2.9±1.0 (1.3-4.8)          | 0.06 |
| AMH (ng/ml)              | 1.5±0.6 (0.3-2.7)          | 0.8  |
| AFC*                     | 3.2±1 (2-6)                | 0.6  |

\*AFC=Antral follicle count, SD=Standard deviation, BMI=Body mass index, FSH=Follicular stimulating hormone, LH=Luteinizing hormone, DHEA-S=Dehydroepiandrosterone sulfate, TSH=Thyroid stimulating hormone, AMH=Antimullerian hormone.
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**Table 2: Comparison of hormonal profile in two groups post therapy**

| Characteristic | Group 1 (mean±SD) | Group 2 (mean±SD) | P value within groups | P value between groups |
|---------------|-----------------|-----------------|---------------------|----------------------|
| | Baseline | 3 months | 6 months | | Baseline | 3 months | 6 months | | |
| FSH (mIU/ml) | 16.9±5.5 | 14.9±5.7 | 14.7±6.2 | <0.001 | 17.1±7.2 | 17.6±7.7 | 18.4±10 | 0.26 | 0.29 |
| LH (mIU/ml) | 7.8±5.3 | 5.9±3.4 | 5.7±3.16 | <0.001 | 8.4±5.5 | 8.3±3.2 | 8.1±5.17 | 0.14 | 0.16 |
| Estradiol (pg/ml) | 86.6±75.7 | 101.1±67.3 | 105.6±54.3 | 0.002 | 85.1±40.5 | 85.5±39.2 | 87.2±40.6 | 0.5 | 0.6 |
| AMH (ng/ml) | 1.5±0.6 | 1.9±0.4 | <0.001 | 1.4±0.5 | 1.5±0.6 | 0.6 | <0.001 |
| Total testosterone (ng/ml) | 0.86±1.09 | 0.72±0.88 | 0.68±0.72 | 0.06 | 0.63±0.56 | 0.53±0.37 | 0.49±0.41 | 0.16 | 0.29 |

FSH=follicular stimulating hormone, LH=luteinizing hormone, SD=Standard deviation, AMH=Antimullerian hormone

**Table 3: Comparison of mean number of mature follicles and ovulation rate between two groups**

| | 1st cycle | 2nd cycle | 3rd cycle | 4th cycle | 5th cycle | 6th cycle | P value within groups | P value between groups |
|---|---|---|---|---|---|---|---|---|
| Group 1 | n=25 | n=25 | n=25 | n=23 | n=23 | n=22 | <0.001 | 0.001 |
| | 1.0±0.4 | 1.0±0.4 | 1.1±0.4 | 1.8±0.5 | 1.9±0.5 | 2.4±0.8 | | |
| Group 2 | n=25 | n=25 | n=24 | n=24 | n=24 | n=24 | 0.01 | | |
| | 1.02±0.3 | 1.1±0.5 | 1.06±0.7 | 1.2±0.5 | 1.2±0.4 | 1.28±0.5 | | |
| Number of patients with ovulation (%) | | | | | | | | |
| Group 1 | n=25 | n=25 | n=25 | n=23 | n=23 | n=22 | 0.16 | | |
| | 12 (48) | 13 (52) | 15 (60) | 18 (78.2) | 19 (82.6) | 19 (86.3) | | |
| Group 2 | n=25 | n=25 | n=24 | n=24 | n=24 | n=24 | | | |
| | 11 (44) | 12 (48) | 11 (45.8) | 17 (70.8) | 16 (66.6) | 16 (66.6) | | |

SD=Standard deviation

**Table 4a: Mean dose of gonadotropins (HMG) in number of ampoules (1 ampoule=75 IU) in both the groups**

| Groups | Dose of gonadotropins in ampoules | P value within groups | P value between groups |
|---|---|---|---|
| | Mean±SD (range) | 4th cycle | 5th cycle | 6th cycle | | |
| 1 | 13.3±7.5 | 12.2±8.3 | 12.4±7.5 | 0.01 | <0.001 |
| | (6-39) | (6-38) | (6-37) | | |
| 2 | 22.4±8.0 | 25.0±9.3 | 24.1±9.8 | 0.20 | | |
| | (6-41) | (6-42) | (6-44) | | |

SD=Standard deviation, HMG=Human menopausal gonadotropin

**Table 4b: Mean duration of gonadotropins (HMG) in days in both the groups**

| Groups | Duration of gonadotropins in days | P value within groups | P value between groups |
|---|---|---|---|
| | Mean±SD (range) | 4th cycle | 5th cycle | 6th cycle | | |
| 1 | 8.1±2.8 | 7.1±2.1 | 7.4±2.4 | 0.07 | <0.001 |
| | (6-16) | (6-11) | (6-14) | | |
| 2 | 9.8±2.0 | 10.2±2.1 | 10.2±2.5 | 0.27 | | |
| | (6-14) | (6-14) | (6-16) | | |

SD=Standard deviation, HMG=Human menopausal gonadotropin

Most of the previous studies evaluating the role of DHEA were IVF studies except one study by Mamas and Mamas in 2009 who first reported the successful outcomes in 5 non IVF patients with postmenopausal FSH levels >40 mIU/ml who showed an improved hormonal profile and all achieved pregnancy after receiving DHEA therapy for 2–3 months.[9] The first randomized controlled study to evaluate the contribution of DHEA to poor ovarian response was done in 2010 in IVF patients that showed a higher live birth rate among the DHEA-treated patients.[10] Our study was the first randomized study to evaluate the role of DHEA in infertile patients of POA with ovulation induction and IUI and it showed that DHEA supplementation group in patients with POA improved conception rates.

