

## Comparative Study of The Influence of Dehydroepiandrosterone Versus Growth Hormone on The Improvement of Ovarian Reserve Markers in Women With Diminished Ovarian Reserve

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### ABSTRACT

**Background:** The study aimed to evaluate the effects of dehydroepiandrosterone (DHEA) and growth hormone (GH) supplementation on the improvement of the ovarian reserve markers in women with history of POR in the previous In vitro fertilization (IVF) cycles.

**Aim of the work:** To evaluate the effects of DHEA and GH supplementation on the improvement of the ovarian reserve markers in women with history of POR in the previous In vitro fertilization (IVF) cycles.

**Patients and methods:** 90 adult female with POR were randomly allocated into 3 groups; each group included 30 patients. Control group received HMG/GnRH antagonist protocol. GH group received GH/HMG/GnRH antagonist protocol. Patients received daily subcutaneous injection of 2.5mg of GH from day 21 of previous cycle, until the day of HCG injection. DHEA group received DHEA/HMG/GnRH antagonist protocol. Patients received 25 mg of micronized DHEA, administered orally three times a day, for 12 weeks before starting the cycle of ovulation induction. The number of retrieved oocytes, fertilized oocytes, and embryos transferred, chemical pregnancy rate, the clinical pregnancy rate and LBR were recorded.

**Results:** The mean values of the number of the oocytes retrieved, the fertilized oocytes, the transferred embryo, the chemical pregnancy rate, clinical pregnancy rate, ongoing pregnancy rate and live birth rate (LBR) were statistically significant higher in the DHEA group compared to the control and the GH groups ( $P < 0.05$ ). While, there was no significant difference between the control group and the GH group ( $P > 0.05$ ).

**Conclusion:** The DHEA supplementation to the IVF protocol improved the number and quality of retrieved oocytes, the rate of clinical pregnancy and the LBR compared to the control group or the GH co-treatment to the IVF protocol.

**Keywords:** DHEA; IVF; Infertility Pregnancy rate.

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### INTRODUCTION

The ovarian reserve reflects the woman's pregnancy chance; it differs between individuals and, at least partially, is under genetic control operated by Fragile X mental retardation 1 gene.<sup>1</sup> Ovarian reserve defines both total ovarian reserve, a pool of growing follicles at different stages of maturation, and functional ovarian reserve, which is related to the size of the follicle pool and the follicle recruitment rate.<sup>2</sup> The European Society of Human Reproduction and Embryology published the Bologna criteria in 2011 in order to standardize the definition of poor ovarian response (POR).<sup>3</sup>

Dehydroepiandrosterone (DHEA), an endogenous androgen, is produced in the zonarectularis of the adrenal gland and by ovarian theca cells, and converted to testosterone and estradiol (E2) in peripheral tissues.<sup>4, 5</sup> The oral administration of DHEA before gonadotrophin stimulation to increase ovarian response in poor responder patients was proposed by.<sup>6</sup>

Growth hormone (GH) regulates the effect of follicle-stimulating hormone (FSH) on granulosa cells, by increasing the synthesis of Insulin-like growth factor 1, augments the effect of gonadotropin on granulosa and theca cells, and plays an essential role in ovarian function, including follicular

development, estrogen synthesis and oocyte maturation.<sup>7,8</sup>

This study aimed to evaluate the effects of DHEA and GH supplementation on the improvement of the ovarian reserve markers in women with history of POR in the previous In vitro fertilization (IVF) cycles. The primary outcomes of the study were the number of oocytes retrieved and the clinical pregnancy rate.

## PATIENTS AND METHODS

After obtaining approval from the Institutional Ethics Committee and written informed consent from all the patients, 90 adult female with POR were included in this prospective randomized controlled trial (RCT). They were divided into 3 groups; each group included 30 patients. This study was conducted in Private Based IVF Units. All the data of patients were confidential with secret codes and private file for each patient, all given data were used for the current medical research only. Couples were counseled about the treatment protocols.

**Inclusion criteria:** Adult females with POR defined according to the Bologna criteria<sup>9</sup> that included presence of at least two of the three following features; maternal age ( $\geq 40$  years), a previous POR ( $\leq 3$  oocytes with a conventional stimulation protocol) and an abnormal ovarian reserve tests including antral follicle count (AFC)  $< 5$  and Anti-Müllerian hormone (AMH)  $< 1.1$  ng/mL and / or elevated FSH on days 2 or 3 of the menstrual cycle more than 10 IU/L. All the included female had normal uterine cavity.

