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ROLE OF DHEA IN DIMINISHED OVARIAN RESERVE, SYSTEMATIC REVIEW

Vinita Singh*, Pushpawati Thakur, Sarita Agrawal, Anjum, Byasdev.

All India Institute of Medical Science, Raipur.

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***Correspondence for Author**
Dr. Vinita Singh
All India Institute of Medical Science, Raipur

ABSTRACT

Introduction: DHEA is the major circulating steroid in human blood and it is a central intermediate in the metabolic pathway of sex steroid hormone formation. Dehydroepiandrosterone (DHEA) has been reported to improve pregnancy chances with DOR, and is now utilized by approximately one third of all IVF centres world-wide. Published data suggests that DHEA improves oocyte yields, oocyte quality and hence embryo quality (decreases aneuploidy) & quantity, increases IVF outcomes, pregnancy rates and spontaneous pregnancy chances. **Aim**: This systematic review aims to summarize the role of DHEA as an adjuvant to stimulation protocol in women with diminished ovarian reserve or poor-responders based on meta-analysis of the published controlled studies. **Methods**: All published articles on the role of DHEA in infertile women from JAN 2000 to OCT 2014 were reviewed. **Result:** Combined, these data suggest that DHEA supplementation may be effective in improving pregnancy chances in women with DOR. Treatment with DHEA both reduces ovarian oxidative stress and rates of atresia. Several studies have suggested an improvement in pregnancy rates with the use of DHEA. Potential mechanisms include improved follicular steroidogenesis, increased IGF-1, acting as a pre-hormone for follicular testosterone, reducing aneuploidy, and increasing AMH and antral follicle count. While the role of DHEA is intriguing, evidence-based recommendations are lacking. **Conclusion:**. Considering absence of significant side effects and availability of DHEA as a food supplement, here presented data support utilization of DHEA in association with DOR, though attempts should be made to further define best suited patient populations for such treatment, maximally effective treatment protocols and best delivery systems. Large randomized prospective trials are needed. Until such trials are conducted, DHEA may be of benefit in suitable, well informed, and consented women with diminished ovarian reserve.

KEYWORDS: Dehydroepiandrosterone (DHEA), Diminished ovarian reserve (DOR), Poor ovarian response, *In vitro* fertilization (IVF).

INTRODUCTION

Ovarian reserve (OR) is generally perceived as the sum of all still available follicles/oocytes within ovaries.[1, 2] Various methods have been proposed to assess OR. The most utilized are FSH, anti-Müllerian hormone (AMH) and the antral follicle count (AFC), the latter assessed by ultrasound.[3] Because the number of recruited follicles is believed to correlate with the size of the resting follicle pool, AMH, which, together with AFC, best represents small growing follicles, is now by many considered also best to represent total OR[4,5] AMH is, however, less specific than FSH at older ages, and, in general, does not as well reflect the pre-ovulatory, gonadotrophin-sensitive follicle pool.[6] It is estimated that 5–18% of all in vitro fertilization (IVF) cycles are ended by poor ovarian response. However, there is currently no uniform definition of 'poor response'.[7] Poor ovarian response (POR) implies a reduced follicular pool and results in a low number of oocytes retrieved at pick up or a low number of developing follicles and low estradiol (E2) levels, despite the high dose of gonadotropins administered during "Controlled Ovarian Hyperstimulation."[8] Caisson and associates were first to suggest therapeutic benefits from supplementation with dehydroepiandrosterone (DHEA) in women with diminished ovarian reserve (DOR).[9] They also reported that DHEA is well tolerated and increases IGF-1 levels.[10] A main focus of this group's work was, thus, the compensation of adrenal cortical changes in aging women with DHEA.[11] Casson et al. did not claim direct DHEA effects on DOR ovaries. They, instead, suggested that DHEA supplementation appears to augment ovarian stimulation with gonadotropins in poor responders, resulting in improved oocytes yields However, Caisson's paper was appropriately criticized for methodological errors, such as the bias introduced with changing the stimulation regimen, as well as the choice and type of gonadotrophins used Likely due to their small study population, their paper failed to elicit follow up until previously noted index patient, five years later, rediscovered their publication.[12] It was left to a 43 year old infertility patient to rediscover their paper, searching the literature for remedies to overcome DOR. She, in a first in vitro fertilization (IVF) cycle, had produced only a single egg and embryo, and was advised to consider oocyte donation.[13] This lay-person, reviewing the medical literature, amongst various suggested treatment options for improving low egg counts, chose DHEA. In a second IVF cycle she produced three oocytes/three embryos. Her oocyte and embryo yields after that increased from cycle to

