

Preliminary Results of DHEA in Poor Responders in IVF

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Abstract

Objective: Dehydroepiandrosterone (DHEA) has been previously reported to improve ovarian response in IVF for poor responders. Its effect remains uncertain. The purpose of this study was to evaluate the effect of DHEA given during two years in our unit, in order to build hypothesis for a future randomized controlled trial. **Design:** Cohort of exposed and non-exposed DHEA study. **Patient(s):** 224 patients with AMH under 1.6 ng/ml undergoing IVF with a short antagonist protocol adding FSH and LH rec were enrolled for 327 IVF cycles. 176 patients had been treated with DHEA before IVF, and 151 had not. **Intervention(s):** None. **Main Outcome Measure(s):** Cancellation cycle rate, amount of gonadotrophins used, estradiol level on day six of stimulation, number of oocytes retrieved, metaphase II oocytes, blastocysts and frozen embryos, clinical pregnancy rate and miscarriage rate. **Results:** The cancellation rate was significantly higher in the group without DHEA (29.8% versus 13.1%, $p = 0.002$). The amount of gonadotrophins used for stimulation, the estradiol level on day six of stimulation, the number of oocytes retrieved, metaphase II oocytes, blastocysts, frozen embryos and miscarriage rate were not different in both groups. The clinical pregnancy rate per included patient in the DHEA group was 17.1% versus 8.6% in the non-treated group ($p = 0.02$). **Conclusion:** DHEA appears to improve clinical pregnancy rate by decreasing the cancellation rate.

Keywords

DHEA, IVF, Poor Responders

1. Introduction

Poor ovarian response (POR) represents a significant challenge in assisted reproduction. It is encountered in 5% to 18% of women undergoing *in vitro* fertilization (IVF) [1] [2]. It is increasing because of the delay to the first pregnancy: about 26.5 years old in 1977, between 29 and 31 in 2009 in most of European countries [3]. Patient with POR have very low successful pregnancy rate: 2% to 18%, depending on maternal age and number of oocytes retrieved [4]. Less oocytes are collected, and lower is the pregnancy rate.

Over the years, many adjuvant therapies or protocols have been tested for POR to improve clinical pregnancy rate such as gonadotrophins-releasing hormone (GnRH) flare protocols, high dose of gonadotrophins, antagonist protocol, arginine, testosterone, letrozole, luteal estradiol, or low dose of aspirin [5]-[14]. A recent study showed that addition of r-LH to r-FSH increased pregnancy rate in POR patients [15]. The Cochrane review has concluded that adjuvant therapy offered no clear benefit and could not be recommended [16].

Idea that dehydroepiandrosterone (DHEA) could be an adjuvant therapy appeared in 2000 with Casson *et al.* [17]. DHEA is an endogenous steroid synthesized by the adrenocortical reticularis zone and ovarian theca cells [18]. It is converted into androstenedione and estrone, the source of testosterone and estradiol according to the two cell theory [19] [20]. This hormone circulates in high amount before menopause with a peak at the age of 20 years and decreases progressively with age [21].

Its mechanism of action on the ovary remains hypothetical. Different hypothesis have been described over the years. It may increase the bioavailability of IGF-I, as reflected by an increase in IGF-I and a decrease in IGFBP-1 levels [17] [22]. IGF1 may potentiate gonadotrophins actions [17]. Gleicher *et al.* reported that DHEA created a polycystic ovary (PCO) like characteristics during stimulation [23]. It had indeed been used to induce PCO like ovarian phenotypes in rats and mice [24] [25]. An increased level of androgens characterizes this PCO situation. And androgens had previously been reported to suppress apoptosis [26] [27]. Hyman *et al.* suggests that DHEA does not influence early state of folliculogenesis but antral follicles representing the recruitable follicles cohort that has escaped from atresia [28].

Effect of DHEA is controversial. Many studies showed a significant clinical pregnancy rate improvement [2] [17] [28]-[30]. Other authors did not found statistically significant difference in the outcome of IVF treatment [3] [31]-[33]. Most of the studies are retrospectives and observational or small effectives randomized controlled trials. Despite insufficient evidence, there is actually a worldwide use of DHEA, which is given to 25.8% of the POR patients [34]. It seems important to evaluate this self-service treatment suitability.

We did a pilot study in our hospital in Lyon to make a current situation of our practices regarding DHEA. This study can help us to build hypothesis for our future randomized, controlled, multi-center, large population trial on DHEA versus placebo we plan to organize.

This retrospective cohort study aims to compare IVF outcome in DHEA treated women versus no treatment.

