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Effects of Dehydroepiandrosterone on the Response of Ovarian Stimulation During In Vitro Fertilization Cycle in Infertile Women With Diminished Ovarian Reserve: Before and After Clinical Trials

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Abstract

Objectives: The use of dehydroepiandrosterone (DHEA) before initiating in vitro fertilization (IVF) cycles to increase the ovarian reserve is considered as one of the best therapies in women with diminished ovarian reserve (DOR). Therefore, the present study aimed to compare the effect of DHEA on women (below and above 35 years old) with DOR and to find if this therapy is useful at an earlier age.

Materials and Methods: This clinical trial study was conducted on 35 infertile women with DOR who referred to Imam Khomeini hospital in Sari, Iran, during 2017. The intervention lasted for 6 weeks and DHEA tablets were used before the start of the intra-cytoplasmic sperm injection-embryo transfer (ICSI-ET) cycle. Antral follicular counts (AFCs) and the serum levels of anti-Mullerian hormone (AMH) were estimated before and after the intervention, followed by performing the ICSI. Finally, the changes in AMH levels and AFC, the number and quality of ovum and embryos and pregnancy, along with the rates of implantation and abortion were measured as well.

Results: The mean AMH levels ($P=0.02$) and AFC ($P<0.001$) after DHEA consumption varied significantly from those before administering the DHEA, and the increase in the AFC was more significant in the age group under 35 years ($P=0.03$). In addition, these changes were more significant in body mass of less than 25 kg/m^2 ($P=0.04$).

Conclusions: In general, the supplementation of DHEA in women with insufficient ovarian capacity probably improves IVF prognosis and other parameters including AFC and AMH, especially in women under 35 years old. Further, based on different evidence, the probability of pregnancy occurrence in women is lower with increased body mass index (BMI).

Keywords: Dehydroepiandrosterone, Ovarian reserve, Anti-Mullerian Hormone, Infertility

Introduction

Ovarian reserve or residual ovarian reserve can be used to predict the success of using assisted reproductive technology. In fact, a patient is believed to have a diminished ovarian reserve (DOR) when she has ovarian counts lower than what is expected for her age (1). DOR is one of the major obstacles for a successful assisted pregnancy. In addition, DOR is reported in 5-18% of in vitro fertilization (IVF) cycles and the pregnancy rate in these patients, who undergo various fertility protocols, is as low as 2%-4% (2,3).

Dehydroepiandrosterone (DHEA), in an androgenic steroid, is produced by the zona reticularis cells of the adrenal cortex and the ovarian theca cells. DHEA is an important pre-hormone in the production of intra-follicular steroids by the ovaries and its positive effects on ovulation stimulation were first described in 2009 (4).

However, the mechanism of actions regarding DHEA consumption remains theoretical. DHEA affects early follicular maturation by modified androgen receptor (AR) transcription, enhances follicle-stimulating hormone (FSH) receptor expression, regulates FSH action in granulosa cells (GCs), and increases the antral follicular counts (AFC) and the expression of AR pre ovulatory GCs (5-10).

Taking DHEA oral supplements causes an increase in serum levels of insulin-like growth factor I, which increases the maturity and quality of oocytes. (8). Various

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studies reported an increase in oocyte production after treatment with DHEA supplements (1,5,11-14)

Further, Barad et al (15) found that DHEA increased the ovarian reserve and the response to ovarian stimulation in DOR and their further effectiveness in younger patients (6). Based on the results of one study, the ovarian reserve testing (e.g., AFC, FSH, estradiol, anti-Mullerian hormone [AMH], and inhibin-B) were meaningfully affected by DHEA supplementation (16). Furthermore, the results of another study indicated that the high-quality embryos were more in DOR women who used DHEA (17). Similarly, the findings of a meta-analysis demonstrated that there was inadequate data to confirm the effectiveness of DHEA in DOR (13). Likewise, Yeung et al (18) observed no changes in the ovarian reserve testing (e.g., AFC, AMH, or FSH) and the ovarian response to IVF and pregnancy rate in DOR women who underwent pretreatment with DHEA. Therefore, further research is required in this field in order to provide more information on the effectiveness of DHEA.

