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Original Research Article

Vitamin D supplementation in women with diminished ovarian reserve: a randomized controlled trial

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ABSTRACT

Background: Diminished ovarian reserve (DOR) predicts decreased ovarian response to stimulation. Low serum anti-Mullerian hormone (AMH) is associated with DOR. AMH is a marker of ovarian reserve and acts as a predictor of ovarian response to ovarian stimulation protocol. The AMH is up regulated by vitamin D via vitamin D response elements that bind the vitamin D receptor. Vitamin D supplementation has a role in increasing serum AMH. The objective was to compare the combined effect of vitamin D and DHEA vs DHEA alone on serum AMH in DOR.
Methods: This randomized controlled trial was conducted in the Department of Reproductive Endocrinology and Infertility, Bangabandhu Sheikh Mujib medical University (BSMMU), Dhaka, from March 2021 to February 2022. A total of 44 infertile women with DOR, 20 to 39 years were allocated into two groups, one received vitamin D plus DHEA for 8 weeks and the other received DHEA alone for the same duration. After 8 weeks of treatment, both groups had repeat assessment of AMH, FSH and transvaginal sonography for AFC.
Results: There was no significant difference in serum AMH after vitamin D supplementation in women with DOR. But the spontaneous pregnancy during intervention was 2.57 times more in those given vitamin D supplementations in addition to dehydroepiandrosterone (DHEA).
Conclusions: Short term vitamin D supplementation adds little to the effect of increasing AMH but favors spontaneous pregnancy in women with DOR.

Keywords: DOR, AMH levels, Vitamin D, DHEA supplementation

INTRODUCTION

Diminished ovarian reserve (DOR) describes women of reproductive age whose response to ovarian stimulation or fecundity is reduced compared to women of comparable age. The term 'ovarian reserve' has traditionally been used to describe a woman's reproductive potential, specifically the number and quality of oocytes she possesses.[1] AMH is one of the most reliable markers of ovarian reserve and commonly used as a predictor of ovarian response in ovarian stimulation protocol.[2,3] AMH, a member of the TGF-beta (transforming growth factor-beta) super family of proteins, is produced by granulosa cells and secreted by pre-antral and antral follicles of the ovary.[4] Women with DOR have low serum AMH, below the threshold of 1 ng/mL.[5]

DHEA is an endogenous steroid produced mainly in the zona reticularis of the adrenal cortex and ovarian theca cells in women. It is believed that androgens can promote folliculogenesis, potentiate the effects of gonadotropin and reduce follicular arrest.[6] A prospective self-controlled study indicates that the baseline ovarian reserve parameters such as AFC, FSH, E2, AMH and inhibin B significantly improves after DHEA supplementation.[7] The acute supplementation of high dose vitamin D in young

women with AMH levels in the lower end of the range was reported by Dennis et al.[8] Forty nine young women were subjected to a randomized double-blind design and were administered a single oral dose of vitamin D (50,000 IU) or placebo. It resulted in a significant increase of serum AMH the following week in the women receiving vitamin D. Serum AMH was significantly increased in infertile women with low AMH level,[9] where 30 women received oral vitamin D (50000 IU) weekly for 3 months in a clinical trial. These studies suggest the benefits of the supplementation of vitamin D in increasing serum AMH in women of normal and DOR.

Vitamin D supplementation is cheap, easily available and easy to administer. In addition to being cost friendly Vitamin D seems to have relatively fewer tolerable side-effects. If better effect of vitamin D supplementation combined with DHEA in increasing AMH can be proved, it will be an additional help to clinicians in the management of women with DOR. With this background, vitamin D was tested for its efficacy to improve the AMH level in infertile women with DOR.

METHODS

The open label parallel design randomized controlled trial was conducted in the Department of Reproductive Endocrinology and Infertility of Bangabandhu Sheikh Mujib Medical University from March 2021 to February 2022. Participants were infertile women with DOR defined by serum AMH less than 1 ng/ml. Exclusion criteria were premature ovarian failure/primary ovarian insufficiency (D2 FSH >25 IU/ml on two occasions at least 4 weeks apart), previous ovarian surgery, previous chemotherapy/ radiotherapy, genital tuberculosis, endocrine disorders like diabetes mellitus, hypothyroidism, endometriosis, and vitamin D supplements in previous three months. Study was approved by institutional review board. Informed consent was taken from each participant.