cycle. In the ninth IVF cycle, now age 44, gonadotropin dosages had to be reduced because of concerns about potential ovarian hyperstimulation, she still produced 17 oocytes (16 embryos) in that cycle alone. Her use of DHEA was unknown to her treating physician until the 6th cycle. This change in her ovarian function resulted in the initiation of a prospective investigation of the role of DHEA in patients with diminished ovarian reserve.[14] There are also studies who propose that DHEA has hopeful role in DOR but physician should not rampantly use it unless large randomized placebo controlled trials is available. This triggered the idea to review all the available published literature on DHEA and its role in women with DOR. Hence this systematic review aims to summarize the role of DHEA as an adjuvant to stimulation protocol in women with diminished ovarian reserve or poor responders.

MATERIAL AND METHOD

Every published study, addressing DHEA supplementation in infertile women with DOR, was reviewed and is cited in this manuscript. No selection of materials for inclusion or exclusion, therefore, took place. All publications were reviewed by all authors, who agreed with analysis and interpretation of data. Since only 4 randomized studies have been published, publications, independent of evidence levels and quality assessment, were reviewed. We searched EMBASE , MEDLINE, PubMed, Cochrane and Ovid Medline between 1995-2014 under the following strategy: [<dehydroepiandrosterone or DHEA or androgens or testosterone > and <ovarian reserve or diminished ovarian reserve or ovarian function >]. Bibliographies of relevant publications were further explored for additional relevant citations.

RESULTS

Benefits of DHEA supplementationhave been reported since the beginning of this decade (Casson et al.,2000; Barad and Gleicher, 2005, 2006; Barad et al., 2007; Gleicheret al., 2009, 2010a,b; Sonmezer et al., 2009; Mamas and Mamas, 2009a, b, Wiser et al., 2010). The evidence on DHEA use in women to enhance the ovarian reserve is based on retrospective analyses (Gleicher *et al*., 2010b), prospective self-controlled studies (Casson *et al*., 2000; Barad and Gleicher, 2006;Sonmezer *et al*., 2009, Gleicher *et al*., 2010a), case reports/series (Barad and Gleicher, 2005; Mamas and Mamas, 2009b), case–control studies (Barad *et al*., 2007; Gleicher *et al*., 2009) and a single randomized controlled trial (Wiser *et al*., 2010). All the manuscripts accessed were analyzed and their information have been summarized in the table below: The table highlights the study design , intervention , inclusion

criteria, doses, outcome, limitations and remarks of other researchers on their as well as other study.

Table 1

ARTICLES	STUDY DESIGN	INCLUSION CRITERIA	(DHEA DOSES) &Duration	INTERVENTION	OUTCOMES	REMARKS
1.Casson *et al*. 2000[15]	self-controlled trial	5 women with a H/O poor response, i.e. less than two mature follicles or a peak estradiol (E_2) level of 500 pg/ml despite high levels of stimulation.	80 MG/day 2 months	OI/IUI	Increased peak E_2 levels (939.8 ± 418.9 versus 266.3 ± 69.4 pg/ml, $P = 0.02$) and yielded more oocytes (2.2 versus 1)	This report was criticized due to its methodological errors such as bias caused by the change in the stimulation protocol, as well as the type and dose of gonadotrophins administered.[31]
2.(Barad and Gleicher, 2005)[16]	Case report	1 index patient, 42.7 years old woman who took DHEA by herself and undergone nine IVF treatment cycles in 11 months	75 mg/day 11 months	IVF	66 embryos. Her peak E_2 level in the first trial was 1211 pmol/ml and it increased up to >18000 pmol/ml in her eighth trial.	
3. Barad and Gleicher, 2006[17]	Case series Retrospective study	25 patients with DOR that was defined as a history of prior IVF cycle with less than four oocytes and uniformly poor quality embryos. 1 IVF CYCLE before &1 IVF cycle after DHEA.	75 mg/ day 17.6 ± 2.13 weeks	IVF	An increased oocyte yield (4.4 ± 0.5 versus 3.4 ± 0.5, $P < 0.05$), a higher fertilization rate (67 versus 39%, $P < 0.001$) and a higher embryo grade (3.4 ± 0.09 versus 2.9 ± 0.1, $P < 0.02$) were achieved.	

