

## ORIGINAL RESEARCH

# To Assess The Role Of Dehydroepiandrosterone Supplementation In Improving Anti-Mullerian Hormone Levels And Rates Of Conception In Patients With Infertility Due To Ovarian Causes

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### ABSTRACT

**Introduction:** Diminished ovarian reserve (DOR), defined by age specific follicle stimulating hormone (FSH) levels and/or Anti mullerian hormone (AMH) levels < 1.5 ng/ml is seen in 10% cases of infertility which occur due to ovarian failure. Dehydroepiandrosterone (DHEA) supplementation for treatment of infertility in such cases is a recent development. This study aimed to determine whether DHEA supplementation objectively improves ovarian reserve as assessed by AMH levels since AMH has been recently validated as a specific marker for ovarian reserve and also whether these values are predictive of the outcome of treatment in terms of number of patients who conceive.

**Material and methods:** The study was done on 50 patients who presented to the OPD of Obstetrics and Gynaecology at Santokba Durlabhji Memorial hospital in the age group of 20-40 years with primary or secondary infertility due to DOR as determined by AMH levels <1.5 ng/ml. They were given DHEA 25 mg three times daily for at least 1 month till they conceived or till 6 months (whichever was earlier). Patients above the age of 40 years, those with infertility due to causes other than ovarian, with polycystic ovarian disease, endometriosis, ovarian cancers ; with chronic diseases and who conceived within 1 month of starting the treatment were excluded.

**Results:** The mean age of the study population was 31.14±6.00 years, mean duration of infertility was 4.26±3.25 years and the mean baseline AMH level was 0.73±0.48 ng/ml. The conception rate in this study was 26%. Following treatment with DHEA, the AMH levels increased significantly with the mean AMH level after 1 month of treatment being 1.08±0.82 ng/ml (p=0.007 for patients who did not conceive and p<0.001 for patients who conceived) while that at the end of 6 months were 1.64±0.98 ng/ml (p<0.001 for patients who conceived and who did not conceive). Only pre treatment AMH was found to be an independent predictor of conception [odds ratio = 7.5533 (95 % CI 1.5499 to 36.8106)].

**Conclusion:** DHEA supplementation positively affects the ovarian reserve in patients

**with DOR and also leads to better pregnancy outcome. Hence DHEA can be a low cost option for treatment of infertility in patients with DOR.**

**Keywords: Diminished ovarian reserve, infertility, Anti Mullerian Hormone, DHEA**

## **INTRODUCTION**

Infertility is defined as one year of unprotected intercourse without conception. It can either be primary or secondary depending on whether the couple has never conceived or has failed to conceive after a previous pregnancy despite cohabitation and exposure to pregnancy. Out of the three main causes of infertility female factor contributes about 55% to infertility. Failure to ovulate is the major problem in approximately 40% of female infertility, another 40% is due to tubal pathology and pelvic pathology and less than 10% due to problems such as anatomic abnormalities or thyroid diseases.<sup>1</sup> In approximately 10% women with ovulation failure occurs a condition called as premature ovarian failure (POF) or occult primary ovarian insufficiency or diminished ovarian reserve (DOR).<sup>2,3</sup>

DOR is defined by elevated age specific baseline Follicular stimulating hormone levels and /or decreased Anti-mullerian hormone levels <1.5ng/ml, indicative of DOR at all ages under 40 years.<sup>3,4</sup> Causes of DOR are idiopathic, genetic, iatrogenic, environmental toxins, infections, autoimmune conditions.

Of the numerous biochemical and ultrasonographic tests that have been developed to test the ovarian reserve serum Anti Mullerian hormone (AMH) levels have recently been validated as a more specific marker for quantitative assessment of ovarian reserve. This is because AMH is believed to be the earliest marker to change with increasing maternal age and hence can identify DOR sooner than other markers.<sup>5</sup> Also there is little or no change in the serum AMH levels with respect to different days of the menstrual cycle<sup>6</sup> and also in between cycles because AMH derives from preantral and small follicles and thus levels are gonadotropin independent.

The treatment options for DOR are many with one common target-pregnancy. These include treatment with clomiphene citrate, gonadotropins, estrogens, GnRH analogues, oral contraceptives, corticosteroids, a combinations of these or, if nothing else succeeds, egg donation. With these treatments 6.3% of all women suffering from POF become pregnant.<sup>7</sup> But a recent development in the treatment of such cases is Dehydroepiandrosterone (DHEA) supplementation.