The participants were randomized into experimental and comparator groups. The experimental group A was given cap vitamin D 40,000 IU single weekly dose and tab DHEA 25 mg 3 times daily for 8 weeks. The comparator group B was given tab DHEA 25 mg 3 times daily for 8 weeks. Non-fasting venous blood samples (3 ml) were collected in vacutainer (ANC medical device Bd. Ltd. Bangladesh) by laboratory technician in the Department of Microbiology, BSMMU, Dhaka, any day of the menstrual cycle before treatment and 8 weeks later. The samples were clotted at room temperature for 30 minutes and then centrifuged at 7000 to 10,000 rpm for 10 min. AMH levels were determined by automated chemiluminescence immunoassay (Beckman Coulter, Unicel DxI 600). Antral follicle count was done in both ovaries on day 2-4 of the menstrual cycle by transvaginal sonography (Mindray, DP-2200 plus) and transvaginal probe 6.5 MHZ. Diameter of the follicles (2 to 9 mm) were taken in two dimensions. Serum FSH was also measured on day 2 to 4 of the menstrual cycle by automated chemiluminescence immunoassay in the Department of Microbiology in BSMMU, Dhaka. All participants were instructed not to take any medications during trial without consultation with primary investigator. The participants were contacted every month to check for compliance. Response assessed after 8 weeks. Primary outcome measure was changed in serum AMH. Secondary outcome measures were changed in AFC, serum FSH.

Random sequence generation was done by computer generated random numbers. Permuted block randomization was done with stratification for age. Random allocation of treatment was done by someone not involved with care of the patients. Allocation concealment was done by sequentially numbered sealed opaque envelops; each had a card inside labeled with an alphabet representing the intervention type. Allocation was never changed after opening the closed envelops. All data were collected by principal investigator. There was no blinding.

Sample size of participants was calculated as 22 in each group, for a power of 0.80, a significance level of 0.05 and an effect size of 3.2. Statistical analyses were carried out by the SPSS program for windows, version 22.0 (SPSS, Chicago, IL). The data were tested for homogeneity prior to analysis. The mean ± SD values or median, interquartile range were calculated as appropriate for outcome variables. Data was tested using the parametric tests such as unpaired t test, paired t test, non-parametric test as Mann Whitney U test and chi-square test as appropriate. $P<0.05$ was considered as statistically significant.

RESULTS

This randomized controlled trial was conducted in the Department of Reproductive Endocrinology and Infertility, Bangabandhu Sheikh Mujib Medical University, Dhaka from March 2021 to February 2022. A total of 85 women were approached, of which 67 women fulfilled the eligibility criteria. They were randomized into two groups, 36 in vitamin D+DHEA group (experimental group or group I) and 31 in DHEA only group (control group or group II). But out of 67, 23 participants dropped out from this study in both groups due to various reasons (Table 1). The final analysis included 24 in vitamin D+DHEA group and 20 in DHEA only group.

Table 1: Recruitment, intervention and participant flow.

Variables	Vit D+DHEA group (I)	DHEA only group (II)
Started	36	31
Received intervention	36	31
Completed	24	20
Not completed		
Lost to follow up	4	8
Pregnancy	6	2
Non-compliance due to cost of drugs	2	1

Table 2: Baseline demographic and clinical characteristics of study participants.