2. Materials and Methods

2.1. Patients and Design

A cohort of exposed and non-exposed DHEA patient was performed in the Femme Mere Enfant hospital in Lyon, between January 2013 and December 2014. All patients with AMH under 1.6 ng/ml treated for an IVF cycle with an antagonist protocol adding FSH and LH were enrolled for this study. Women above 43 years old were not included. Patients were not excluded according to the Body Mass Index (BMI), the rank of stimulation or the parity. In our department, some patients with a predictable poor ovarian response had received a daily dose of 75 mg DHEA for a minimum period of 60 days. The remaining patients with the same characteristics who did not receive DHEA were used as the control group. For the first part of the statistical analysis, all patients were included. Patients who had a cycle cancellation were excluded for the second part of the analysis.

2.2. Treatment Protocols

All patients underwent IVF cycle with the use of Gonadotrophins Releasing Hormone (GnRH) antagonist protocol adding FSH and LH. They began an oral combined hormonal contraceptive on the first period day. After 3 or 4 weeks of daily treatment, they stopped it and began stimulation five days later with 150 - 300 IU of recombinant FSH and 75 - 225 of recombinant LH.

Response to ovarian stimulation was monitored by hormonal blood test on day 6 and we performed an ultra-

sound every two or three day from day 6. Daily injection of GnRH antagonist was administered from the first control day to prevent premature ovulation. Recombinant hCG was given to trigger ovulation when at least three leading follicles reached 17 mm. It was followed 36 hours later by transvaginal oocytes retrieval. ICSI was performed for all, as routine practice for PORs in our department. Number of oocytes, metaphase II oocytes, fertilized oocytes, cleavage embryos, blastocysts, number and day of embryos transferred or frozen, estradiol level on day 6 of stimulation, total dose of gonadotrophins were documented. Luteal phase was supported by vaginal progesterone 600 mg a day from the day of retrieval. A quantitative pregnancy test, serum B HCG was performed 16 days after the day of retrieval. In case of pregnancy, an ultrasound was performed one month after the embryo transfer.

The stimulation was cancelled if less than three leading follicles reached 17 mm or when endometrium measured less than 6 mm.

2.3. Statistical Analysis

Quantitative variables were expressed as means \pm standard deviation when the distribution was normal or median and minimum and maximum when the distribution was not normal.

The hypothesis of normal distribution of quantitative variables was tested using the Kolmogorov-Smirnov and graphically confirmed with a histogram. If necessary, the variable will be converted to Log and/or specifically analyzed after exclusion of outliers.

Categorical variables were compared using the Chi 2 test or Fisher's exact test when the conditions of application of Chi square test were not met.

Quantitative variables were compared between groups using Student's t test after verification of equality of variances when data were normally distributed, and with the nonparametric test of Wilcoxon when the hypothesis of normality of distribution was not verified.

A logistic regression was conducted in order to quantify the association between patients' success to pregnancy or positive retrieval oocytes and explicative variable such as DHEA status, or AMH level, first as a univariate analysis and second as a multivariate analysis including significant variable in the univariate analysis and potential confounding factors such as age.

The statistical tests are bilateral and the level of significance was set to 5% ($p < 0.05$).

Statistical analyses were conducted using SAS version 9.1.3 (SAS Institute Inc, NC).

3. Results

During the study period, 224 patients were enrolled for 327 IVF cycles. 176 had been treated with DHEA before IVF, 151 had not. In the group with DHEA 153 had oocyte retrieval and 127 had embryo transfer versus 106 and 86 in the control group.

The demographics of the two groups are shown in **Table 1**. Patients treated with DHEA were significantly younger (35.9 versus 37.2 years old; $p = 0.002$), with a shorter infertility history (5.0 versus 5.9 years; $p = 0.002$) and had more AMH < lower than 1.1 ng/ml (129 versus 92; $p = 0.01$). There was no difference between the two groups regarding the type of infertility, the AMP rank, AFC or spermatic pathology.

The cancellation rates were significantly higher in the group without DHEA (29.8% versus 13.1%, $p = 0.002$) (**Table 1**). Among retrieved patients, four (0.03%) had no oocyte and 22 (14.4%) had no embryo transferred in the DHEA group versus one (0.001%) and 19 (18.0%) in the DHEA treated group, which was not different between both groups.

The amount of gonadotrophins used for stimulation and the estradiol level on day six of stimulation was not different in both groups. There was no improvement in the number of oocytes retrieved, metaphase II oocytes, blastocysts or frozen embryos (**Table 2**).