Accordingly, the current study sought to determine the rate of success (e.g., the increased chance of pregnancy, the reduced rate of abortion, and the like) in treatment with DHEA. AMH, as a biomarker, plays the role of either a surrogate outcome or a prognostic factor while no clear borders exist to differentiate the two above-mentioned variables. Therefore, in the present study, the response to treatment in women (over and under 35 years old) who were diagnosed with DOR (AMH<1.5 ng/mL) was evaluated and analysed to determine whether or not and to what extent the age of the patient can be considered an intervening factor in response to treatment. Finally, it attempted to identify the appropriate age cut-off for prescribing DHEA as a promising treatment option.

Materials and Methods

This study is a before-after clinical trial that was implemented on infertile women who attended the infertility clinic of Imam Khomeini hospital during 2017 and had a poor ovarian response (POR) to stimulation. The treatment plan for these patients was intra-cytoplasmic sperm injection-–embryo transfer (ICSI-ET). Based on the inclusion criteria, thirty-five patients were included in this study.

Inclusion Criteria

Patients within the age range of 20-45 years old (19) under treatment with ICSI-ET, not detected with endometrial pathology using hysterosalpingography or hysteroscopy, with an AMH value <1.5 ng/mL or <7 antral follicles in the ovaries or <3 failed ICSI-ET cycles and/or <5 oocytes or <3 embryos (Bologna criteria) in the previous ICSI-ET.

Exclusion Criteria

The existence of an abnormal uterus structure detected upon hysterosalpingography or hysteroscopy, a normal response in ovulation cycles or ICSI-ET cycles, an AMH level of over 1.5 ng/mL, >7 antral follicles in the ovaries and a history of >3 failed ICSI-ET cycles.

Age, body mass index (BMI), and infertility duration were considered as demographic variables. In addition, serum AMH levels and antral follicle counts were taken into account as the surrogate outcomes while clinical pregnancy was regarded as the final outcome.

Patients who were eligible to enter the study and had a history of a POR, <7 antral follicles, and an AMH level of <1.5 ng/mL were consulted and entered the study upon giving informed consent. These patients were prescribed DHEA pills (DHA, Puritan pride, USA, Tab 25mg, TDS) for a 6-week course before initiating an ICSI-ET cycle and a vaginal ultrasound was performed on the third day of the menstrual cycle in order to evaluate the antral follicle count of both ovaries. Further, a blood test was conducted to measure the AMH levels and then the patients underwent GnRH antagonist protocol that included gonadotropin injections (SC, Gonal-F 75 IU/mL, produced by Merck Serono Company, Germany) based on each patient's age and ovarian reserve, in addition to subcutaneous Cetrorelix injections (SC, Cetrotide 250 µg/d, produced by MerckSerono Company Germany) which were started when follicular diameter reached 12-14 mm. The folliculography and evaluation of endometrial thickness were performed routinely. Furthermore, the dosage of gonadotropin injections was adjusted based on the size and the number of follicles which were visualized in ultrasonography. Next, when two or more follicles reached the minimum size of 17 mm, the patient were injected with 10 000 units of human chorionic gonadotropin (hCG, Choriomon, 5000 IU, IM, produced by IBSA Company, Switzerland), 34-36 hours before retrieving the oocytes (20). Moreover, ICSI was implemented according to the conventional methods, in which the oocytes were denudated by the mechanical and enzymatic approach. The fertilization of oocytes and embryo transfer were performed as well. Concisely, after inspection of the oocytes for fertilization process and 16-18 hours after the insemination, the two pronuclei zygotes were cultured for 24-48 hours in Sage Media (Cooper Surgical, Inc, Trumbull, CT) complemented with 10% serum protein substance (SPS, Irvine Scientific, Santa Ana, CA). Eventually, two or three embryos (based on each patient's age), each containing 4-8 cells, were transferred on the third day of conception (21).