4.Barad D, et al. (2007)[18]	Case–control	**POA** defined by age-specific baseline FSH levels > 95% CI of mean value for the age group; but < 12 mIU/ml **DOR** defined as baseline FSH > 12 mIU/ml and/or estradiol level ≥ 75 pg/ml . 89 cases* and 101 controls *only 64 of 89 undergoing IVF	Cases : DHEA 25 mg three times daily for mean duration 73 days continuously until + pregnancy test	Day 3 embryo transfer	Clinical pregnancy rate -No. of retrieved oocytes - Implantation rate - Miscarriage rate -Normal day 3 embryos -Time from initial visit to pregnancy (Cox regression analysis) DHEA patients demonstrated shorter time to pregnancy and higher pregnancy rates (cumulative clinical pregnancies, 28.1% vs. 10.9%; 95% CI 1.2-11.8; $p < 0.05$), despite prognostically more favorable controls (more oocytes, $P < 0.01$; normal day-3 embryos, $P < 0.05$; and more embryos transferred, $P < 0.05$). Moreover, study patients were also older (41.6 ± 0.4 vs. 40.0 ± 0.4 years)	Cases were slightly older ($P < 0.05$) -Fertility treatments were different ($P < 0.001$) - Women in control entered IVF cycle more rapidly.
5.Mamas [19]	Case report	**5(POF)**	50–75 mg/day for 3–6 months	4 natural conceptions and 1 clomid + IUI	All 5 patients became pregnant and crossed period of viability except 1 who had missed abortion at 7 wks.	
6.Bedaiwy , 2009. [20]	Case control	47 (prior CC failure)	75 mg/day, 2months	CC/IUI	DHEA patients demonstrated significantly higher antral follicle counts, significantly improved	

					pregnancy rates (29.8 vs. 8.7%; CI 1.3-14.8) and live births (21.3% and 6.5%, respectively.	
7.Sönmezer [21]	Case control	19 (poor responders)	75 mg/day 90-180 days	IVF/ICSI	A favourable decrease was noted in mean day 3 serum oestradiol concentrations after DHEA supplementation (75.14 +/- 28.93 versus 43.07 +/- 11.77; P < 0.01). Increased number of >17 mm follicles (3 +/- 0.7 versus 1.9 +/- 1.3; P < 0.05), MII oocytes (4 +/- 1.8 versus 2.1 +/- 1.8; P < 0.05), top quality day 2 (2.2 +/- 0.8 versus 1.3 +/- 1.1; P < 0.05) and day 3 embryos (1.9 +/- 0.8 versus 0.7 +/- 0.6; P < 0.05) were achieved in DHEA-supplemented cycles. Cycle cancellation rates were reduced (5.3% versus 42.1%; P < 0.01), and the pregnancy rate per patient and clinical pregnancy rate per embryo transfer (47.4% versus 10.5%; P < 0.01 and 44.4% versus 0%; P < 0.01) were improved after DHEA supplementation.	