DHEA is a c19 steroid and is the principal androgen of adrenal along with its sulfated prohormone, dehydroepiandrosterone sulfate. It is an essential prohormone in ovarian follicular steroidogenesis.<sup>8</sup> The exact mechanism by which DHEA improves fertility and ovarian reserve are still under investigation but it has been suggested that it improves steroidogenesis, influences ovarian follicular growth, increases intrafollicular IGF-1, creates PCOS-like characteristics and increases LH, acts as the pre-hormone for follicular fluid testosterone, reduces age-related aneuploidy by affecting meiotic chromosome segregation and increases the number of small antral follicles.<sup>9</sup>

This study was done to determine whether DHEA supplementation objectively improves the ovarian reserve in infertile women with DOR by assessing the AMH levels and also whether these levels are predictive of the outcome of treatment in terms of the number of women who conceive. This may, in future, help in providing prognostic information which will thus guide the clinician in deciding the choice of treatment and make use of the available resources in the best possible way. Also the results of this study can add to the already existing evidence regarding the role of DHEA supplementation in improving ovarian reserves to find alternate therapy to assisted reproductive techniques as many people in India cannot afford these techniques due to economic and cultural restraints.

## MATERIAL AND METHODS

It was a tertiary care centre based interventional study without control type of prospective study conducted in the department of Obstetrics and Gynaecology, Santokba Durlabhji Memorial Hospital cum Medical Research Institute, Jaipur from January 2017 to December 2017 on 50 patients who presented to the outpatient department with infertility due to DOR. Patients were given DHEA 25 mg three times daily for a period of at least 1 month till the time they conceived or for a maximum period of 6 months (whichever was earlier).

## INCLUSION CRITERIA

Women in the age group 20-40 years with infertility, either primary or secondary due to diminished ovarian reserve as indicated by AMH < 1.5 ng/ml and patients giving consent for the study.

## EXCLUSION CRITERIA

Women with age < 20 years and > 40 years being treated for infertility; with infertility due to causes other than ovarian causes; with chronic diseases like hypertension, diabetes mellitus, rheumatoid disorders; with polycystic ovarian syndrome, endometriosis, ovarian cancers; non cooperative patients and patients not giving consent and women who conceive within 1 month of beginning the treatment.

Continuous variables were expressed as mean and standard deviation. Nominal or categorical variables were expressed as percentage. Paired t test, One Way ANOVA test and Pearson Correlation Coefficient were used for continuous variables. Chi square test, Fischer exact test and Mc Nemar test were used for nominal or categorical variables. P value < 0.05 was taken as significant. MedCalc 16.4 version software was used for all statistical calculations.

The primary outcome of the study was documentation of any change in the Anti-mullerian hormone levels by comparing levels of the hormone before and after initiation of treatment while the secondary outcome was documentation of pregnancy.

## RESULTS

The mean age of the study population was 31.14±6.00 years, mean duration of infertility was 4.26±3.25 years and the mean baseline AMH level was 0.73±0.48 ng/ml.

Following treatment with DHEA, the AMH levels increased with the mean AMH level after 1 month of treatment being 1.08±0.82 ng/ml, at the end of 3 months being 1.36±0.99 ng/ml while that at the end of 6 months were 1.64±0.98 ng/ml.

The mean percentage increase in the AMH levels at the end of 1, 3 and 6 months of treatment was 54.78±64.62, 150.78±231 and 318.40±456.20 respectively.

The mean duration of treatment came out to be 5.11±1.62 months. (TABLE 1)

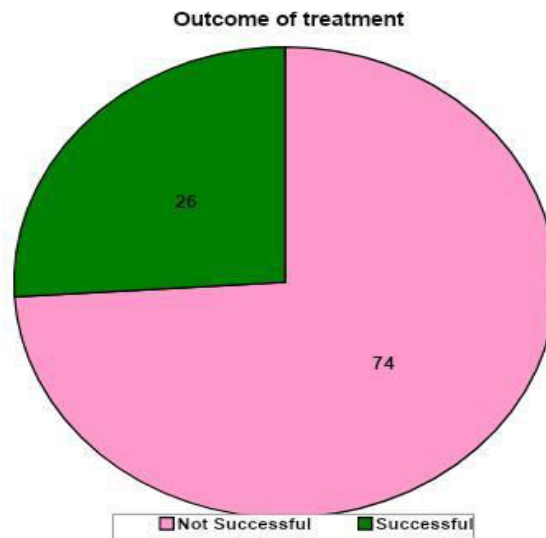
**Table 1: Characteristics of study group**

