ORIGINAL ARTICLE

Does Dehydroepiandrosterone (DHEA) improve in vitro fertilisation (IVF) outcomes in poor responders?

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ABSTRACT

Background: In reproductive medicine poor ovarian response (POR) among women undergoing in vitro fertilisation (IVF) is of great concern. Meta-analysis showed that Dehydroepiandrosterone (DHEA) administration resulted in a significant increase in the number of oocytes retrieved in women with POR. The aim of this study was to assess the effectiveness of DHEA supplementation on IVF outcomes among poor responders undergoing IVF.

Methods: Sixteen patients who were diagnosed with POR scheduled to undergo their second cycle of Intracytoplasmic sperm injection (ICSI)/embryo transfer cycle were enrolled. All enrolled patients had earlier undergone their first ICSI/embryo transfer cycle at least four months prior to this study. All subjects were given DHEA supplementation of 25mg three times daily for at least three months prior to their second ICSI/embryo transfer cycle. Statistical analysis of various ovarian response and ICSI outcomes parameter were compared pre and post DHEA.

Results: Sixteen women with the mean age of 35 years were enrolled in the study. The comparative analysis of results showed a significant increase in the number of good quality of embryos obtained ($p<0.05$). After the treatment with DHEA, there was an improvement in the number of oocytes retrieved, Metaphase II (MII) oocyte (mature) oocytes obtained, fertilised and transferrable embryos and the pregnancy rate. There was no significant effect of DHEA treatment on the number of days of stimulation and cumulative dose of gonadotrophins used.

Conclusion: Our results is able to show that DHEA supplementation may help to enhance IVF-ICSI outcomes in women with POR especially in those age 35 years and below.

KEY WORDS:
Dehydroepiandrosterone, Poor ovarian response, Intracytoplasmic Sperm Injection, Infertility, embryos, oocytes

INTRODUCTION

Poor ovarian response (POR) among women undergoing in-vitro fertilisation (IVF) is of great concern in reproductive medicine. The first description of a patient who was a poor responder was described 28 years ago.[1] It was manifested as low ovarian reserve and early ovarian aging leading to a decline in oocyte quantity and quality.[2,3]

Certain modalities such as increasing gonadotrophin dose or using different down-regulation protocols have been used to improve IVF outcomes and increase the clinical pregnancy rates for this cohort of patients.[4-6] Others strategies include administration of Dehydroepiandrosterone (DHEA), a C19 androgenic steroid that is secreted primarily by the adrenal zona reticularis and to certain extent by ovaries which is synthesized by the steroidogenic enzyme P450c17.

DHEA has been shown to increase follicular insulin-like growth factor I (IGF-I) which can promote the gonadotrophin effect.[7,8] It has also been reported to suppress apoptosis and thus increase the oocyte and embryo numbers and improve overall the quality of embryos produced in each cycle. Meta-analysis showed that DHEA administration resulted in a significant increase in the number of oocytes retrieved in women with POR.[9]

MATERIALS AND METHODS

This retrospective observational study utilised data of patients from Reproductive Unit of Hospital Sultanah Bahiyah, Kedah, Malaysia from 1 June 2014 till December 2018. Ethical approval was obtained from the institutional review board before the commencement of the study (NMRR-18-1375-41922). We reviewed data of 16 patients with evidence of POR during previous treatment in this single centre study. The patients received 25mg three times daily (75mg/day) of DHEA for a minimum of 12 weeks prior to their next IVF/ICSI cycle. The study was carried out comparing the results obtained respectively with the pre-DHEA and the post-DHEA treatments.

Data of patients who were poor responders in previous IVF/ICSI cycle were retrieved from the registry kept at the Reproductive Unit. Their medical records were reviewed to gather information such as demographics, use of DHEA supplementation, as well as clinical and laboratory results. To investigate the effect of patient age on study parameters, the patients were divided into two groups: ≤35 years and >35 years.