The exclusion criteria included body mass index (BMI)  $\geq 30$  mg/m<sup>2</sup>, FSH  $> 20$  IU/L, endocrine or metabolic disorders, such as diabetes mellitus, thyroid disorders, and polycystic ovarian syndrome, severe endometriosis, abnormal gynecological bleeding of undetermined origin, allergy to the used medications, medical treatment with corticoids, azospermia or women with uterine malformation or abnormality.

The patients were randomized through a computer-generated randomization sequence into the three groups through using 90 sealed opaque envelopes. The patients were allocated in one of three groups (30 patients each):

**Control group (HMG/GnRHant protocol) (30 patients):** Women of this group received HMG/GnRH antagonist protocol.

**GH group (GH/HMG/GnRHant protocol) (30 patients):** Women of this group received GH/HMG/GnRH antagonist protocol. Patients received daily subcutaneous injection of 2.5mg of GH (equivalent to 7.5 IU) (Norditropin, Novo Nordisk) from day 21 of previous cycle, until the day of HCG injection.

**DHEA group (DHEA/HMG/GnRHant protocol) (30 patients):** Women of this group received

DHEA/HMG/GnRH antagonist protocol. Patients received 25 mg of micronized DHEA, administered orally three times a day, for 12 weeks before starting the cycle of ovulation induction.

The participating females underwent full history taking, medical and gynecological examination. Transvaginalsonographic evaluation was done.

**Treatment protocol:**

Ovarian stimulation was started in all women in the three studied groups from the second day of menstrual cycle with 300 IU of HMG. Ovarian response monitoring was performed using serial vaginal ultrasonography and measuring serum E2 levels. When dominant follicles reached to 14 mm in mean diameter, 0.25 mg/day of GnRH antagonist was started and continued to prevent premature luteinization until the day of HCG injection in both groups. When at least two follicles with a mean diameter of 17 mm were observed, 10,000 IU HCG was injected. Endometrial thickness and serum E2 levels were measured in the day of HCG injection. Oocyte retrieval was done 34–36 h after HCG injection using a 17-gauge needle under vaginal ultrasonography guidance, and conventional IVF or intracytoplasmic sperm injection (ICSI) was performed appropriately. Embryos were transferred using a labotect catheter (labotect, Gottingen, Germany) 48–72 h after oocytes retrieval. At most three embryos were transferred in each In vitro fertilization-Embryo transfer (IVF-ET) cycle and excess embryos were cryoprecipitated. Luteal phase support was started with progesterone in oil 100 mg daily IM on the day of oocyte retrieval and continued until the documentation of fetal heart activity by ultrasound.

Quantitative  $\beta$  HCG was performed 14 days following embryo transfer and was considered positive if  $\geq 50$  IU/L. In cases with confirmed pregnancy, transvaginalsonographic was performed two weeks later to confirm the presence of an intrauterine sac with positive fetal pulsations. Pregnant cases were followed up till delivery.

Primary outcomes were the number of oocytes retrieved and the clinical pregnancy rate. Secondary outcomes were the number of fertilized oocytes, number of embryos transferred and live birth rate (LBR).

Fertilization of oocytes was defined with observation of at least one pronucleus or cleaved oocytes. Implantation rate defined by the number of gestational sacs per transferred embryos was calculated. Cycle cancellation rate, chemical pregnancy rate, ongoing pregnancy rate and early miscarriage rate were calculated.

Cycle cancellation is identified when no embryo is transferred because of failed oocyte retrieval (no obtained oocyte on the day of ovarian puncture), or failed fertilization and/or cleavage (no obtained embryo after IVF/ICSI). Chemical pregnancy is defined as a serum beta HCG  $\geq 50$  IU/L, 14 days after embryos transfer. Clinical pregnancy is identified as observation of fetal heart activity by trans-vaginal ultrasonography performed 5 weeks

after positive beta HCG. Ongoing pregnancy is defined as pregnancy proceeding beyond the 12th gestational week. Early miscarriage was defined as loss of pregnancy before 12 weeks of gestation. LBR was defined as the number of achieved live birth after 28 weeks of gestation.