Parameters	N	Mean	SD	Median	Min	Max
Age (years)	50	31.14	6.00	31.50	21	40
Duration of infertility (years)	50	4.26	3.25	4.00	1	18
Pre t/t AMH (ng/ml)	50	0.73	0.48	0.72	0.02	1.45
Month 1 AMH (ng/ml)	50	1.08	0.82	0.88	0.08	4.01
Months 3 AMH (ng/ml)	42	1.36	0.99	1.35	0.12	6.11
Months 6 AMH (ng/ml)	37	1.64	0.98	1.60	0.16	5.89

Percent increase in AMH after 1 month	50	54.78	64.62	33.47	-5.8	350
Percent increase in AMH after 3 month	42	150.78	231.54	75.99	16.55	1300
Percent increase in AMH after 6month	37	318.40	456.20	171.67	32.41	2450
Total duration of t/t (months)	50	5.11	1.62	6.00	1.5	6

The conception rate in this study was 26%; 13 patients conceived out of a total 50 patients. (Figure 1)

**Figure: 1**

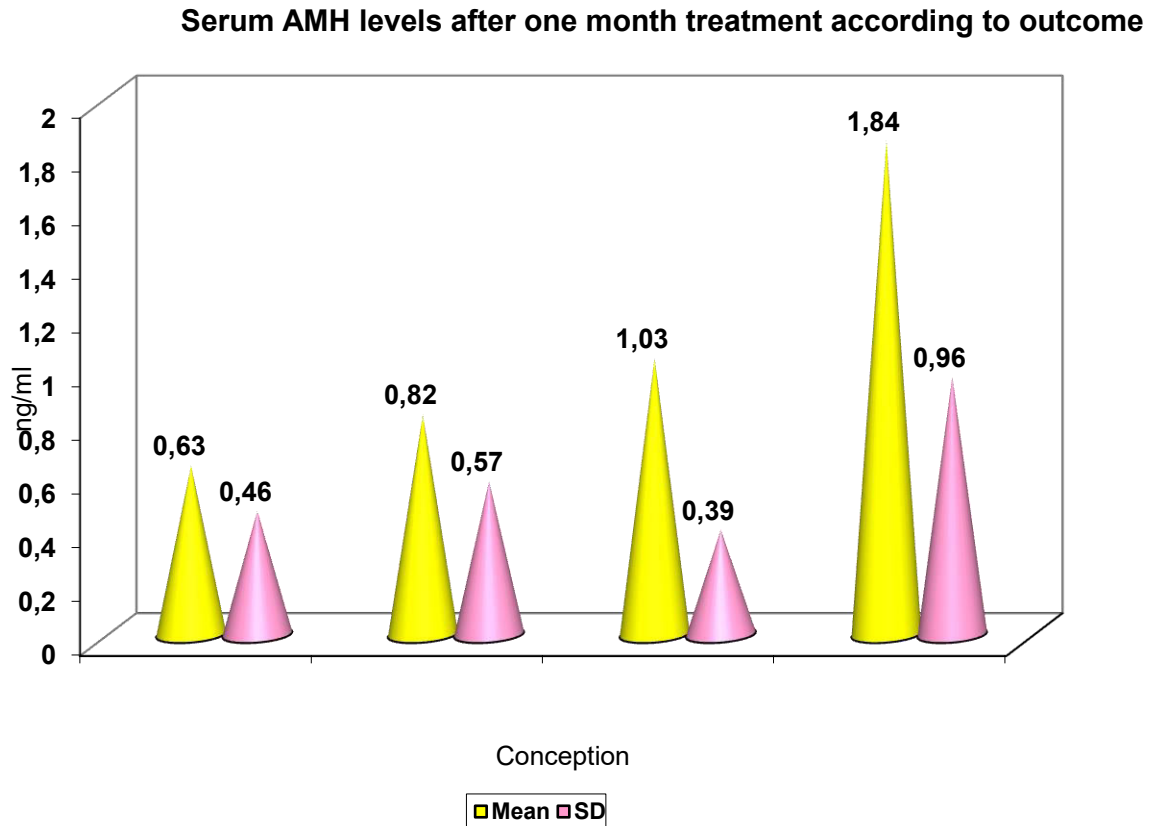


A significant increase in the AMH levels was found after 1 month of treatment ( $p=0.007$  for patients who did not conceive and  $p<0.001$  for patients who conceived). The increase in AMH levels in the patients who conceived was found to be 0.81 and who did not conceive was found to be 0.19. (Table 2) (Figure 2)