All enrolled patients underwent their first ICSI/embryo transfer cycle of at least four months prior to the current study. The inclusion criteria were those patients with POR, that was determined as having at least two of the following three criteria (Bologna Criteria): (i) Advanced maternal age (>40 years) or any other risk factor for POR such as primary

This article was accepted: 31 October 2019
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ovarian insufficiency, chemotherapy -especially with alkylating agents or ovarian surgery, endometriomas (ii) A previous POR (≤3 oocytes with a conventional stimulation protocol). (iii) An abnormal ovarian reserve test (ORT) i.e. antral follicle count (AFC) less than 5-7 follicles or anti-Mullerian hormone (AMH) below 0.5-1.1ng/ml. Exclusion criteria was patients with history of the following clinical situations: single ovary, abnormal uterine cavity such as uterine synechiae or thin endometrium, diabetic women on insulin (as insulin lowers DHEA levels and might reduce its effectiveness), patients who was not consistent or defaulted oral DHEA therapy for three months, diagnosed as pregnant during three months of DHEA therapy or allergy to DHEA.

Patients in both pre and post treatment with DHEA underwent the same control ovarian hyper stimulation protocol.[10] They were stimulated with GnRH agonist and antagonist in which gonadotrophin (daily s.c: Puregon, Organon; Gonal-F, Serono) was started on second day of the menstrual cycle. Follicular monitoring was performed on day-6, -8 and -10. Daily GnRH antagonist (s.c.: 0.2mg Cetrorelix, Serono or Ganirelix, Organon) was commenced at day-6 of stimulation or when the largest follicle reached 12mm in diameter. Human chorionic gonadotrophin (hCG) 10,000IU (s.c: Pregnyl, Organon) was used to trigger ovulation when the two or more leading follicles were >17mm in diameter. Oocyte retrieval was performed 36 hours following the HCG trigger. The number of embryos and the mode of their transfer were determined by their availability as well as by age and clinical history. Progesterone for luteal phase support was given orally or in the form of vaginal pessaries (Crinone 8% 900; Uterogestan 100mg, Solvay Pharmaceuticals BV, Holland). Two weeks following embryo transfer, serum beta human chorionic gonadotropin (hCG) was performed and if positive, two weeks later, a clinic appointment was given and ultrasound was performed to confirm gestational sac.

Statistical analysis

Data analysis was done using the SPSS version 22.0 software system. Descriptive data such as mean and standard deviation were computed for continuous variables. After ensuring that the data followed approximate normal distribution, statistical analysis on the mean values computed during pre and post treatment period on the same subjects were performed using student's independent t-test. A value of $p<0.05$ is considered statistically significant.

RESULTS

As shown in Table I, 16 patients who met the criteria for POR based on Bologna criteria were recruited in the study. The patients were mainly Malays with primary infertility (81%) and mean BMI of 24.00kg/m^2. Majority of them were healthy with the mean age of 35 years old and with a mean infertility period of seven years. The medication was well tolerated by all patients.

Comparison between the two groups revealed higher clinical pregnancy rate among the DHEA group patients (Table II). However, these findings did not have statistical significance. There was statistically significance of higher good grade or quality of embryo obtained after 12 weeks of DHEA, 0.81±0.91 versus 1.62±1.45, respectively (p=0.04; Table II). No significant differences were noted for the other IVF cycle characteristics.

To investigate the effect of age of the patients on the study parameters, the patients were divided into two groups: ≤35 years and >35 years. As shown in Table III, among younger women with POR who were less ≤5 years old, DHEA treatment during ovarian stimulation allow for more number of day-2 or -3 embryos to be obtained. The average of number of day-2 or -3 embryos obtained were two in non DHEA group and three in those with DHEA treatment group.

DISCUSSION

The goal of ovarian stimulation in IVF is the recruitment of multiple follicles in an effort to compensate for the inefficiencies of embryology culture, embryo selection for transfer and subsequent implantation.[11] Hence, poor response to ovarian stimulation usually indicates a reduction in follicular response resulting in a reduced number of retrieved oocytes. Failure to respond adequately to standard protocols and to recruit adequate follicles is called 'poor response' resulting in a reduced numbers of retrieved oocytes, cycle cancellation and, overall, is associated with a significantly diminished probability of pregnancy.[12,13].

Poor responders has been reported in 9-24%[13] of patients who had undergone IVF cycle and this causes frustration for both patients and the physician in-charge. Various strategies had been studied to improve IVF outcome and to increase the clinical pregnancy rate for this subpopulation of patients.