Luteal protection began upon the transfer and patients received vaginal progesterone suppositories (Cyclogest 400 mg/twice daily, production by Actover Company, UK). Additionally, β-hCG levels were measured 15 days after the embryo transfer and luteal protection was continued until the twelfth week of gestation if the test was positive. In addition, vaginal ultrasonography was performed in the case of β-hCG test positivity in order to confirm a gestational sac and clinical pregnancy. The Outcomes

measures such as AMH levels and its rise, antral follicle counts on the third day of the menstrual cycle and its rise, the number and quality of oocytes, embryo and the clinical pregnancy and the rate of implantation and the abortion rate were included. The rate of implantation was defined as the number of gestational sacs that were observed upon ultrasonography, divided by the total number of the transferred embryos. Further, a spontaneous abortion was considered as the loss of the viable embryo prior to the 20th gestational week. The test results after 6 weeks of treatment with DHEA were compared for each patient with the results obtained before the beginning of the treatment.

All patients signed a formally informed consent form before entering the study and their participation was terminated if they experienced medication side effects such as headache, irritability, hair loss, and general intolerance.

To detect the differences with the effect size equal to 50% in AFCs, changes in women under 35, from 3.7 to 5.6 that is considered significant (16) by using G power software (the power of 90% and the confidence interval of 95%), a sample size of 34 patients was needed.

The evaluation of the distribution of variables and the Kolmogorov–Smirnov test results were represented by a histogram. Statistical analysis was performed using paired t-test or Wilcoxon test based on the data distribution. The results were analyzed in the subgroups under and over 35 years old. Furthermore, the time-to-event analysis was implemented based on the occurrence of clinical pregnancy in the two age subgroups in order to establish an age as a determinant of treatment success. The other statistical tests such as long-rank, along with a Kaplan-Meier plot were used to calculate two-sided *P*-value.

Results

The average age of the patients in this study was 36.24±5.20 years, ranging from 25 to 45 years old. Fifteen patients were under 35 while twenty patients were over 35 years old. Moreover, the average BMI was 25.14±3.49 (kg/m^2), ranging from 18 to 32 (kg/m^2), the details of which are provided in Table 1.

The results of the statistical analysis showed that except for the number of IVF cycles (*P*=0.001), the duration of DHEA use (*P*=0.001), induction days (*P*=0.001), the antral follicle count before beginning the treatment (*P*=0.04), the number of transferred embryos (*P*=0.001), and β-hCG titre (*P*=0.001), other variables had a normal distribution pattern (data were not shown).

Initially, all patients were scheduled to undergo an antagonist protocol while the level of AMH increased in two cases, thus an agonist protocol was used instead. Except for two cases that underwent an agonist protocol (2.7%), an antagonist protocol was used for the remaining 33 patients (94.3%). Based on the results of the paired t-test, a significant difference was found between AMH levels that were obtained before and after the treatment with DHEA ($P=0.02$). This difference was observed in the difference of AFC before and after treatment ($P<0.001$) as well (Table 2). Analysing the relationship between the age group of the patients, as well as the average AMH levels and the AFC demonstrated that the age of the patients failed to statistically affect the average AMH levels after treatment with DHEA ($P=0.1$) by using the independent *t* test. However, the AFC showed a significant relationship ($P=0.03$) with the patients' age group (Table 3). Based on the analysis of the relationship between average AMH levels and the AFC after treatment with DHEA in the two groups of BMI, the average AMH level after treatment with DHEA was not statistically significant in the two BMI groups using the independent *t* test ($P=0.21$). while it was significant ($P=0.04$) regarding the AFC (Table 2).