8. Wiser A, et al. (2010)[22]	Prospective RCT (open-labeled)	Age ≤ 41 yr, Poor response, previous IVF cycle with high dose Gn (FSH 300 IU) with oocyte <5 or cycle cancellation 17 Cases 16 controls	Cases : DHEA 75 mg/day orally ≥ 6 weeks before stimulation	Day 2–3 embryo transfer	The DHEA group demonstrated a non-significant improvement in estradiol levels on day of hCG (P ¼ 0.09) and improved embryo quality during treatment (P ¼ 0.04) between first and second cycles. Patients in the DHEA group also had a significantly higher live birth rate compared with controls (23.1% versus 4.0%; P ¼ 0.05), respectively. Six of seven deliveries were among patients with secondary infertility (P ¼ 0.006).	Counted 55 IVF from 33 patients (both arms went through) Including of repeat cycles without adjustment of randomisation. this paper should be interpreted cautiously because it suffers from significant shortcomings such as the low number of subjects (*N* = 33; 17 used DHEA and 16 did not) and cycles (*N* = 51) in the trial, lack of power analysis before starting the trial, the short duration of DHEA use, inability to compare appropriately the groups (6 weeks for the initial group, and 16–18 weeks for those who did not conceive and underwent a second IVF cycle; 17 completed one cycle and 9 completed a second cycle), and whether there was indeed a significant difference among women who used DHEA. Wiser et al. also counted one patient who spontaneously conceived in the study group rather than excluding her.[32] Excluding this one patient would have resulted

						in a non-significant difference between the two groups. In addition, Kolibianakis reported that the statistical test used by Wiser et al. (Fisher's Exact Test) is not the appropriate test to use since this test requires that the observations are independent from each other.[33] Further study was neither blinded nor placebo controlled
9. Gleicher N, et al. (2010)[23]	Case–control	DOR defined by abnormally (age specific hormone levels deviated from 95% CI; elevated FSH or low AMH 22 Cases 44 matched Controls (1st single IVF cycle analysis only)	Cases : DHEA 25 mg three times daily At least 4 weeks before stimulation		Pregnancy and live birth rates (secondary outcome) -Aneuploidy rate No. of oocytes retrieved Total gonadotrophin dosage	Clinical pregnancy rate, miscarriage and No. of oocyte retrieved (our outcomes) are not the main outcome of the study.
10.Moawad &Shaeer, 2012 [24]	Prospective Randomized Controlled study	133(Poor Responders)	75 mg/day, 12 weeks	IVF	The amount of r-FSH used was significantly lower, and peak estradiol level and endometrial thickness were significantly higher in the DHEA group : The study group had statistically significant higher numbers of retrieved oocytes(5.9 ± 3.6) compared to the control group (3.5 ± 2.9) – P <	it is not clear why the authors chose oocyte yield rather than clinical or ongoing pregnancy rates as studies using oocyte yield are notoriously erroneous secondary to cycle to cycle variability even without any change in stimulation protocol.[34] The study suggested that DHEA improves IVF outcomes

					0.001. Also, the study group had a statistically significant lower cancellation rate (13.4%) and a higher number of embryos transferred (2.8 ± 0.9) compared to the control group (28.8% and 1.7 ± 1.1, respectively) – P < 0.01 &<0.001, respectively. Although the pregnancy rate (per embryo transfer) was higher in the study group (24.1%) compared to the control group (21.3%), no statistically significant difference was observed. However, if we calculate pregnancy rate per cycle, it was significantly higher in the studygroup (20.9%) compared to (15.2%) in the control group – P < 0.05. There were no differences in miscarriage rates between the two groups (5.2 % and 6.4 %, respectively).	in poor responders.[35]
11.N.yilmaz et al 2013[26]	prospective cross-sectional study	40 patients with DOR	25 mg t.i.d. 6 wks	ART	There were significant differences in day 3 FSH, oestradiol, antral follicle count, AMH and inhibin B	Limitations: the study was not randomized and only 13 women underwent ART so it was not possible to compare AMH &

					levels before and after DHEA supplementation in all patients (p = 0.001, 0.001, 0.002, 0.001 and 0.001, respectively). The study population was divided into two age groups (<35 and ≥35 years) to determine whether there was a difference in the effect of DHEA supplementation between younger and older patients with diminished ovarian reserve. Significant differences were found in all of the parameters in both study groups (p < 0.05).	Inhibin B level of women who conceived with those who did not conceive. Also could not hypothesize threshold level of improvement in these levels to predict pregnancy.
12.Richen Zangmo, Neeta Singh et al[27]	Prospective Cohort Study	50 Patients with POR in the previous cycle	Oral micronized 25 mg t.i.d. for 3 months	ART	After treatment with DHEA, a significant increase in number of mature follicles was seen in the post treatment period (⩽35 years P < 0.001; ⩾36 years P = 0.002). There were significant increases in numbers of oocytes retrieved, fertilization rates and, consequently, the total number of embryos available. More embryos were vitrified among patients ⩽35 years (P <	