**Table 2: Increment in amh levels after 1 month of treatment**

Conception	AMH	N	Mean	SD	Increase	'p' Value*
Not Successful	Pre t/t	37	0.63	0.46	0.19	0.007
	Month 1	37	0.82	0.57		
Successful	Pre t/t	13	1.03	0.39	0.81	<0.001
	Month 1	13	1.84	0.96		

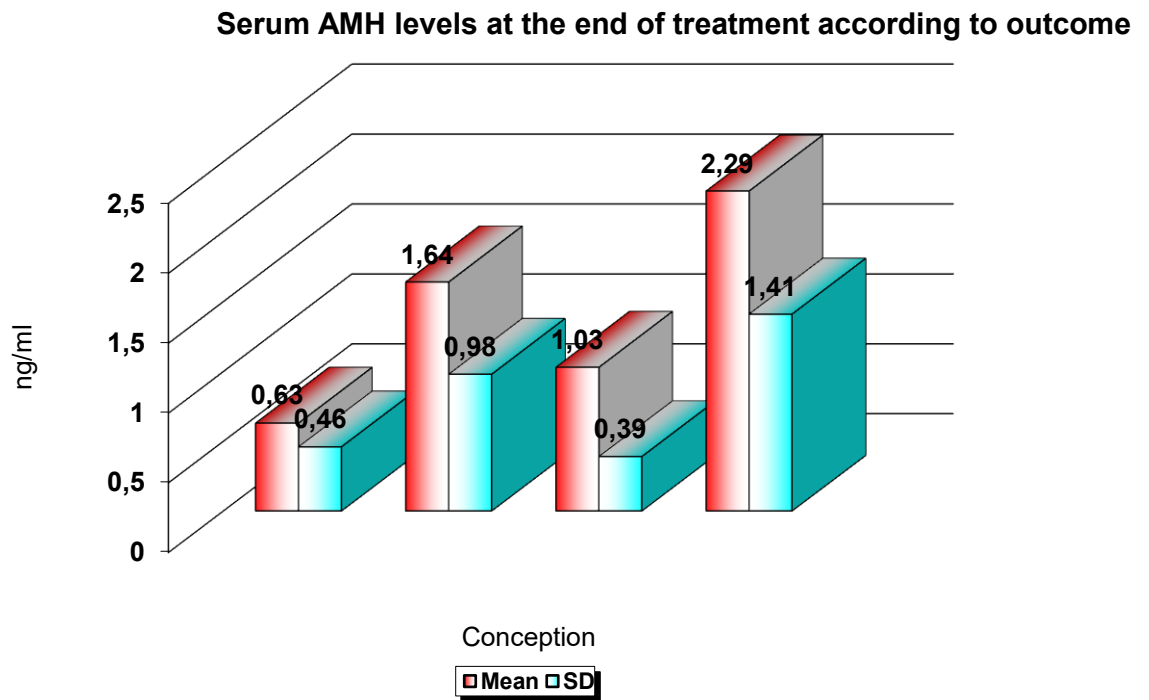
Figure: 2

**PAIRED T TEST**

Similarly a significant increase in the AMH levels was found after 6 months of treatment with DHEA ( $p < 0.001$  for patients who conceived and who did not conceive). The increase in the AMH levels in the patients who conceived before the end of treatment was 1.26 while in those who did not conceive within 6 months of treatment was 1.01. When compared statistically the difference in the increment of AMH levels in both the groups was not found to be statistically significant ( $p = 0.408$ ) (Table 3) (Figure 3)

**Table 3: Increment in amh levels after 6 months of treatment**

Conception	AMH	N	Mean	SD	Increase	'p' Value*
Not Successful	Pre t/t	37	0.63	0.46	1.01	<0.001
	End of t/t	37	1.64	0.98		
Successful	Pre t/t	13	1.03	0.39	1.26	<0.001
	End of t/t	13	2.29	1.41		

**Figure: 3****Table: 4**

Variable	Coefficient	Odds ratio	95% CI	'p' Value*
Pre t/t AMH	2.02198	7.5533	1.5499 to 36.8106	0.0123
Constant	-2.7354			

#### \*STEPWISE MULTIVARIATE LOGISTIC REGRESSION

Stepwise multivariate logistic regression was done to find out independent predictors of successful outcome (conception). Probability of variables to be retained in the model was kept <0.05 and probability of removal from model was kept >0.10. Age, type of infertility, duration of infertility, significant past history and pre treatment AMH levels were put in the model. Overall the model was found fit to predict outcome ( $p = 0.0063$ ). All variables except pre treatment AMH were removed from the model and only pre treatment AMH was found to be an independent predictor of conception [odds ratio = 7.5533 (95 % CI 1.5499 to 36.8106)].