Table 1. Demographic Data and Cycle Characteristics of Infertile Women

Variables	Mean±SD* (N = 35)
Mean age (y)	36±5
BMI (kg/m^2)	25±3.5
Infertility duration (year)	4.53±3.80
AMH level before DHEA (ng/mL)	0.97±0.62
AMH level after DHEA (ng/mL)	1.32±0.65
Endometrial thickness on HCG day (mm)	8.13±1.55
hCG injection days	11.97±1.48
The mean dose of gonadotropins used	31.80±19.79
No. of Antral follicles before DHEA	2.7±2.05
No. of Antral follicles after DHEA	5.3±2.5
No. of injected ovum	4.31±2.71
No. of fertilized eggs	3±2
No. of divided ovum	3±2
No. of embryos	3±2
No. of embryos transferred	2±1
Time between DHEA and pregnancy (months)	3.9±2.1

*Data are presented as mean±SD.
BIML: Body mass index; AMH: Anti-Mullerian hormone; DHEA: Dihydroepiandrosterone; hCG: human chorionic gonadotropin.

Table 2. Mean AMH Levels and Antral Follicular Counts Before and After Treatment With DHEA and its Relation With Different Age and BMI

Variables	(Mean ± SD)* (N=35)	*P* Value
AMH levels (ng/mL)		
Before DHEA	0.97±0.621	0.02
After DHEA	1.32±0.651	
≤35 years	1.53±0.71	0.1
>35 years	1.16±0.58	
BMI ≤25	1.45±0.69	0.21
BMI >25	1.18±0.59	
AFCs		
Before DHEA	2.71±2.05	<0.001
After DHEA	5.31±2.57	
≤35 years	6.33±2.63	0.03
>35 years	1.16±0.58	
BMI ≤25	6.17±2.68	0.04
BMI >25	4.41±2.18	

*Data are presented as Mean±SD.
SD, standard deviation; BMI, body mass index; DHEA, dehydroepiandrosterone; AMH, anti-Mullerian hormone.

Table 3. Clinical Outcomes and DHEA Side Effects in Women With Diminished Ovarian Reserve Undergoing IVF

Variables	No.	%
Clinical pregnancy rate (%)	12	34.3
Ongoing pregnancy rate (%)	9	25.7
Implantation rate (%)		35.7
Miscarriage rate (%)	4	11.4
Multiple pregnancy rate (%)	3	8.57
Live birth rate (%)	11	31.4
Total	12	34.3
DHEA side effects (%)	0	0

DHEA: Dehydroepiandrosterone; IVF, In vitro fertilization.

The quality of the retrieved oocytes was evaluated (Data not shown) and presented as follows.

Totally, 20 cases (57.1%) were metaphase II while 13 cases (37.1%) were metaphase I and a quality of GV and MTII+MTI each was represented by one patient (2.9%). The distribution of embryo grading showed that cases were graded A (n=25, 71.4%), A+B (n=6, 17.1%), and B (n=4, 11.4%, data were not shown). Among the 35 cases of embryo transfer, 6 (17.1%) of them were fresh and 29 (82.9%) cases were freeze. The results of the regression analysis showed that the probability of achieving a clinical pregnancy was higher in women with a lower BMI. Finally, pregnancy was achieved in 12 cases, three of which were multiple pregnancies (Table 3).

