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Original Research Article

To Study Effect of Dehydroepiandrosterone Supplementation on Diminished Ovarian Reserve Markers

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Abstract: Dehydroepiandrosterone (DHEA) has been proposed to improve pregnancy rates in women with diminished ovarian reserve undergoing in vitro Fertilisation (IVF) treatment. However, there are limited studies showing its efficacy. So, this study shows the effect of DHEA on ovarian reserve markers. The objectives of this study was to evaluate the effect of dehydroepiandrosterone (DHEA) supplementation on ovarian reserve by measuring markers such as antral follicle count, serum anti-Mu¨ llerian hormone (AMH) and serum follicular stimulating hormone in patients with diminished ovarian reserve. This prospective study was done at sawai man singh medical college, Jaipur. Thirty patients with diminished ovarian reserve were included in the study and received supplementation with DHEA 75 mg OD, for 3 months. Serum AMH, follicle-stimulating hormone (FSH) and antral follicle count were determined before and after DHEA supplementation. Those showing poor response were given DHEA for 6 months. Baseline ovarian reserve parameters such as antral follicle count, FSH, AMH, factors affecting ovarian reserve, and pregnancy rates were studied. There were significant differences in FSH, antral follicle count and AMH levels before and after DHEA supplementation ($p < 0.05$). The study population was divided into two age groups (<35 and 35 years and above) 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 S.AMH and AFC in both study groups ($p < 0.05$). DHEA supplementation is an effective option for patients with diminished ovarian reserve. Prior to assisted reproductive technology, patients with diminished ovarian reserve should be offered DHEA supplementation as an alternative to oocyte donation.
Keywords: follicle stimulating hormone, antral follicle count, serum antimullerian hormone, dehydroepiandrosterone

INTRODUCTION

With the changing lifestyle including the increase pace of social life and delayed age of reproduction today, it is common to find infertility patients with Diminished ovarian reserve (DOR). DOR is a progressive decline of ovarian oocyte quality and quantity, with an elevated basal follicle stimulating hormone (FSH) level and less antral follicle count. It is reported in 9–24% of in-vitro fertilization (IVF) cycles [1]. Patients with DOR have high cancellation rate, low pregnancy rate, and high abortion rate during IVF [2].

Over the years, numerous techniques and therapies have been developed in an effort to help the poor responder, but a few have met the success [3, 4]. The ideal stimulation regimen for poor responders is currently unknown. Androgens are thought to be essential for normal folliculogenesis and female fertility. Dehydroepiandrosterone (DHEA) is an endogenous steroid that originates from the adrenal and ovarian theca cells [5]. DHEA is an essential pro-hormone as it is important in the formation of testosterone and oestradiol in ovarian follicular steroidogenesis [6]. The concentration of DHEA declines progressively with age [7], and DHEA supplementation may increase the levels of these precursor hormones in the ovarian follicular pool. Casson *et al.;* were the first to describe the beneficial effect of DHEA supplementation on ovarian stimulation in a case series of five poor responders undergoing stimulation and consecutive intrauterine insemination [6]. Subsequently, DHEA supplementation has been

used by some clinicians prior to ovulation induction in ART in patients with DOR.S.AMH and AFC are reliable markers for prediction of diminished ovarian reserve.

AIMS & OBJECTIVES:

- To see the improvement in ovarian reserve after DHEA supplementation.
- To evaluate the effect of DHEA supplementation on poor ovarian reserve markers S.FSH, S.AMH & Antral Follicle Count.

MATERIAL & METHODS

This was a prospective interventional study conducted in Department of Obstetrics & Gynaecology, SMS Medical College, and Jaipur from February 2015 to September 2016. The study was approved by the hospital's ethics committee. All patients were informed about the effects of DHEA supplementation and informed consent was obtained. 40 infertile women that filled the inclusion criteria were enrolled for study after preliminary work up. DOR was defined as antral follicle count <5 or AMH <1.1 ng/ml and a previous poor ovarian response [8]. Women aged >40 years were not included in the study in order to exclude patients with physiological ovarian ageing, so the first Bologna criterion was not accepted as an inclusion criterion. The second and third Bologna criteria were accepted as inclusion criteria.