The clinical pregnancy rate per included patient in the DHEA group was 17.1% versus 8.6% in the non-treated group ($p = 0.02$) (**Table 3**). This difference was significant independently from the age and the AMH level ($p = 0.0002$, data not shown). Due to sparse data and small sample size, additional adjustment was not conducted.

The clinical pregnancy rate per retrieval in the DHEA group was 23.6% versus 15.1% in the non-treated group ($p = 0.13$) (**Table 3**).

The clinical pregnancy rate per transfer in the DHEA group was 17.3% versus 9.3% in the non-treated group ($p = 0.1$) (**Table 3**).

Table 1. Characteristic of patients (327 IVF cycles).

	No DHEA	DHEA	p value
	151	176	
age	37.2 (4.0)	35.9 (4.3)	0.002/
infertility duration	5.9 (2.5)	5 (2.5)	0.002/
primary infertility	72 (52.5)	109 (65.6)	0.5#
secondary infertility	46 (33.6)	34 (21.7)	
primo-secondary infertility	13 (9.5)	17 (10.8)	
AMP rank	2.1 (1.3)	2.1 (1.3)	0.08/
AMH > 1.1	59 (39.1)	47 (26.7)	0.01#
AFC	7.2 (4.6)	6,9 (3.6)	0.90/
oligospermia	29 (29.0)	41 (28.1)	0.88#
cryptozoospermia	3 (3.0)	7 (4.8)	0.48#
sperm anomaly	54 (54.0)	79 (54.1)	0.21#
cancellation cycle	45 (29.8)	23 (13.1)	0.0002#

#Chi-square; /Wilcoxon.

Table 2. Stimulation characteristics, biological and clinical evolution in patients without cancellation.

	No DHEA	DHEA	p value
	86	127	
gonadotrophin			
dose (IU)	4231.9 (905.3)	4238.4 (885.8)	0.97/
duration (d)	11.36 (1.8)	11.49 (1.7)	0.58/
estradiol level on day 6	326.27 (300.3)	344.69(252.0)	0.33/
number			
oocyte retrieved	6.21(4.0)	6.31 (3.9)	0.73/
metaphase 2 oocytes	5.05 (3.5)	5.75 (3.8)	0.16/
blastocysts	0.73 (1.6)	0.98 (1.8)	0.18/
frozen embryos	1.43 (0.8)	1.88 (2.5)	0.99/

/Wilcoxon.

Table 3. Clinical pregnancy rate.

	No DHEA	DHEA	p value
per included patient (n = 326)	13 (8.6%)	30 (17.1%)	0.02#
per retrieval (n = 213)	13 (15.1%)	30 (23.6%)	0.13#
per transfer (n = 213)	8(9.3%)	22 (17.3%)	0.10#

#Chi-square.

Among patients transferred, the miscarriage rate was 4.6% in the non-treated group and 6.3% in the DHEA group ($p = 0.6$).

4. Discussion

The critical evaluation of the many published protocols on DHEA and fertility is very difficult mainly because of a lack of uniformity in the definition of “poor responders. To avoid this, Ferraretti *et al.* on behalf of the ESHRE, presented Bologna’s criteria to standardize the definition of POR [35]. Only few studies have used it since [29] [32]. In other studies, poor responders are defined according to the number of oocytes retrieved, ultrasound findings, use of hormonal ovarian reserve markers such as day 3 FSH or AMH. For this study, we did not use the Bologna’s criteria either: the practice in our department is to enlarge our treated population to patients with an AMH level less than 1.6 ng/ml. We noted that our population treated with DHEA is significantly younger than the non-treated group, which is why we did a multivariate analysis and concluded that the differences observed are independent from the age. It seems that we have been giving DHEA to the patients with a significantly lower AMH and the worst prognosis. We can also criticize the fact that AMH has been tested in different laboratories with different kits. However, the variability between methods is weak for the lower values so we can consider it rather reliable. This marker is also used on a daily basis in our ward.

Our patients were going through a short antagonist protocol adding r-FSH and r-LH. A significant benefit of r-FSH plus r-LH versus r-FSH alone on clinical pregnancy rate in the poor responders subgroup (RR 1.30; 95% CI 1.01 - 1.67) was demonstrated in a meta-analysis done by Leherter and al [15]. Sunkara *et al.* showed that there was no significant difference between long agonist and antagonist regimens (4.42 ± 3.06 vs. 3.30 ± 2.91) [36]. In our unit we are used to give a short antagonist to POR patients and most of the recent studies on DHEA also used this protocol [29] [31] [32].