Variables	Vit D + DHEA group, (n=36) (%)	DHEA only group, (n=31) (%)	P value
Age (years) (Mean±SD)	34.11±4.59	33.52±4.32	0.589
Age type (years)			
<30	5 (45.5)	6 (54.5)	0.726
30-35	16 (59.3)	11 (40.7)	
>35	15 (51.7)	14 (48.3)	
Residence			
Urban	25 (55.6)	20 (44.4)	0.795
Rural	11 (50)	11(50)	
Occupation			
House wife	28 (54.9)	23 (45.1)	0.884
Service	7 (50)	7 (50)	
Student	1 (50)	1 (50)	
Husband's occupation			
Service	19 (54.3)	16 (45.7)	0.559
Business	17 (53.1)	15 (46.9)	
Household income (Monthly) (Taka)			
Low (≤10,000)	6 (42.9)	8 (57.1)	0.699
Middle (>10,000-30,000)	14 (58.3)	10 (41.7)	
High (>30,000)	16 (55.2)	13 (44.8)	
Education (years)			
<10	12 (54.5)	10 (45.5)	0.952
10-12	16 (55.2)	13 (44.8)	
>12	8 (50)	8 (50)	
Type of infertility			
Primary	17 (50)	17 (50)	0.353
Secondary	19 (57.6)	14 (42.4)	
Duration of infertility (years)			
<5	17 (51.5)	16 (48.5)	0.941
5-10	15 (57.7)	11 (42.3)	
>10	4 (50)	4 (50)	
BMI (kg/m^2) (mean±SD)	25.84±3.28	27±3.64	0.174
Menstrual cycle (days)			
<24	3 (75)	1 (25)	0.740
24-35	27 (51.9)	25 (48.1)	
>35	6 (54.5)	5 (45.5)	
Menstrual duration (days)			
<3	7 (63.6)	4 (36.4)	0.297
3-5	23 (57.5)	17 (42.5)	
6-7	6 (37.5)	10 (62.5)	

Table 2 describes the socio demographic and clinical characteristics of study participants. Regarding demographic variables, there was no significant difference between group I and group II (p>0.05). Most of the patients were above 30 years of age. Most of the participants had normal menstrual cycle and duration. Table 3 shows that nearly half of the patients in both groups had very low AMH. Mean AFC were around 6. Mean FSH level of the participants were above 10 mIU/ml Serum AMH, AFC and FSH in group I and group II were not significantly different (p>0.05).

Table 3: Baseline ovarian reserve markers of study participants.

Variables	Vit D+DHEA group, (n=36)	DHEA only group, (n=31)	P value
Serum AMH (ng/ml), mean±SD	0.44±0.29	0.43±0.29	0.995
AMH levels (ng/ml) (%)			
Very low≤0.5	18 (50)	18 (50)	0.340
Low=0.5-<1	18 (58.1)	13 (41.9)	
Antral follicle count, mean±SD	6.25±3.32	6.32±2.57	0.922
Serum basal FSH (mIU/ml), mean±SD	13.66±6.16	12.52±5.04	0.415

Table 4: Serum AMH, AFC and serum FSH compared between two groups of participants (Vit D+DHEA group vs DHEA only group).

Variables	Vit D+ DHEA group, (n=24)	DHEA only group, (n=20)	P value
AMH (ng/ml)			
Pre-treatment, median, interquartile range	0.32 (0.14-0.66)	0.40 (0.17-0.64)	0.588
Post-treatment, median, interquartile range	0.47 (0.24-0.77)	0.55 (0.18-0.85)	0.934
AFC			
Pre-treatment, median, interquartile range	5.00 (4.00-7.75)	7.00 (5.00-8.00)	0.312
Post-treatment, median, interquartile range	6.00 (4.00-8.00)	6.50 (4.25-8.50)	0.906
Serum FSH (mIU/ml)			
Pre-treatment, median, interquartile range	12.62 (8.66-20.77)	12.20 (8.46-16.59)	0.377
Post-treatment, median, interquartile range	11.09 (8.14-15.56)	10.55 (7.96-13.13)	0.654

Table 4 shows that there is no significant (p>0.05) difference post treatment in serum AMH, serum, antral

follicle count and serum FSH between vit D+DHEA group and DHEA only group. Mann Whitney U test was done to analyze the data, as variables have non-Gaussian distribution. Table 5 shows that pregnancy was 2.57 times more in group I vit D+DHEA group than in DHEA only group.

Table 5: Pregnancy during intervention in two groups of participants (Vit D+DHEA group vs DHEA only group).

Vit D + DHEA	DHEA only	Relative risk	95% CI of RR	
			Low	High
(6/36) 16.7%	(2/31) 6.5%	2.57	0.57	11.86

DISCUSSION

This randomized controlled trial was carried out on 44 infertile women with DOR with an objective to assess the combined effect of vit D supplementation and DHEA on serum AMH. The experimental group of 24 women had vit D supplementation in addition to DHEA for 8 weeks and the comparator group had DHEA only. The AMH and other ovarian reserve markers were measured at the end. There was no statistical difference in AMH levels post treatment between women who received vit D supplementation and DHEA and women who received DHEA only.