All women included in the study received supplementation with DHEA 75 mg OD for 3 months. None of the patients reported any side-effects of DHEA treatment. Serum AMH, FSH, and antral follicle count (AFC) were determined before and after DHEA supplementation. During this period 10 cases were lost to follow up. Women showing poor response were given DHEA for additional 3 months and again same ovarian reserve markers were tested. To evaluate the effect of DHEA supplementation in younger and older patients with DOR, the study population was divided into two age groups: <35 years and >= 35 years. Thirty-five years was chosen as the cut-off as the decline in ovarian follicular number has been reported to accelerate from this age [9]. Influence of Factors like type of infertility, duration of infertility and BMI were also studied after DHEA supplementation in diminished ovarian reserve patients. Statistical analysis was done using paired t test. The level of confidence was kept 95%, p-value of <0.05 was considered statistically significant.

RESULTS

There was significant difference in all three parameters S.AMH, AFC & S.FSH before and after DHEA supplementation for 3 months (p value <0.002, <0.001, 0.05 respectively) (Table 1). 11 patients showing poor response were given DHEA till 6 months, they showed significant increase in S.AMH, AFC (p value 0.012, 0.008 respectively) whereas decrease in S.FSH is not statistically significant (p value =0.38) (table 2). Increase in ovarian reserve markers over 3 to 6 month as compared to increase in first 3 month is not statistically significant (p –value >0.05)(table 3). Table 4 shows significant increase in parameters AFC, S.AMH in age < 35 years (p-value of <0.05, <0.05 respectively) and no significant increase in S.FSH (p-value 0.079). In ≥35 years age group there was significant increase in AFC (p value <0.05), but no significant change in S.AMH & S.FSH (p-value 0.06 & 0.17 respectively). There is significant difference in all three parameters in patients with primary infertility (p value <0.05) and the difference is more significant than secondary infertility patients (table 5). Increase in AFC and S.AMH is more significant (p-value 0.001) in 5-8 years of infertility. Decrease in S.FSH is more significant in (p-value 0.036) in 9-12 years of infertility.(table 6). Increase in AFC and S.AMH is more significant in patients with BMI <25 kg/m^2 (p-value <0.001, 0.001 respectively) than with BMI ≥25 kg/m^2 (p-value 0.001, 0.021 respectively). (Table 7)

Table 1: Increase in Ovarian Reserve Markers Over 3 Months (n = 30)

Marker	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference		t	d.f.	p- value
				Lower	Upper			
AFC	2.23	1.52	0.28	2.80	1.66	8.03	29	<.001
S.AMH	0.61	0.68	0.12	0.86	0.35	4.91	29	<.002
S.FSH	-1.56	4.15	0.76	-0.01	-3.11	-2.06	29	0.05

Table 2: Increase in Ovarian Reserve Markers between 3 Months and 6 Months (n = 11)

Marker	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference		t	d.f.	p- value
				Lower	Upper			
AFC	1.36	1.36	0.41	2.27	0.44	3.32	10	0.008
S.AMH	0.36	0.401	0.12	0.63	0.09	3.05	10	0.012
S.FSH	-0.65	2.37	0.72	0.93	-2.25	-0.91	10	0.38

Table 3: Increase in Ovarian Reserve Markers Over 6 Months (n = 11)

	Mean	Std. Deviation	Std. Error Mean	d.f.	Sig. (2-tailed) p-value
AFC	0.455	1.809	0.545	10	0.424
S.AMH	0.15091	0.43475	0.13108	10	0.276
S.FSH	-0.52636	2.95773	0.89179	10	0.568

Table 4: **Comparison of Ovarian Reserve Markers Over 3 Months According to Age (n = 30)**

Factor	Age Group	D1		3 Months		p-value
		Mean	Std. Deviation	Mean	Std. Deviation	
AFC	**Age <35**	3.05	0.805	5.43	1.469	0
	Age ≥35	3.11	0.601	5	1.118	0.002
S.AMH	**Age <35**	1.1248	0.637	1.8105	1.077	0
	Age ≥35	1.0611	0.646	1.4822	0.693	0.068
S.FSH	**Age <35**	9.8924	5.489	7.9195	3.662	0.079
	Age ≥35	7.5778	3.265	6.9889	2.907	0.178