Discussion

Over the years, DHEA has been suggested as a promising infertility treatment in women with a POR. Moreover, taking DHEA supplements before ovarian stimulation was proven to be related to a higher spontaneous pregnancy rate in women with high levels of FSH or very low levels of AMH (4,12). In an animal study conducted by Anderson and Lee (22), the administration of DHEA in rats was associated with higher levels of serum androgen, estradiol, and prolactin while other studies demonstrated improvement in the development of the primary follicles after DHEA administration in rats (23). Human studies that evaluated the efficacy of DHEA treatment reported inconsistent and conflicting results, therefore, the present study was designed and conducted to evaluate the effect of DHEA on the ovarian stimulation response in infertile women with a DOR. Thirty-five patients with an average age of 36.24+-5.20 years were included in the study. Fifteen patients were under 35 whereas twenty of them were over 35 years old. In a similar study and prospective review implemented in Taiwan, Tsui et al (5) evaluated the effect of DHEA on women with a POR and a failed IVF cycle on their first attempt of an antagonist cycle. These women were assigned a 30 mg DHEA/ three time a day regimen that continued for three months. Totally, 10 patients with an average age of 36.6±4.2 years were included in the study. The average age of patients of the above-mentioned study is very similar to the average age of the patients of the current study with the difference that the present study had a larger sample size and an antagonist protocol was used for 33 patients (94.3%) except for the two cases who underwent an agonist protocol (2.7%).

According to our results, the average AMH levels significantly differed before and after the treatment with DHEA. This difference was attributed to the AFCs as well. Both of these values increased after the treatment. Conversely, the average AMH levels were not significantly different between the two age groups. As regards the AFC, a significant difference was found between the two age groups, which was higher in the group in which the patients were 35 or younger. Contrarily, the average AMH values after the treatment with DHEA was not statistically significant in the two BMI groups when analyzed using the independent t-test while this was significant regarding the AFC which was higher in patients with a BMI score of 25 or less. In an American retrospective study conducted by Gleicher et al (6), patients with a POR (i.e., high FSH and low AMH levels) used DHEA supplements for an average duration of 34-119 days. Based on their results, the AMH levels increased significantly after DHEA treatment and this increase in AMH levels was much more substantial in patients who were under 38 years old when compared to older patients. Additionally, clinical pregnancy was achieved in 23.64% of the cases. The result of the above-mentioned study regarding the effect of age on AMH levels contradicts that of the current study. In addition, the cut-off age in the present study was 35 years, which is younger than the 38 years old cut-off chosen by Gleicher et al (6). Clinical pregnancy was achieved in 34.3% of the cases in the present study, which is a higher success rate compared to the mentioned study. However, they examined 120 women with a longer duration of DHEA consumption, which differs from the number of women of the current study.

In another study, Yilmaz et al (16) examined the effect of DHEA supplements on the improvement of predictor parameters of a DOR such as AMH, Inhibin-B, and AFC in 41 women. Serum AMH, FSH, and estradiol levels, along with AFC were measured before and after the treatment with DHEA. After the treatment with DHEA, a statistically significant change was found in the above-mentioned parameters ($P = 0.001$, 0.001, 0.002, 0.001, and 0.001). The study population was divided into two groups of over and under 35 years old in order to compare the effect of DHEA on these parameters among younger and older patients and to determine the possible effect of age on the success rate, with is in line with the results of the present study. The results of the study demonstrated a statistically significant difference in both groups regarding all variables before and after DHEA supplementation while these changes were not different before and after the age of 35, which is not in conformity with the findings of the current study which found more increase in AMH levels before the age of 35. In addition, Yilmaz et al investigated

more ovarian reserve parameter such as inhibin-B, FSH, and estradiol.

In the present study, the qualities of the retrieved oocytes were evaluated and included 20 cases (57.1%) of MTII, 13 cases (37.1%) of MTI, and the quality of GV and MTII+MTI each was represented by one patient (2.9%). The distribution of embryo grading showed that 25 (71.4%), 6 (17.1%), and 4 (11.4%) cases were graded A, A+B, and B, respectively. Further, among 35 cases of embryo transfer, 6 (17.1%) of them were fresh whereas 29 (82.9%) others were freeze. The results of regression analysis revealed that the likelihood of achieving a clinical pregnancy was higher in those women who had a lower BMI. Pregnancy was achieved in 12 cases, three of which were multiple pregnancies (Table 3). Tsui et al found an increase in the number of retrieved and fertilized oocytes and transferred embryos using DHEA in 10 women with prior fail attempt and POR undergoing IVF again. Furthermore, three patients with an insufficient ovarian reserve became successfully pregnant and it was shown that using DHEA supplements in women with an insufficient ovarian reserve can improve the chances of a successful IVF and other predicting parameters such as FSH, estradiol, and AMH (5). Moreover, the mean age of the patients in the above-mentioned study was 36.6 years, similar to that of the current study. However, Tsui et al studied a lower number of patients with prior fail IVF attempt, which differs from the number of patients in the present study.