Arefi et al showed a highly significant association of vit D deficiency with reduced ovarian reserve (p<0.001).[10] This study concluded that concealing dress code was an independent risk factor for vit D deficiency due to lack of sunlight exposure and that could be a cause of reduced ovarian reserve. Though Bangladesh is a tropical country there is inadequate exposure of women to sunlight due to covered dress style (headscarf, face cover, gloves, long-sleeved and floor length skirt) during outdoor activities. There is high prevalence of vit D deficiency in Bangladeshi adults (67%, 95% CI 50-83%).[11]

Dey et al did a case control study on 156 infertile women at BSMMU, 78 with DOR and 78 with normal ovarian reserve.[12] The prevalence of vit D deficiency (<20 ng/mL) was 94.9% in DOR cases and 80.8% in the controls, odds ratio was 4.40 (95% CI 1.28-16.64). There was positive significant correlation (r=0.433; p=0.001) between vitamin D levels and serum AMH, also between vitamin D levels and AFC (r=0.419; p=0.001). The study concluded that vitamin D deficiency was associated with DOR.

Dennis et al did a randomized double-blind study to observe the effect of vitamin D supplementation in young women (18-25 year) with normal ovarian reserve during early spring when the serum vitamin D levels are at nadir.[8] An oral dose of 50,000 IU of vitamin D was given and serum AMH increased significantly (<0.01) the following week. The serum vitamin D level before the treatment was 20.67±8.85 ng/mL and after 7 days of treatment the mean rise was 6.30±0.04 ng/mL in the control group given placebo, the serum vitamin D level (ng/mL) was 21.67±10.37 ng/mL before the treatment and the mean rise after 7 days of treatment was 0.48±0.28 (p<0.01), much less than that in women having vitamin D. The mean change of AMH was 12.9%±3.7% (with a range -13% t0 68%) which was statistically significant (p=0.01). This study concluded that acute rise in vitamin D in women with normal ovarian reserve led to an increase in circulating AMH.

As most of our women are either insufficient or deficient for vit D the t randomized controlled study was designed for our women with DOR without defining them as vit D deficient or insufficient. The vitamin D was administered for minimum duration of 8 weeks keeping in mind the findings of Dennis et al.[8] However the population of interest in the present study was women with low AMH who, unlike the young women with normal ovarian reserve in the study of Dennis et al did not have any significant rise in serum AMH with vit D complementation.

Our women were in their thirties on average comparable to the studies on women with DOR.[9,13,14] Middle and higher socioeconomic status and urban living provide easier access to health care as well as better control over reproductive health in comparison to people living in lower socioeconomic condition or rural areas. In this study, maximum participants had household monthly income over 10,000 taka per month. This may reflect the increased prevalence of DOR among the women in both middle and higher socioeconomic status. Most of the participants were housewives; more participants lived in urban area. The prevalence of primary and secondary infertility was similar among the study participants. These findings clearly reflect the impact of DOR on infertility. The duration of infertility was less than 5 years in most of them, suggesting DOR as the more probable cause of infertility.

The comparator arm of 31 women was given DHEA only. There was no significant difference in AMH over 8 week's supplementations with DHEA in the 20 women who completed the study. There was spontaneous pregnancy in 2/31 women during the period of intervention. Yilmaz et al did a prospective study on 41 women with DOR (AMH<1.1 ng/ml) given DHEA 75 mg /day for at least 6 weeks. One patient conceived spontaneously and another two following in vitro fertilization.[7] There was significant increase in AMH in 19 patients aged <35 years (0.79±0.52 ng/mL vs 0.43±0.31 ng/ml) and in 22 patients aged ≥35 years (0.72±0.94 vs 0.22±0.20 ng/ml). Statistically significant rise in their study may be because the analysis included all patients including the ones who got pregnant.