					0.001) post treatment, and clinical pregnancy rate in this group was 26.7%. DHEA treatment resulted in a higher number of oocytes retrieved, oocytes fertilized, embryos overall and of grade-I embryos	
13. Artini PG etal[28]	Controlled Randomized Trial	Study group:12 patients, Control group: 12 patients	25 mg T.I.D. for 3 months	COH & IVF	FF levels of HIF1 were statistically significant lower in women treated with DHEA (14.76 ± 51.13 vs. 270.03 ± 262.18 pg/ml; p = 0.002). On the contrary, VEGF levels did not differ between the two groups. Concerning COH, in the DHEA-group the mean duration of treatment was significantly shorter (9.83 ± 1.85 vs. 12.09 ± 2.81; p = 0.023). Total numbers of oocytes retrieved, fertilized oocytes, good quality embryos, number of transferred embryos and clinical pregnancies tended to be higher in study group, but the results were not significant. On the other hand, considering the oocytes retrieved in selected	

					F3-F4 follicles, there was a relation between HIF1 levels and oocytes quality. In fact, mature oocytes retrieved in selected follicles were significantly more numerous in DHEA-group (0.50 ± 0.52 vs. 0.08 ± 0.29; p = 0.018).	
14. Bei Xu, Zhou Li, Jing Yue, Lei Jin et al 2014[28]	Retrospective Cohort Study	This study investigated 386 poor ovarian responders that fulfil the Bologna criteria. Study 189 &control197	(25 mg three times daily)	IVF-ET	The study and control groups did not show statistically significant differences in terms of patient demographics characteristics, mean numbers of oocytes retrieved, mature oocytes, fertilization rate, cleavage rate, or embryo availability. While the DHEA group demonstrated significantly higher implantation rates (18.7% vs. 10.1%; *P*<0.01) and ongoing PRs (26.7% vs. 15.8%; *P*<0.05) as compared with the control.	
15. Yeung TW[1], Chai J[2], Li RH[2], Lee VC[2], Ho PC[2], Ng	**Randomized, double-blind, placebo-controlled pilot study**	Thirty-two women with anticipated poor ovarian response. Randomization into DHEA group (n=16) r or placebo (n=16)	25 mg three times a day) for at least 12 weeks	IVF	Measurement of monthly ovarian response markers, including antral follicle count (AFC), serum antimüllerian hormone (AMH), and follicle-stimulating hormone (FSH)	he DHEA supplementation resulted in statistically significantly higher serum DHEA-S, free androgen index, and follicular DHEA-S levels. No statistically significant differences in the ovarian

EH, 2014[29]					levels; comparison of ovarian response to a standard dose of gonadotropin stimulation at week 8 and IVF outcomes; and AFC after 12 weeks (primary outcome).	response markers (AFC, AMH, or FSH), the ovarian response to standard-dose gonadotropin stimulation, or IVF outcomes were found between the two groups
16. Jirge PR, Chougule SM, Gavali VG, Bhomkar DA[30]	**Prospective case-control study**	31 infertile women with POR diagnosed as per the Bologna criteria	DHEA supplementation for 2 months	IVF cycle, after two previous IVF cycles with POR	Dose and duration of gonadotropin therapy, oocyte yield, embryo number and quality, pregnancy and live birth rate.	No difference was seen in gonadotropin requirement before and after DHEA supplementation. There was a significant increase in total and metaphase II oocytes (5.9 ± 0.68 vs. 2.73 ± 0.24; 4.45 ± 0.47 vs. 2.09 ± 0.26), fertilization (3.65 ± 0.49 vs. 2.00 ± 0.27), Grade I embryos (1.52 ± 0.25 vs. 0.55 ± 0.18), pregnancy rate (30% vs. 9.1%) and live birth rate (25% vs 0%) in those who completed the cycle, following DHEA supplementation.