Table 5: Comparison of Ovarian Reserve Markers Over 3 Months According to Type of Infertility (n = 30)

Factor	Type of Infertility	D1		3 Months		p-value
		Mean	Std. Deviation	Mean	Std. Deviation	
AFC	**Primary Infertility**	3.11	0.737	5.42	1.261	0
	Secondary Infertility	3	0.775	5.09	1.578	0.003
S.AMH	**Primary Infertility**	1.0511	0.652	1.6379	0.995	0.001
	Secondary Infertility	1.2	0.608	1.84	0.98	0.014
S.FSH	**Primary Infertility**	8.8442	5.514	6.8237	2.652	0.087
	Secondary Infertility	9.8091	4.996	9.0509	4.244	0.335

Table 6: Comparison of Ovarian Reserve Markers Over 3 Months According to Duration of Infertility (n = 30)

Factor	Duration of Infertility	D1		3 Months		p-value
		Mean	Std. Deviation	Mean	Std. Deviation	
AFC	0-4 yrs	3	1	5	1	0.184
	5-8 yrs	3.45	0.522	5.45	1.368	0.001
	9-12 yrs	2.86	0.69	6.14	1.345	0.001
	13-16 yrs	2.8	0.837	4.2	1.095	0.052
	17-20 yrs	2.75	0.957	5	1.414	0.078
S.AMH	0-4 yrs	0.3933	0.66403	0.5267	0.84388	0.331
	5-8 yrs	1.1236	0.70557	1.7955	1.12527	0.009
	9-12 yrs	1.3671	0.45489	2.2857	0.88587	0.022
	13-16 yrs	1.164	0.75305	1.754	0.62176	0.182
	17-20 yrs	1.06	0.18974	1.315	0.23573	0.072
S.FSH	0-4 yrs	13.6667	11.59023	7.4867	4.40256	0.416
	5-8 yrs	9.0773	3.60107	7.6045	1.69918	0.182
	9-12 yrs	7.8257	1.64417	5.9057	1.91961	0.036
	13-16 yrs	6.276	5.16866	6.412	4.27843	0.782
	17-20 yrs	12.2325	6.56342	12.425	4.40331	0.926

Table 7: Comparison of Ovarian Reserve Markers over 3 Months According to BMI (in kg/m^2) (n = 30)

Factor	BMI (in kg/m^2)	D1		3 Months		p-value
		Mean	Std. Deviation	Mean	Std. Deviation	
AFC	BMI <25	3.11	0.737	5.47	1.577	<0.001
	BMI ≥25	3	0.775	5	0.894	0.001
S.AMH	BMI <25	0.9705	0.48647	1.6489	1.04533	0.001
	BMI ≥25	1.3391	0.79383	1.8209	0.88702	0.021

DISCUSSION

In this study 30 infertile women were included in the study according to inclusion criteria out of which most of the women 13(43.34%) belong to age group 31-35 years age group (this shows ovarian ageing is increasing with increasing age). Study show that 21 (70%) women belong to urban area and 11 (36.67%) women belong to upper middle socioeconomic status. Maximum number of patients were having normal BMI 18 (60%) , normal onset of menarche 27 (90%), normal menstrual pattern 24 (80%). 19 (63.33%) cases belong to primary infertility and 11 (36.77%) cases belong to secondary infertility, maximum number of cases 11 (36.67%) were having 5-8 years of infertility which shows that patient report late for further evaluation and management, after initial years have passed taking ovulation induction several times or being investigated at various centres.