Naderi et al did a non-comparative clinical trial on 30 infertile women with DOR and vit D insufficiency or deficiency.[12] AMH increased significantly (p<0.05) after weekly administration of 50,000 IU vitamin D orally for 3 months. After treatment, mean level of serum vitamin D

was higher in women with mean AMH level of >0.7 ng/ml (19 women), than in women with mean AMH level of <0.7 ng/ml (11 women) (59.332±21.751 vs. 38.881±17.281 ng/ml, p=0.013). After treatment, mean AMH level was higher in women with normal serum vitamin D than the women with insufficient serum vitamin D (1.048±0.644 vs. 0.513±0.284 ng/ml), which shows a significant difference (p=0.043). That study suggested that vitamin D levels were associated with AMH levels.

Aramesh et al did a before-and- after intervention study on 51 women with DOR (AMH <1 ng/ml) and vit D deficiency (Vit D less than 20 ng/ml) without any control group.[13] The study showed that serum levels of both AMH and Vit D increased significantly (p<0.05) after an oral dose of vitamin D 50,000 IU per week for 3 months. Before the treatment the median serum vitamin D level was 12.1 ng/ml and after the treatment it increased to 26 ng/mL which was statistically significant (p<0.001). The median level of serum AMH before the treatment was 0.50 ng/mL and after the treatment it increased to 0.79 ng/ml which was statistically significant (<0.05). The study clearly suggested that vitamin D supplementation increased serum vit D level and had the potential to increase serum AMH in women with DOR.

Bacanakgil et al did a prospective non comparative observational study on 62 infertile women aged 22 to 41 years with DOR and vitamin D deficiency.[14] They administered 300,000 IU vitamin D monthly for 2 months. Mean AMH (ng/ml) increased from before to after treatment (0.82±0.87 versus 1.05±1.01) and mean AFC also increased (2.85±1.54 versus 3.53±1.22). The increase was significant (p<0.01). Results of the study suggest probable beneficial effect of vitamin D supplementation in DOR patients. The FSH level (mIU/ml) in this study decreased significantly (<0.01) after the treatment (16.44±17.47 versus 14.16±13.87). The present study also has an insignificant decrease in FSH in women having vitamin D.

In contrast to the above studies, the present study did not have significant change in ovarian reserve markers. For small effect size, the sample size needs to be large to have a significant result.[15] The intervention arm of our study included only 24 women, a sample size much smaller than Aramesh et al (n=51) and Bacanakgil et al (n=62).[13,14]

The study was a randomized controlled trial to assess the effect of vitamin D on women with low AMH. The trial had additional incidental findings about the more clinically relevant outcome, pregnancy. There was pregnancy during the two months of study in 16.5% of women receiving vitamin D supplementation in addition to DHEA, 2.57 times more than those having DHEA alone. The occurrence of pregnancy may not be entirely explained by the rise in AMH. Administration of DHEA and vitamin D should be tried for a reasonable time before resorting the women with low AMH to more expensive and invasive procedures like assisted reproductive techniques or intra-ovarian injection of PRP (platelet rich plasma) or stem cell.

A systematic review of clinical trials which gave ≤2800 IU/day vitamin D supplementation for one year or longer, reported that long term high dose vitamin D supplementation did not increase the risks of total adverse events or kidney stones.[14] Vitamin D supplementation for a longer period can be given safely to a population with highly prevalent vitamin deficiency.

Limitations

The study was limited by small sample size, short study period and study population recruited from one selected center challenging the external validity of study findings. The population of interest was not specified as vitamin D deficient before intervention. The AMH estimation was done over different days of cycle, not in follicular phase. AFC measurement was done by different persons on same ultrasonogram machine. There was use of DHEA as co treatment and control instead of placebo. Selection bias was eliminated by random allocation and allocation concealment but there was absence of blinding of participants and personnel dispensing the drugs and absence of blinding of outcome assessment. Outcome data was incomplete as there was drop out of participants in both arms.

CONCLUSION

Short term supplementation of Vitamin D adds little to the effect of DHEA supplementation in increasing AMH in women with DOR (AMH <1 ng/ml), but the rate of spontaneous pregnancy during intervention is more than doubled. There should be longer duration of the vit D supplementation and subsequent follow up with dichotomous outcome of clinical significance such as pregnancy and pregnancy complications.

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