#### DISCUSSION

In our study the mean age of the study population was  $31.14 \pm 6.00$  years which was comparable with the mean ages of the study population of Yilmaz et al<sup>10</sup> ( $33.78 \pm 4.11$  years), Agarwal et al<sup>11</sup> ( $33.10 \pm 4.29$  years), Hu et al<sup>12</sup> (33.28 years), Kara et al<sup>13</sup> ( $30.97 \pm 5.76$  years).

We observed that the mean duration of infertility was  $4.26 \pm 3.25$  years which was comparable with that observed by Moawad et al<sup>14</sup> ( $6.58 \pm 2.17$  years), Singh et al<sup>15</sup> (5.2 years) and Hu et al<sup>12</sup> ( $3.81 \pm 2.61$  years).

The mean duration of treatment was  $5.11 \pm 1.62$  months which was comparable with the studies of Barad et al<sup>16</sup> ( $17.6 \pm 2.13$  weeks), Wisner et al<sup>17</sup> (13.5 weeks).

The mean baseline AMH was  $0.73 \pm 0.48$  ng/ml. Following treatment with DHEA statistically significant improvement in the AMH levels was noted with the mean levels being  $1.08 \pm 0.82$

ng/ml at the end of 1 month of treatment ( $p = 0.007$ ),  $1.36 \pm 0.99$  ng/ml at the end of 3 months,  $1.64 \pm 0.98$  ng/ml at the end of 6 months ( $p < 0.001$ ). In similar studies by Gleicher et al<sup>18</sup> [mean baseline Amh was  $0.22 \pm 0.22$  ng/ml and mean post treatment Amh was  $0.35 \pm 0.05$  ng/ml ( $p = 0.0001$ )]; Yilmaz et al<sup>10</sup> [mean pre treatment Amh was  $0.32 \pm 0.29$  ng/ml, post treatment mean Amh was  $0.75 \pm 0.70$  ng/ml ( $p = 0.001$ )] ; Agarwal et al<sup>11</sup> [mean pre treatment Amh was  $1.15 \pm 1.49$  ng/ml while post treatment Amh was  $1.53 \pm 1.62$  ng/ml ( $p = 0.048$ )].

The rate of conception was found to be 26%. These results were comparable with those of Gleicher et al<sup>18</sup> (23.64%), Wisner et al<sup>17</sup> (23%), Jirge et al<sup>19</sup> (30%).

In our study after applying stepwise multivariate logistic regression analysis pre treatment AMH was found to be the only independent predictor of conception [odds ratio = 7.5533 (95% CI 1.5499 to 36.8106)] out of all the other variables that were put in the model like age, type of infertility, duration of infertility and past significant history. This has also been established previously in the study conducted by Kadam et al<sup>20</sup> where they reported that pregnancy was achieved after treatment with DHEA in patients with better baseline AMH levels as compared to the levels in those who did not conceive. In other studies by Hazout et al<sup>21</sup>, Leakmge et al<sup>22</sup>, Barad et al<sup>23</sup> even though DHEA supplementation was not given to the patients but baseline AMH levels were found to predict pregnancy rates in patients with diminished ovarian reserve.

When compared with conception the increment in mean AMH levels at the end of 1 month of treatment was found to be more in patients who conceived i.e. 0.81 while in those who did not conceive it was 0.19. Similarly when increment in mean AMH levels was seen at the end of 6 months of treatment, the increase was more in patients who conceived within 6 months i.e. 1.26 while in those who did not conceive the increment in mean AMH level was 1.01. Similar observations were made by Gleicher et al<sup>18</sup> and Weghofer et al<sup>24</sup> who found that improvements in AMH levels after DHEA supplementation are statistically highly predictive of pregnancy.

## CONCLUSION

In this study a significant improvement in the AMH levels was found following DHEA supplementation in infertile patients with diminished ovarian reserve. This provides objective evidence that DHEA supplementation positively affects the ovarian reserve in such patients. Also the study strongly suggested that improved ovarian reserve following DHEA supplementation leads to better pregnancy outcome. These findings can help improve patient counseling in women with diminished ovarian reserve. Also DHEA can be an alternate low cost option for such patients as not everybody can afford assisted reproductive techniques due to economic and cultural restraint.

## LIMITATIONS

The sample size was relatively small and the duration of the study was limited.

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None

## CONFLICT OF INTEREST

None

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