Majority of the evidence on DHEA use in women to enhance the ovarian reserve was based on retrospective analyses [14], prospective self-controlled studies,[12,14] case reports/series,[16] case-control studies[17] and a single randomised controlled trial.[19] They concluded that DHEA may be of benefit in women with POR but recommended conducting large randomised trials to confirm this benefit.[18,19]

In our study, we found that DHEA supplementation had a positive impact on women with POR undergoing IVF/ICSI cycles. Although the study design and sample size are important limitation of this study, our findings show a statistically significant increase of good quality embryos among the DHEA-treated patients that were available for embryo transfer which later lead to higher clinical pregnancy rate; although the outcome was not significant. The DHEA supplementation group achieved three clinical pregnancies (18.7%) compared with none in the pre DHEA treatment group. Mohamed MM et al.,[19] in their RCT study showed that DHEA increases the number of oocytes, fertilisation rate, fertilised oocytes, and clinical pregnancy rate and ongoing pregnancy rate in women with POR according to the Bologna criteria. However, our study was only able to show significant finding in higher grade of good quality embryos available, since this study had a small number of patients.

Table I: Traits of individuals based on picture of acne skin and digitally created clear skin

Baseline Variable	Age ≤35 (n=9)		p value	Age >35 (n=7)		p value
	Before DHEA	After DHEA		Before DHEA	After DHEA	
Antral Follicle count (AFC)	6.78	6.44	0.32	5.71	5.43	0.32
Endometrial thickness on HCG day	10.44	11.78	0.34	9.43	10.14	0.16
Cumulative dose of Gonadotrophin (IU)	2488.89	3038.89	0.129	3339.2	3157.14	0.34
Days of stimulations (n)	9.44	11.22	0.03	10.714	10.14	0.19
Follicles > 16mm (n)	3.00	3.56	0.44	2.28	1.71	0.73
Oocytes retrieved (n)	2.89	3.89	0.18	2.28	2.28	1.00
MII oocytes (n)	2.56	3.89	0.10	2.00	2.14	0.85
Fertilised embryo	2.11	3.11	0.26	2.00	2.00	1.00
Total embryos (n)	1.44	2.78	0.07	1.71	2.00	0.68
Day 2/3 embryos	1.89	2.89	0.03	2.28	2.57	0.58
Transferred embryos	1.22	1.89	0.27	0.86	1.57	0.19
Frozen embryos	0.00	0.56	0.18	0.28	0.00	0.32
Grade 1 embryos	0.89	1.89	0.08	0.71	1.28	0.26
Grade 2 embryos	0.22	0.67	0.10	0.43	0.28	0.56
Clinical pregnancies	0	2 (12.5)		0	1(6.25)	
Cancelled cycles	2(12.5)	0	3(18.8)	1(6.25)		

Values are mean ± SD or n (%)

Table I: Characteristics of the subjects (n=16)

Characteristics	Mean (SD)
Age (years)	35.62±3.80
Ethnicity	
Malay	11
Chinese	5
Indian	0
Others	0
Duration Infertility (years)	7.00±4.32
Type of Infertility	
Primary	13(81)
Secondary	3(19)
Cause of Infertility	
Male	06(38)
Female	10(62)
BMI (kg/m^2)	24.00±3.46
Comorbid medical illness	
Yes	2(12)
No	14 (88)

Values are mean ± SD or n (%).
SD =standard deviation

Table II: IVF cycle characteristics before and after Dehydroepiandrosterone (DHEA) supplementation

Baseline Variable	Before DHEA	After DHEA	p value
Antral Follicle count (AFC)	6.31±1.99	6.00±2.20	0.16
Endometrial thickness on HCG day	10.00±2.92	11.06±1.91	0.06
Cumulative dose of Gonadotrophin (IU)	2860.94± 896.33	3090.62±794.19	0.32
Days of stimulations (n)	10.00±2.13	10.75±1.39	0.18
Follicles > 16mm (n)	2.68±1.58	2.75±1.77	0.69
Oocytes retrieved (n)	2.62±1.74	3.1875±1.97	0.30
MII oocytes (n)	2.31±1.66	3.12±1.93	0.14
Fertilised embryo	2.06±1.48	2.62±1.93	0.34
Total embryos (n)	1.56±1.46	2.4375±1.63	0.09
Day 2/3 embryos	2.06±1.29	2.75±1.06	0.09
Transferred embryos	1.06±1.18	1.75±1.18	0.41
Frozen embryos	0.13±0.50	0.31±0.87	0.08
Grade 1 embryos	0.81±0.91	1.62±1.45	0.04
Grade 2 embryos	0.31±0.48	0.50±0.73	0.317
Clinical pregnancies	0	3	_
Cancelled cycles	5	1	_

