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Does dehydroepiandrosterone improve pregnancy rate in women undergoing IVF/ICSI with expected poor ovarian response according to the Bologna criteria? A randomized controlled trial

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ABSTRACT

Objective: To provide the best available evidence on the role of dehydroepiandrosterone (DHEA) treatment in improving the outcome of in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI) in women with poor ovarian response (POR).

Study design: A randomized controlled trial conducted in Cairo University hospitals and Dar Al-Teb subfertility and assisted conception centre, Giza, Egypt. 140 women undergoing IVF/ICSI with POR according to the Bologna criteria were randomly divided into 2 equal groups. The study group received DHEA 25 mg three times daily for 12 weeks before the IVF/ICSI cycles and the control group did not receive DHEA. Controlled ovarian stimulation (COH) was started on the second day of menstruation using human menopausal gonadotropins, cetrotide 0.25 mg was started when the leading follicle reached 14 mm. The main outcome measures were the clinical pregnancy rate, ongoing pregnancy rate, retrieved oocytes, fertilization rate, gonadotropins doses and COH days.

Results: The DHEA group had significantly higher clinical pregnancy rate (32.8% vs 15.7%, $p = 0.029$), ongoing pregnancy rate (28.5% vs 12.8%), retrieved oocytes (6.9 ± 3 vs 5.8 ± 3.1, $p = 0.03$), fertilization rate (62.3 ± 27.4 vs 52.2 ± 29.8, $p = 0.039$), significantly less gonadotropins doses (3383 ± 717.5 IU vs 3653.5 ± 856 IU, $p = 0.045$) and COH days (11.6 ± 1.8 vs 12.6 ± 1.06, $p = 0.001$).

Conclusion: DHEA increases the number of oocytes, fertilization rate, fertilized oocytes, and clinical pregnancy rate and ongoing pregnancy rate in women with POR according to the Bologna criteria. DHEA was well tolerated by the patients and was associated with less COH days and gonadotropins doses.

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Introduction

Poor ovarian response (POR) is encountered in about 9–24% of women in IVF cycles [1]; women with POR yield sub-optimal number of oocytes and lower quality embryos resulting in decreased implantation and pregnancy rates [2]. Several treatments have been used to improve the pregnancy outcome in women with POR including dehydroepiandrosterone (DHEA). DHEA is produced as an intermediate step during steroidogenesis by the adrenal glands and ovaries to synthesize estradiol and testosterone [3]. The most favourable results with DHEA supplementation use regimens of about 12 weeks suggesting that deficiency of DHEA might mediate its effect on the earliest stages of follicle growth [4].

Casson et al. were the first group to suggest using DHEA in women with POR. They reported that DHEA may enhance ovarian response and pregnancy rates in women with reduced ovarian reserve [5]. Since then several studies evaluated the role of DHEA in women with POR [6–8,3,9,10], however these studies used different definitions of POR and consequently had conflicting results.

In the absence of a clear definition of POR, randomized trials with clear evidence based criteria defining POR were needed to evaluate the role of DHEA [11]. The European Society of Human Reproduction and Embryology provided these criteria introducing the Bologna criteria. At least two out of three criteria are required to define POR during IVF: 1 – Maternal age > 40 or any other risk factor for POR. 2 – A previous POR (≤ 3 oocytes with a conventional stimulation protocol). 3 – An abnormal ovarian reserve test (i.e. antral follicle count (AFC) less than 5–7 follicles or anti-Müllerian

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hormone (AMH) less than 0.5–1.1 ng/ml). They also suggested that history of 2 episodes of POR after maximum stimulation protocol is sufficient to define POR [12].

Two studies investigated the role of DHEA in women with POR according to the Bologna criteria but none of them was randomized [13,14]. The objective of the study was to provide the best available evidence to evaluate the role of DHEA treatment in women undergoing IVF/ICSI with POR according to the Bologna criteria.

Patients and methods

This was a multicentre, randomized balanced (allocation ratio 1:1), controlled and parallel groups study. The study was conducted in Cairo University Hospitals and Dar Al-Teb subfertility and assisted conception centre, Giza, Egypt from May 2014 to May 2015. Dar Al-Teb is a private centre which treats about 15,000 subfertile couples each year. We obtained ethical committee approval for both sites from the research ethics committee of Cairo University. The inclusion criteria were women undergoing IVF/ICSI with POR according to the Bologna criteria and age from 20 to 45 years. Exclusion criteria were body mass index >35 kg/m^2, women with a single ovary, allergy to DHEA, and diabetic women on insulin as insulin lowers DHEA levels and might reduce its effectiveness [12].

One hundred and forty women were randomly divided into two equal groups. A registrar generated the allocation sequence using computer generated random numbers. Allocation was concealed using opaque sealed envelopes kept with another registrar who allocated the patients to the study or the control group. The DHEA group received oral DHEA (DHEA®, Natrol, USA), 25 mg three times daily for three months before IVF/ICSI and the control group started the cycles without receiving DHEA.