### Statistical analysis

Data were fed to the computer and analyzed using IBM SPSS software package version 20. (Armonk, NY: IBM Corp). The Kolmogorov-Smirnov test was used to verify the normality of distribution. Quantitative data were described using mean  $\pm$  standard deviation and were analyzed using one way ANOVA with Post Hoc Tukey test for pair wise

comparisons. Qualitative data were described using number and percent. Comparison between categorical data was performed using Chi square test. Significance of the obtained results was judged at  $P < 0.05$ .

## RESULTS

A comparison between the three studied groups regarding demographic data including, age, BMI, duration of marriage and duration of infertility, and the basal levels of FSH, luteinizing hormone (LH), E2, AFC and AMH were insignificant different among the three groups ( $P > 0.05$ ). (Table 1)

	Control group	DHEA group	GH group	P value
Age (years)	37.27 $\pm$ 3.03	38.6 $\pm$ 2.91	37.7 $\pm$ 2.72	0.199
BMI (Kg/m <sup>2</sup> )	25.57 $\pm$ 2.13	26.20 $\pm$ 2.47	25.97 $\pm$ 2.24	0.556
Duration of marriage (years)	9.0 $\pm$ 2.79	8.36 $\pm$ 4.53	9.93 $\pm$ 3.77	0.274
Duration of infertility (years)	6.23 $\pm$ 2.48	6.5 $\pm$ 4.28	7.27 $\pm$ 1.99	0.407
AFC	4.47 $\pm$ 2.27	4.77 $\pm$ 2.18	4.96 $\pm$ 2.19	0.679
AMH (ng/ml)	0.85 $\pm$ 0.77	0.90 $\pm$ 1.06	0.89 $\pm$ 0.82	0.978
Basal E2 (pg/mL)	116.77 $\pm$ 49.64	111.23 $\pm$ 45.21	108.43 $\pm$ 49.32	0.792
Basal FSH (IU/L)	12.23 $\pm$ 1.44	12.73 $\pm$ 1.85	11.99 $\pm$ 1.48	0.191
Basal LH (IU/L)	4.84 $\pm$ 2.33	4.68 $\pm$ 2.54	4.43 $\pm$ 2.28	0.797

Data presented as mean  $\pm$  SD. Data presented as mean  $\pm$  SD.

**Table 1:** Basal patients' characteristics.

The mean values of the total dose of HMG (IU) and the duration of stimulation were statistically significant higher in the control group as compared to the DHEA and GH groups ( $P < 0.05$ ). They were lower in the DHEA group than the GH group ( $P < 0.05$ ). A Comparison between the mean values of the number of the oocytes retrieved, MII oocytes, the

fertilized oocytes and the transferred embryo were statistically significant higher in the DHEA group compared to the control and the GH groups ( $P < 0.05$ ). While, there was no significant difference between the control group and the GH group ( $P > 0.05$ ). (Table 2)

	Control group	DHEA group	GH Group	P value	Post Hoc Test (Tukey)		
					P1	P2	P3
Dose of HMG (IU)	3830.0 $\pm$ 514.71	3050.0 $\pm$ 394.57	3340.0 $\pm$ 470.94	$< 0.001$	$< 0.001$	$< 0.001$	0.045
Duration of stimulation (days)	12.77 $\pm$ 1.72	10.16 $\pm$ 1.32	11.13 $\pm$ 1.57	$< 0.001$	$< 0.001$	$< 0.001$	0.045
E2 on the HCG day	929.73 $\pm$ 387.36	1760.0 $\pm$ 683.72	1678.17 $\pm$ 743.97	$< 0.001$	$< 0.001$	$< 0.001$	0.868
Endometrial thickness (mm)	9.6 $\pm$ 0.97	10.17 $\pm$ 1.29	9.97 $\pm$ 0.99	0.133			
N oocyte collected	4.2 $\pm$ 1.94	5.96 $\pm$ 2.80	4.5 $\pm$ 2.03	0.008	0.01	0.868	0.04
N MII oocyte	2.63 $\pm$ 1.33	4.53 $\pm$ 2.15	3.2 $\pm$ 1.4	$< 0.001$	$< 0.001$	0.389	0.007
N fertilized oocyte	1.80 $\pm$ 0.99	4.07 $\pm$ 1.98	2.77 $\pm$ 1.55	$< 0.001$	$< 0.001$	0.056	0.005
N transferred embryo	1.57 $\pm$ 0.86	2.23 $\pm$ 0.94	1.67 $\pm$ 0.8	0.008	0.01	0.896	0.035