Our study shows significant difference in all parameters after DHEA supplementation for 3 months .Similarly, Casson PR *et al.;* in 2000 [10] showed a small increase in follicle number after DHEA administration only for two months. Barad DH *et al.;* in 2005 [11] showed dramatic increase in oocyte production beginning after four months of treatment. Mamas L *et al.;* in 2009 [12] Gleicher N *et al.;* in 2010 [13] showed that DHEA supplementation for at least 3 months has been associated with spontaneous and treatment-induced pregnancies in women with very high FSH or very low anti-mullerian hormone (AMH) levels .Yilmaz N *et al.;* in 2013 [14] found that ovarian reserve markers, including AMH ($p < 0.001$), AFC ($p < 0.002$), inhibin B ($p < 0.001$), FSH ($p < 0.001$) and E2 ($p < 0.001$) significantly improved after DHEA therapy over 12 weeks. According to Tsui KH *et al.;* in 2014 [15] after DHEA treatment, there was a significant increase in antral follicle count, from ($p < 0.05$), and anti-Müllerian hormone, ($p < 0.001$). A significant decrease of Day 3 follicle stimulating hormone and estradiol, (both $p < 0.001$), was noted. According to Vlahos N *et al.;* in 2015 [16] supplementation with DHEA for at least 12 weeks resulted in a modest, but statistically significant, increase in AMH levels and decrease in baseline FSH ($p < 0.001$ and $p = 0.007$, respectively). This study shows significant increase in ovarian reserve markers and no adverse effect of this drug has been noted at this dose, so there is no harm in giving this drug and it can be given for 6 months duration especially in cases with prior miscarriage as duration of therapy decrease miscarriage rates. Similarly, Gleicher N *et al.;* in 2011 [17] showed AMH increases in parallel to length of DHEA supplementation.

Our study shows significant increase in S.AMH and AFC in <35 years of age while in >=35 years of age there is significant increase in AFC only, this is due to depletion of follicles with increasing age .Yilmaz N *et al.;* in 2013 [14] showed significant differences were seen in all of the parameters in <35 year age group ($p < 0.05$). Primary outcome of study is good response shown by 21 (70%) of women. Secondary outcome is assessed by pregnancy rates. There were 2 live pregnancy, 7 biochemical pregnancy and 4 miscarriages. Similar results were shown by Sonmezer [18] M *et al.;* in 2009 who reported that DHEA treatment resulted in significantly higher pregnancy. In a case control study by Gleicher N *et al.;* in 2010 [13]. 89 DOR patients with DHEA supplementation and 101 controls, cumulative clinical pregnancy rates were significantly higher in the DHEA group (28.4% vs. 11.9%; $p < 0.05$).Tsui KH *et al.;* in 2015 [15] demonstrated that pregnancy rates were supposed to rise after DHEA treatment, because of improved ovarian reserve and possibly improved oocytes/embryo yields and quality. Other confounding factors contributing to infertility were maximum 13 (43.34%) patients were having uterine cause like fibroid, septa, polyp, etc, followed by tubal factor in 3 (10%) patients like pyosalpinx, salpingectomy for ectopic pregnancy and 1 (3.33%) patient with pelvic adhesions.

Strengths of this study were: -

1. Clinical data were collected prospectively;
2. Serum AMH and AFC were measured in the same women before and after DHEA supplementation.

Limitations of this study were:

1. The study was not randomized, as most patients with DOR do not want to enter randomization when one of the treatments is a placebo; and
2. Sample size was small which lead to difficult subgroup and secondary outcome analysis.
3. Live birth rate should be the ideal outcome measure in studies assessing fertility outcomes.

CONCLUSION

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 AMH levels. There was also a significant increase in AFC and ovulation rate after DHEA suggesting a primary effect on the ovarian milieu.

The current belief in the potential benefit of DHEA in poor responders was based on the assumption that DHEA increases intraovarian androgen concentrations, which in turn improves the functional ovarian reserve and ultimately the pregnancy rates.

In this study, a DHEA dose of 75 mg/day was used because most of the index patient had utilized this dosage in previous studies. Also, the androgenic effects of DHEA treatment appear to be minimal with the therapeutic dose of 75 mg/day. Age, type of infertility, duration of infertility and BMI have an effect in ovarian reserve markers as shown in my study In conclusion, this study found that DHEA supplementation in patients with DOR improved ovarian reserve. As such, DHEA supplementation is an effective and promising option for DOR. Prior to ART, the benefits of DHEA supplementation should be explained and offered to patients with DOR as an alternative to oocyte donation.

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