DISCUSSION

Fertility in women is known to precipitously declines by age of 35.[36,37] with fecundity being all but lost by the age of 45.[38] The reproductive lifespan of women has become strikingly short in the context of overall lifespan, a discrepancy that is more pronounced today than ever before.[39, 40] This decrease is primarily due to poor egg quality, as successful pregnancies increase significantly in females of advanced maternal age when eggs from young, fertile donors are used.[41] An aneuploidy egg is known to be of poor quality, and in humans, egg aneuploidy is associated with advanced maternal age and occurs most often because of chromosome segregation errors at meiosis.[42] Current best available evidence suggests that DHEA improves ovarian function, increases pregnancy chances and, by reducing aneuploidy, lowers miscarriage rates. DHEA over time also appears to objectively improve ovarian reserve. Recent animal data support androgens in promoting preantral follicle growth and reduction in follicle atresia. Improvement of oocyte/embryo quality with DHEA supplementation potentially suggests a new concept of ovarian aging, where ovarian environments, but not oocytes themselves, age. DHEA may, thus, represent a first agent beneficially affecting aging ovarian environments. Others can be expected to follow. The possible mechanism that has been suggested is a direct effect of DHEA on the aging ovary by increasing the pool of follicles up to the pre-antral stage or reducing apoptosis of the originally recruited follicles or affecting non-dysfunctional events happening during meiosis.[43,44] Gleicher presents DHEA as the first medication to improve the ovarian environment to obtain better oocyte and embryo quality as well as higher pregnancy and lower miscarriage rates.[45] At the moment, there is no evidence of this effect at the molecular, cellular or tissue level in animal or human tissue models. Surprisingly no contradictory reports have been published so far. The reasons may be any, like others also found similar results and preferred not to publish similar types of reports. Alternatively, there may be contradictory findings, but researchers may be waiting to have a sample size of sufficient power to report their findings. The other explanation could be the possibility of a publication bias. It is a because caregivers who seek more therapeutic options that they can offer to patients have a greater interest in viewing positive results.[46] Despite their limitations, well-designed, optimal quality RCTs is still considered to be the most reliable source of evidence. Wiser's study showed us that it is hard but still possible to perform RCT on patients with a poor ovarian response.[47] Although findings reported in the literature merit further consideration, until well-designed large-scale studies prove beyond considerable doubt that DHEA improves ovarian reserve, its use should at best be regarded as

experimental. Despite worldwide utilization of DHEA supplementation in women with DOR, lack of enough controlled studies is still regretful. With the small study by Wiser et al representing the only prospective clinical trial (Level I evidence), studies of more substantial size are all based on lower levels of evidence and, therefore, have to be interpreted cautiously. This fact is reemphasized by most publications coming from only a small number of centers, including, these authors' own centre. Some may argue that no treatments should be routinely applied in clinical practice, unless based on prospectively randomized studies. Recognizing that Level I clinical trials may, at times, be too costly and/or too difficult to conduct, such an approach has, however, recently been questioned in the academic community.[48-50]

CONCLUSION

We believe that large-scale, well-designed confirmatory studies are necessary to prove the efficacy of DHEA before it could be recommended for routine use. Indications, optimal dose and duration of treatment should also be determined. We agree with Gleicher and Barad that these studies will be extremely hard if not impossible to perform.[51] These concerns should be shared by physicians, the pharmaceutical industry and regulatory agencies. While DHEA's use is considered experimental, until (and if) such studies are published, and considering the absence of significant side effects, the low cost, and the increase in spontaneous pregnancies, we suggest that utilization of DHEA in suitable, consented, and well informed patients may improve ovarian reserve, response to ovarian stimulation, and potentially pregnancy outcome.

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