**Table 2:** cycle characteristics.

The cancelled cycle, the implantation rate and early miscarriage rate were statistically insignificant different among the three groups ( $P > 0.05$ ). The chemical pregnancy rate, clinical pregnancy rate, ongoing pregnancy rate and LBR per cycle start or per embryo transfer were statistically significant

higher in the DHEA group compared to the control group and the GH group ( $P < 0.05$ ), while they were statistically insignificant different between the control and the GH group ( $P > 0.05$ ). (Table 3, 4)

	Control group	DHEA group	GH group	P value	Post Hoc Test (Tukey)		
					P1	P2	P3
Cancelled cycle	5/30; (16.7 %)	3/30; (10 %)	4/30; (13.3 %)	0.749			
The fertilization rate	62.5±34.03	82.88±29.82	78.39±34.42	0.046	0.048	0.152	0.857
The implantation rate	5/47; (10.6%)	15/65; (23%)	6/56; (10.7 %)	0.096			
The chemical pregnancy rate /cycle	7 /30; (23.3%)	16/30; (53.3%)	8/30; (26.7%)	0.028	0.017	0.766	0.035
The clinical pregnancy rate/cycle	3/30; (10%)	12/30; (40%)	5/30; (16.7%)	0.014	0.007	0.448	0.045
Ongoing pregnancy rate/cycle	2/30; (6.7%)	10/30; (33.3%)	3/30; (10%)	0.011	0.01	0.64	0.028
Early miscarriage rate/cycle	1/30; (3.3 %)	2/30; (6.7 %)	2/30; (6.7 %)	0.809			
LBR/cycle	2/30; (6.7%)	10/30; (33.3%)	3/30; (10%)	0.011	0.01	0.64	0.028

**Table 3:** Reproductive outcomes.

	Control group	DHEA group	GH group	P value	Post Hoc Test (Tukey)		
					P1	P2	P3
The chemical pregnancy rate/ET	7/25; (28%)	16/27; (59.2%)	8/26; (30.8%)	0.037	0.023	0.828	0.037
The clinical pregnancy rate/ET	3/25; (12%)	12/27; (44.4%)	5/26; (19.2%)	0.018	0.01	0.478	0.049
Ongoing pregnancy rate/ET	2/25; (8%)	10/27; (37%)	3/26; (11.5%)	0.014	0.013	0.671	0.031
Early miscarriage rate/ET	1/25; (4 %)	2/27; (7.4 %)	2/26; (7.7 %)	0.836			
LBR/ET	2/25; (8%)	10/27; (37%)	3/26; (11.5%)	0.014	0.013	0.671	0.031

**Table 4:** Reproductive outcomes/ embryo transfer.

## DISCUSSION

The results of the our study demonstrated that the number of retrieved oocytes, MII oocytes, fertilized oocytes, transferred embryo as well as the clinical pregnancy rate, ongoing pregnancy rate and LBR significantly improved in DHEA group as compared to the control and GH groups. However, no difference between the GH group and the control group was detected.

Up to our knowledge, there is no randomized controlled trial comparing the effects of administration of DHEA versus GH as adjuvant to the GnRH antagonists for the patients with POR.

The major mechanism of DHEA supplementation on the improvement of reproductive outcomes in POR patients may be explained by the increased androgen after DHEA supplementation. DHEA, a precursor of E2 and testosterone, serves as a prohormone of follicular fluid testosterone during ovarian induction.<sup>10</sup> ARs have been identified in the granulosa cells at any follicular stage, especially preantral and antral follicles.<sup>11</sup> Granulosa cell-specific androgen receptors are the crucial regulators of follicular development and fertility. In fact, androgen plays important roles in recruitment and initiation of

primordial follicles, promotion of follicular growth through increasing FSH receptor expression, and prevention of follicular atresia by reducing apoptosis.<sup>12,13,14</sup>