As noted previously we found that cancellation rate caused by poor response were significantly lower in the DHEA group. In Barad *et al.* study, the cycle cancellation rate was 32% without DHEA versus 4% post treatment ($p = 0.02$) [23]. Poli *et al.* also showed a significant reduction of cancelled cycles ($p = 0.03$) [37]. In contrast, cancellation rate were not different between the two groups in the prospective case-control study made by Jirge *et al.* but only 31 patients were included [29].

Our study did not find any improvement in any of the stimulation characteristics (gonadotrophins requirements, duration of stimulation oocytes and day 6 estradiol). Other authors have previously reported an improvement. Hyman *et al.* showed an increased peak E2 levels on HCG day (from 2607 ± 2143 to 4710 ± 3869 pmol/L $p = 0.0005$) [28]. Singh *et al.* also reported a significant increase in the serum AMH, peak E2 level on HCG day [38]. In our unit, blood sample are obtained only on day 6 of stimulation, but is not done later during the stimulation and specifically not on HCG day since we used an antagonist: this can explain the difference. In contrast and as noted in our study, Vlahos *et al.* did not found any statistical difference in stimulation duration (from 9.17 to 9.20 days with DHEA) or total gonadotrophins requirement (from 3936 to 3742UI with DHEA) in his study, which includes 48 POR according to Bologna’s criteria and 113 controls [32].

Concerning the number of oocytes retrieved, we did not observe a significant difference between the two groups. In the last randomized controlled trial made by Kara *et al.*, results were not different from ours in terms of number of oocytes retrieved: 5.74 (3.69) in the DHEA group versus 5.35 (3.45) in the control group ($p = 0.44$) [39]. As shown in **Table 2**, the number of oocytes retrieved in our study is not different. Whereas, Barad showed a significant increase of oocytes retrieved [23]. But it was a cross match study with only 25 patients. Poli *et al.* also showed a higher number of oocytes retrieved ($p < 0.01$) but it included only 29 patients [37].

Our study showed a significant higher pregnancy rate per included patient in the group treated with DHEA. We observed a higher pregnancy rate per retrieval and transfer also it did not reach significance, maybe due to a too small sample size in these two groups. Results of the three different randomized controlled trials are controversial. Wisner *et al.* showed a significantly higher live birth rate among study group after two treatment cycles: 23.0% in the DHEA group versus 4.0% in the control group ($p = 0.05$) [2]. But it was found after pooling the results of two treatment cycles with a p-value of 0.05. Yeung *et al.* showed no statically significant difference in the rate of clinical pregnancy 18.8% versus 25.0% ($p = 0.38$) but it included only 16 patients in each arms [31]. Kara *et al.* found 32 and 33% of pregnancy rate in both group but patients were very young (about 30 years old) and pregnancy rate is in astonishment extremely high for the POR population [39].

Narkwiczean *et al.* demonstrated in their meta-analysis a trend of a positive effect of DHEA on pregnancy

rate despite a lack of significance. It was marginally superior in the DHEA group (RR 1.87) [3]. Li *et al.* also made a meta-analysis and found an improvement in the pregnancy rate in the DHEA group (RR 2, $p = 0.02$) [40].

DHEA has previously been reported to decrease miscarriage rate. Gleicher *et al.* showed that after two months of DHEA supplementation, miscarriage rate was significantly lower, most pronounced above 35 years [41]. They then found out that it was due to a significant decrease of number and percentage of embryos with aneuploidy [42]. In the present study, the miscarriage rate is not different between both groups, 5.0% in each but the effective is very low (five and seven miscarriages in each group).

None of the studies on DHEA reported major side effects. Only minor masculinity side effects have been observed such as oily skin, transitional acne, hair loss [17] [30] [31] [41] [43] [44]. Improved feeling of well being and increased libido while using DHEA has been reported [23]. Our study did not reveal any major side effect either.

The aim of this study was to have a feedback of the practice in our ward regarding DHEA, to confirm the interest of a larger study and to build hypothesis for a future randomized controlled trial in our unit and to have a quick feedback of DHEA in our population. It explains why it is not randomized and suffers from all inherent problems of this kind of studies. To limit the weakness of our study we included a high number of patients, which is one of the major strength of our study. To the best of our knowledge this is one of the first studies including such a large cohort of patients (327 stimulation cycles on 224 patients). We collected data in a prospective way so there is no recall bias and we have a low rate of missing data. We accepted the different bias since it was a preliminary study before a multicenter randomized control trial.

5. Conclusion

A significant decrease in cancellation rate was observed in poor responders who received DHEA. This group had significant higher pregnancy rate per included patient but the difference was not significant regarding the pregnancy rate per retrieval or per transfer. A further RCT should be done soon in our unit to evaluate the effect of DHEA with a better reliability.

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