The mechanism of action of DHEA on the ovary is not yet clear. DHEA has been found to be a prehormone of the follicular fluid testosterone during the administration of gonadotropins for ovulation induction which leads to the formation of estradiol.[11,12] It has been proposed in an earlier study by Barad et al. (2006) that androgens can be a metabolic precursor for steroid production and acts as ligands for androgen receptors, thus influencing follicular growth in ovaries.[8] Another possible mechanism was described by Casson et al. who hypothesized that the beneficial effect of DHEA may be due to an increase in insulin-like growth factor-I.[13] Barad and Gleicher...
postulated that the effect of DHEA was due to the creation of PCOS-like characteristics in the aging ovary.\[6\] The effect of DHEA is cumulative as more of the antral follicles become exposed to the treatment.\[14\] This increase in preantral and antral follicles leads to an increase in AMH production and more follicles become available for induction with gonadotropins which is reflected by a fall in serum FSH and rise in serum estradiol. The theory of PCOS-like environment can explain the increase in response from cycle to cycle under DHEA exposure. A significant increase in serum AMH levels and estradiol and fall in serum FSH in our study reflects improved ovarian responsiveness after DHEA supplementation.

Serum AMH was significantly increased in our study after 3 months of DHEA. In 2010 a randomized, prospective, controlled study reported that AMH concentrations significantly improved after DHEA supplementation over time (P = 0.002).\[10\] A recent prospective clinical trial conducted by Singh et al. in 30 patients with history of poor response to previous IVF cycles showed that DHEA resulted in a significant increase in the serum AMH in all age groups (35, 36–38, and >38 years), (P < 0.05). A significant decrease (P < 0.05) was noted in day 2 FSH in all age groups while estradiol level on the day of human chorionic gonadotropin administration also increased significantly.\[13\]

Our study also showed a decrease in mean FSH level from 16.5 ± 5.5 to 14.7 ± 6.2 mIU/ml post DHEA therapy for 6 months. Serum FSH levels though showed significant intra-group reduction at 6 months with DHEA, the inter group difference did not reach statistical significance when compared with placebo probably due to the small sample size. There was also a significant increase in serum estradiol levels from baseline to 6 months in the intervention group as compared to controls although the inter group difference was not statistically significant (P = 0.6) due to relatively small sample size. Mamas and Mamas in 2009 published a case series of women with POF which also reported a significant decrease in the mean FSH level (45.8 mIU/ml vs. 15.28 mIU/ml) and an increase in mean estradiol level from 26.4 pg/ml to 56.6 pg/ml after DHEA therapy for 2–4 months.\[9\] Similar studies in IVF also reported a significant increase in serum estradiol levels.\[6,13,14\] This improvement in ovarian responsiveness in turn is depicted by the dose reduction of gonadotropins as found in our study. DHEA has a beneficial effect on aging ovarian environments thus improving oocyte/embryo quality. In our study, out of the total 6 pregnancies, three ended in early pregnancy loss; two with missed abortion; and one was a molar pregnancy.

A systematic review was done in 2011 that suggested that DHEA improves ovarian function, increases pregnancy chances and lowers miscarriage rates by reducing aneuploidy. DHEA over time also appears to objectively improve ovarian reserve.\[16,17\] Subsequent to this, one more meta-analysis has been published in 2013 which revealed the presence of insufficient data to support a beneficial role of DHEA as an adjuvant to controlled ovarian stimulation in IVF cycle necessitating the need for well-designed, randomized controlled trials.\[18\] The effect of DHEA therapy and its outcome in various studies has been summarized in Table 5. A number of prior studies have given DHEA supplementation for a variable period of time ranging from 6 to 8 weeks to 3–4 months. As this study was done in a non IVF setting in women with POA, DHEA supplementation was prescribed for 3 months to ensure a good ovarian response after stimulation.\[9,10,16,19\]

Though the literature shows possible androgenic side effects with DHEA like weight gain, hirsutism, or voice change but none of our patients reported any adverse effect except mild acne in 8% women receiving DHEA. The side effects such as nausea, loose stools, and bloating seen in some patients in the placebo group may be due to the use of lactulose as placebo.

Although the sample size is a significant limitation of this study, our findings show a beneficial role of DHEA regarding the hormonal profile and ovulation and pregnancy rate in women with POA. The data support previous reports about the beneficial effects of DHEA. In developing countries like India, many patients due to economic and cultural restraints are not able to afford ovum donation or other assisted reproductive techniques. Thus, the possibility of a significant improvement in ovarian response with such an intervention in cases of DOR seems to be very promising. Furthermore, the effect of DHEA therapy in decreasing the dosage and duration requirement of gonadotropins has a promising role due to the high cost involved in treatment with gonadotropins.

**CONCLUSIONS**

DHEA supplementation has a beneficial role as an adjunct to gonadotropins for the treatment of infertility in cases of POA due to its favorable effect on hormone profile, that is, decrease in serum FSH and an increase in serum estradiol and AMH levels. Not only it has an effect on the increase in AFC and ovulation rate but also allows

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**Figure 3:** Comparison of change in AFC between groups

![Graph showing comparison of change in AFC between groups](image)

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**CONCLUSIONS**

DHEA supplementation has a beneficial role as an adjunct to gonadotropins for the treatment of infertility in cases of POA due to its favorable effect on hormone profile, that is, decrease in serum FSH and an increase in serum estradiol and AMH levels. Not only it has an effect on the increase in AFC and ovulation rate but also allows...
for a reduction in dose and the duration requirement of gonadotropins. Although conception rate may increase with DHEA supplementation in women with POA but such women needs to be advised about an early recourse to IVF. However, more randomized clinical trials and further research are required to reinforce our findings.

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**Conflicts of interest**

There are no conflicts of interest.

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