In another study by Wiser et al (12), 33 patients were put on a Long Agonist protocol with no positive results, 17 of whom began daily taking of 75 mg DHEA pills for 6 weeks before the next IVF cycle. Patients who failed to become pregnant followed the second IVF cycle by using DHEA for at least 16-18 weeks while 16 patients were in the control group. A total of 50 IVF cycles were induced for these 33 patients. The serum estradiol levels showed no significant difference on the hCG injection day between the two cycles although the implantation rate and the quality of embryos statistically varied between the first and second cycles. Additionally, the treatment group had a higher number of live births (23% vs. 4%). Unlike the present study, the dosing of the DHEA supplement in the study of Wiser et al was similar to the treatment protocol of the current study, though, they used two IVF cycles in some patients and longer duration of DHEA consumption after the first IVF cycle. They used agonist protocol in all patients with POR while, in the present research, most women underwent antagonist protocol. As regards the design of the study, both the above-mentioned and current study are similar with the exception that there was a separate control group in the above study, which is different from the before-after protocol of the current study. Live birth rate in this study was 23% that was lower compared to that of the present study (31.4%) which may be due to different treatment protocols and the patients' selection.

In a meta-analysis study by Narkwichean et al (13), the reported effects of DHEA were studied in 22 clinical trials and only three of them concluded that DHEA can play a positive role in ART while the remaining studies showed no correlation between using DHEA and fertility and a decrease in abortion rates. Therefore, there are no sufficient data to support the routine prescription of DHEA for these patients. This meta-analysis was limited by a small number of treatment cycles and the heterogeneity of the involved studies. The result of possible effects of DHEA on oocyte quality and ovarian reserve necessitates well-designed randomized controlled clinical trial (RCT) with a sufficient sample size in order to extract important and valid results. In another meta-analysis study from Taiwan (24), 7 prospective and 4 retrospective studies were investigated evaluating the effect of DHEA on patients with a poor response to ovulation stimulation in IVF. One study reported that DHEA may be beneficial in patients with normal ovarian response and the data failed to support DHEA as a beneficial supplement for patients with POR. These results contradict the findings of the current study. The above-mentioned studies demonstrate contradictory results, which is why Triantafyllidou et al (25) suggested that multifocal RCTs can help in better understanding the efficacy of DHEA due to the lack of definitive evidence to support or dispute the use of DHEA. Furthermore, the fact that DHEA has no serious side effects should not be believed, allowing the prescription of this medication with no evidence-based indication.

These inconsistencies between the results of the mentioned studies can be attributed to a difference in sample selection methods, racial differences, a difference in the dosage of the medication and IVF protocol, along with the differences in the study designs. Therefore, a broader study with a larger sample size should be conducted to determine the cut-off age.

Lin et al (26) examined the clinical advantages of DHEA in 72 POR and the potential effects of DHEA on cumulus cells (CCs) and indicated that PORs with DHEA produced an excessive number of high-quality embryos at day 3, as well as a further number of transferred embryos and fertilization rate compared to the controls. They further found that DHEA in PORs reduced DNA destruction and apoptosis in CCs while enhancing the mitochondrial mass and mitochondrial dehydrogenase activity in CCs. Therefore, they concluded that these changes may be due to the improvement of mitochondrial function and the reduction of apoptosis in CCs.