All women had gonadotropin releasing hormone antagonist protocol for controlled ovarian hyperstimulation (COH); on the second day of menstruation, all women received human menopausal gonadotropin (hMG; Merional®, IBSA, Lugano, Switzerland), the initial dose ranged between 300 and 450 IU/day and was adjusted according to the patient's response guided by number and size of the follicles in addition to serum oestradiol (E2) values. When the leading follicle reached 14 mm cetrorelix (Cetrotide® Merck Serono, Darmstadt, Germany) 0.25 mg was given daily, COH was continued until at least three follicles ≥17 mm were obtained. This was followed by the administration of 10000 IU of human chorionic gonadotrophin (hCG; Choriomon®, IBSA). Oocyte retrieval was guided by transvaginal ultrasound and was performed 34–36 h after hCG administration. The procedure was cancelled if less than 3 follicles ≥17 mm in size are present 12 days after starting follicle stimulating hormone (FSH) despite doses reaching 450 IU. Fertilization was performed using ICSI for M2 oocytes and IVF for other oocytes; 16–18 h later, fertilization was confirmed by the presence of two pronuclei in the zygotes. Zygotes were transferred to Global culture medium (LifeGlobal, Ontario, Canada). Excellent quality embryos were defined as those containing 6–8 even blastomeres with <10% fragmentation at day 3.

Embryo transfer was performed on day 5 after oocyte retrieval and if possible, two embryos were transferred and cryopreservation of the remaining embryos was offered. Luteal support was given in the form of vaginally applied progesterone tablets (Prontogest® IBSA) 400 mg/day starting from the day of oocyte retrieval. Serum βhCG measurement was carried out 2 weeks after embryo transfer. The primary outcome was the clinical pregnancy defined as the presence of an intrauterine gestational sac 5 weeks after embryo transfer. Ongoing pregnancy was defined as sonographic confirmation of fetal heart beat at 12 weeks of gestation. Implantation rate was calculated by dividing the number of gestational sacs by the total number of transferred embryos.

Power calculation

Data on the role of DHEA in women undergoing IVF with POR according to the Bologna criteria were not available before starting this study. We chose to recruit 70 women in each group. During the course of our study Jirge et al. and Xu et al. published their studies and used the Bologna criteria to define POR. Jirge et al. found that the pregnancy rate in the DHEA group was 30% versus 9.1% in controls [13]. Based on this, we would have needed to study 55 cases and 55 controls to reject the null hypothesis that the pregnancy rates for women with POR receiving DHEA and controls were equal with probability (power) 0.8. As we had already chosen to study 70 women in each group we would be able to reject this null hypothesis with probability (power) 0.885. Type I error probability associated with this test of this null hypothesis is 0.05. On the other hand Xu et al. found that the pregnancy rate in the DHEA group was 34% versus 18% in controls [14], we would have needed to study 211 cases in each group to reject the null hypothesis. We preferred not to change the study protocol to avoid bias, especially that we have already started recruitment, our sample size could be justified by the results of Jirge et al., both studies were not randomized and our study would provide a better evidence. We used an uncorrected chi-squared statistic to evaluate this null hypothesis. The power was calculated using PS Power and Sample Size Calculations software, version 3.0.11 for MS Windows (William D. Dupont and Walton D. Vanderbilt, USA).

Statistical methods

Data are given as the mean ± standard deviation (SD), or as frequencies and percentages when appropriate. Numerical variables were compared using Student's t tests; Chi-squared (χ^2) tests were used for comparing categorical data; and Fisher's exact test was used instead when the expected frequency was less than 5; p values less than 0.05 was considered statistically significant. Non-normally distributed data were presented as medians and ranges and were compared using the Mann–Whitney U test. All statistical calculations were done using SPSS for IBM (IBM Corp., Armonk, NY, USA).

Results

The flow of patients in the study is described in Fig. 1. There was no difference in the baseline characteristics of the groups (Table 1) and the distribution of Bologna criteria was not different between the groups (Table 2). The number of retrieved oocytes, fertilization rate, fertilized oocytes, excellent quality embryos and implantation rate were higher in the DHEA group. Conversely, the needed hMG doses and the COH days were less in the DHEA group. However, the number of M2 oocytes, total number of embryos and number of transferred embryos were not different in the study groups.

Eight cycles were cancelled in the DHEA group: six for having less than 3 follicles ≥17 mm and two for fertilization failure; and 13 cycles were cancelled in the control group: ten for having less than 3 follicles ≥17 mm and two for fertilization failure. There was no significant difference in the cancelled cycles between the groups. Intention to treat analysis was adopted, women with cancelled cycles were considered to have no retrieved oocytes if cancellation was for POR and no fertilized oocytes if cancellation was for fertilization failure.

Twenty three (32.8%) women got pregnant in the DHEA group and the ongoing pregnancy rate was 28.5%; conversely eleven