Moreover, DHEA administration increases serum concentration of IGF-1,<sup>15</sup> which has been reported to be correlated with oocyte quality and embryo development.<sup>16</sup> Therefore, indirect action of DHEA was mainly presented. However, direct action of DHEA on the target organs has been proposed<sup>17</sup> but is still inconclusive. Regarding the molecular mechanism, DHEA supplementation could improve mitochondrial function and reduce apoptosis in the CC and human GC line.<sup>18</sup>

Concerning the beneficial effects of adding the DHEA to the GnRH antagonists therapy for POR patients on the IVF outcomes, our findings were in concordance with the study carried out by Chern et al.<sup>19</sup> They carried out a retrospective cohort study on 151 PORs fulfilled the Bologna criteria and underwent IVF cycles with the GnRH antagonist protocol and their patients allocated into two groups; the study group received 90 mg of DHEA daily for 3 months before the IVF cycles and the control group underwent the IVF cycles without DHEA pretreatment. They found that the number and quality

of retrieved oocytes, the number of transferable embryo, the clinical pregnancy rate, ongoing pregnancy rate and LBR were higher in the DHEA group than those measured in the control group.

Also, Kotb et al.<sup>20</sup> compared the influence of administration of DHEA 25 mg three times daily for 12 weeks before the IVF/ICSI cycles versus the control group that did not receive DHEA and they concluded that DHEA increases the number of oocytes, fertilization rate, and fertilized oocytes, in women with POR according to the Bologna criteria. The beneficial effect of DHEA supplementation on the IVF outcomes was documented in other studies.  
21-25

In contrast to the results of our study regarding the effects of DHEA supplementation on IVF outcomes, including the clinical pregnancy rate, ongoing pregnancy rate and LBR, Kara et al.<sup>26</sup> assessed the efficacy DHEA on IVF-ICSI outcome of poor responders in a RCT including 208 patients allocated into DHEA group and control group. They documented that the number of retrieved oocytes, MII oocytes, fertilized oocytes and transferred embryo, fertilization rate and pregnancy rates were not different between the groups. Also, Yeunget al.<sup>27</sup> found no statistically significant differences in IVF outcomes in anticipated poor responders who received 12 weeks of DHEA supplementation before the start IVF treatment compared with placebo.

Regarding the effect of GH co-treatment to the IVF outcomes our results are in agreement with Eftekharet al.<sup>28</sup> assessed IVF-ET cycle outcomes after the addition of GH in antagonist protocol in poor responders. Eighty-two poor responder patients selected for ART enrolled the study and were randomly divided into two groups. Group I (GH/HMG/GnRHant group, n = 40) received GH/gonadotropin/GnRH antagonist protocol and group II (HMG/GnRHant group, n = 42) received gonadotropin/GnRH antagonist protocol. There were no significant differences between groups regarding the number and quality of retrieved oocytes, endometrial thickness, and the fertilization, implantation, and chemical and clinical pregnancy rates.

Moreover, Norman et al.<sup>29</sup>, Dakhly et al.<sup>30</sup> and Bassiounyet al.<sup>31</sup> investigated the impact of GH co-treatment to the IVF protocol poor responders. Their studies concluded that the use of GH co-treatment to the IVF had no significant difference in the number and quality of retrieved oocytes, chemical pregnancy, clinical pregnancy and LBR.

On the other hand Yovich and Stanger,<sup>32</sup> reported that GH co-treatment to the IVF/ICSI treatment significantly improved the clinical pregnancy and LBR. Hazout et al.<sup>33</sup> found that Co-stimulation with GH in a special population of patients with no clear explanation for their multiple failure of embryo transfer gave better results in terms of number of oocytes collected and embryos obtained. Pregnancy rate per retrieval was higher than in the control group.

We recommend further studies including a larger number of poor responders to define the place of DHEA supplementation in this challenging clinical situation, confirm the optimal dose and duration for DHEA supplementation. Further studies are recommended to investigate the effects of GH supplementation to the poor responders and to determine the appropriate dose, time of administration and even in which subgroup of patients GH should be used.

## CONCLUSION

The DHEA supplementation to the IVF protocol improved the number and quality of retrieved oocytes, the number of transferable embryo, the rate of chemical and clinical pregnancy rate and the LBR compared to the control group or the GH co-treatment to the IVF protocol. However, the co-administration of the GH to the IVF protocol had no beneficial effects on the quality and number of the collected oocytes, the clinical pregnancy rate and LBR.

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