Buyuk et al (27) examined the association between elevated BMI and ovarian reserve in 290 women with DOR and reported that greater BMI accompanied lower AMH levels in women with DOR while not in women with normal ovarian reserve. Further, the AMH levels were 33% less in overweight and obese women compared to the control group. Furthermore, women with higher BMI and

DOR had a lower amount of oocytes compared to women with normal BMI and DOR (6.4 ± 4.3 vs. 9.4 ± 6). Buyuk et al used no DHEA supplementation for their patients with DOR, which is different from the present research while they found more AMH levels and oocyte retrieval in thinner women with DOR. Therefore, this finding may explain the lower effectiveness of DHEA in obese patients with DOR. The current study is known to be the first study which investigated the correlation between DHEA and DOR and BMI that could be validated in future research.

The three gonadotrophins (i.e., FSH, LH, and hCG) are glycoproteins composed of two subunits including alpha and beta. The alpha subunit is the same in FSH, LH, and hCG while the beta subunits are different from differential biological activity. FSH motivates the recruitment and development of early antral follicles by attaching to the receptors entirely expressed on GCs.

Moreover, LH plays a fundamental role in indorsing steroidogenesis and promoting the dominant follicle. In fact, it has different roles at different phases of the cycle. LH induces androgen secretion by theca cells in the follicular phase. Androgens are then transported to the GC and converted into oestrogens by the aromatase enzyme. Eventually, LH stimulates final follicular maturation through its effects on the GC in the late follicular phase. Additionally, theca and GCs secrete IGF, inhibin, and activin, which regulates LH induced androgen production in the thecal cells (28). Due to the different structure, hCG has a longer half-life of 24 hours compared to LH (30 minutes). In addition, because of their similar structures, hCG binds the same receptor as LH. In the gonadotropin treatment protocol, hCG is used to trigger the final follicular maturation of the immature oocyte at prophase I (the germinal vesicle) by meiotic maturation to metaphase II. The meiotic maturation needs nearly 36 hours for completion, then, ovulation occurs. Therefore, oocyte retrieval is planned with hCG injection in IVF (28) and the mechanism of the effect of DHEA on the IVF outcomes in DOR women remains controversial. DHEA assists as a prohormone of the follicular testosterone during ovarian stimulation with gonadotrophins (29).

The GCs, that is, the androgen receptors, indorse small antral follicle growth and prohibit follicular atresia (30). Hence, androgen is crucial for natural folliculogenesis and reproduction. In GCs, androgen treatment may increases aromatase and progesterone enhancement in response to FSH management (8) and thus can lead to an increased response to ovarian stimulation. Furthermore, DHEA may salvage follicles from atresia, induce pre-antral follicle growth (30-32), overwhelm apoptosis (33), and improve ovarian reserve and oocyte harvests.

The limitations of the present study included poor patient cooperation regarding laboratory studies and leaving the study in different stages, referred patients from other centres with incomplete recorded treatment data, poor medication adherence, and patients' impatience for achieving a clinical pregnancy. Patients who left the study and/or failed to provide the researchers with the required information were excluded from this study to the highest possible extent.

Conclusions

Based on study results, the average AMH level was significantly higher after treatment with DHEA and the increase in the AFC after the treatment was exceptionally greater in women <35 years old and patients who had a BMI of 25 kg/m^2 or less. Further, women with a lower BMI represented a higher overall chance of achieving a clinical pregnancy. The prevalence of pregnancy rate was 34.3% and thus DHEA can probably improve the IVF outcome and other predictive parameters in patients with an insufficient ovarian reserve and lower BMI less than 25. Furthermore, DHEA was less effective in obese patients with DOR. Finally, the present study is the first one to examine the correlation between DHEA and DOR and BMI that could be validated in future research by a larger sample size.

Ethical Issues

This study was approved by the Iranian Registry of Clinical Trials website (identifier: IRCT2017091529374N1), as well as the Ethics Committee of Mazandaran University of Medical Sciences (with an ethical code of IR.MAZUMS.IMAMHOSPITAL.REC.96.2806).

Conflict of Interests

None.

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