Values are mean ± SD or n (%)

DHEA can directly increase the primordial follicles, perantral follicles and AFC development.[16-18] Besides, DHEA increases granulose cells, FSH receptors, increasing follicular sensitivity to FSH, improves steroidogenesis as it acts as the precursor of estradiol and testosterone and improve follicular growth when receiving exogenous gonadotrophin.[19] DHEA is also able to increase insulin growth factors 1 levels which promotes follicular growth and improves oocytes quality as seen in this study.[18,19]

Long-term effects of DHEA supplementation is still unknown. Concerns about the safety issue of DHEA, as a precursor of sex steroids, that it may increase the risk of oestrogen or androgen dependent malignancies is present. Pregnancy, in itself, is a high oestrogen/DHEA state,[20] and women with PCOS, also a high androgen/DHEA state, do not deliver daughters with masculinised external genitalia. This suggests that a low-dosage use of DHEA should be safe.18 In this study, a DHEA dose of 75mg/day was used because most of the index patient had utilised this dosage in previous studies.[21] Also, the androgenic effects of DHEA treatment appear to be minimal with the therapeutic dose of 75 mg/day.[20]

Age is a significant factor that influences the ability of women to conceive, especially with the current social trends of progressively deferred childbearing, leading to increasing number of women who are experiencing age-related infertility. Based on many reports,[22-24] a slow but steady decrease in fertility age has long been recognised from demographic and epidemiological studies especially in women aged between 30 and 35 years, which is followed by an accelerated decline among women aged over 35 years. An important finding in our study was the fact that DHEA has better prognosis in poor responder women who were <35 years old compared to those more ≥35 years old. DHEA treatment in this specific group allowed for more number of day-2 or -3 embryos to be obtained. The average of number of day-2 or -3 embryos obtained were two in non DHEA group and three in those with DHEA treatment group. DHEA is also said to improve oocytes quality thus yielding better embryos without aneuploidy and thereby reducing the risk of abortion.[25] On the other hand, Jirgi et al.,[26] did not find any significant difference between younger and older patients (40 years) in terms of oocyte yield and total numbers of embryos. The limitation of the study was due to the retrospective nature of the analysis consisting of a small sample size with mixed infertility factors. Purists may argue that no treatment should be routinely applied in clinical practice, unless based on prospectively randomised studies. Recognizing that Level I clinical trials may, at times, be too costly and/or too difficult to conduct, such an approach has, however, recently been questioned in the academic community.[27-29] Since Casson et al.,[14] first observed that DHEA supplementation in women with POR led to an enhanced ovarian response, and many studies have reported its beneficial effect,[26-28] it may help this subpopulation of infertile women to conceive.

CONCLUSION

Although DHEA supplementation may have a positive impact on the quality of the embryos, there were limitations in our study as this was a retrospective observational study and it was difficult to control the confounders. Therefore, a more robust method should be employed to determine the effect of DHEA supplementation on poor ovarian responders based on this preliminary results.

ACKNOWLEDGEMENTS

The author thanks Dr Nabilah Azman and staff of Reproductive Unit of Hospital Sultanah Bahiyah for their help in collection of the data; Dr Tan Yap Loong, Dr Nor Rafeah Tumian, Sharifah Nadia Syed Mohammad Salleh for their assistance in editing this manuscript & Staff of CRC unit HSNZKT for the statistical analysis support.

FUNDING

No funding sources.

CONFLICT OF INTEREST

None declared.

ETHICAL APPROVAL

This study was approved by Institutional Ethics Committee (NMRR-18-1375-41922).

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