International Journal of Reproduction, Contraception, Obstetrics and Gynecology
Morán-Orozco EI et al. Int J Reprod Contracept Obstet Gynecol. 2024 May;13(5):1117-1120
www.ijrcog.org
pISSN 2320-1770 | eISSN 2320-1789

DOI: https://dx.doi.org/10.18203/2320-1770.ijrcog20241052

Original Research Article

Dehydroepiandrosterone supplementation improves reproductive outcomes in women of the POSEIDON IV group

Eugenia Irene Morán-Orozco*, Jorge Luis Lezama-Ruvalcaba, Gerardo A. Paladino-Barquera, Jose Carlos Salazar-Trujillo, David Alejandro Laguna-Pérez, Carlos G. Salazar López-Ortiz, Jaime Antonio Hidalgo-Carrera

Department of Gynecology, Hospital Español Fertility Clinic, HISPAREP, Mexico City, Mexico

Received: 15 March 2024
Accepted: 05 April 2024

***Correspondence:**
Dr. Eugenia Irene Morán-Orozco,
E-mail: eugeniamoran969@gmail.com

ABSTRACT

Background: The decrease in ovarian reserve has become one of the main causes of infertility. Recent studies have sought to improve the reproductive outcomes of these women through adjuvant treatments. In patients undergoing assisted reproduction treatments, exogenous Dehydroepiandrosterone (DHEA) or prasterone acts as a precursor to testosterone in the follicular fluid, which increases steroidogenesis and the number of primary and antral follicles.
Methods: A quantitative, quasi-experimental case series study was carried out in the clinical area of assisted reproduction from August 2021 to March 2022. All women included were over 34 years and categorized as POSEIDON IV. They were supplemented with 100 mg of DHEA one month prior to the follicular capture. Data was collected from the records of the patients who met the inclusion criteria, including the antral follicle count on the first three days of the menstrual period before the supplementation and one month after. Finally, the number of metaphase II oocytes and blastocysts obtained were analyzed.
Results: There were 22 women underwent controlled ovarian stimulation; there was a difference in antral follicle count from 5±2.1 SD to 8.23±4.29 SD (p=0.004) and MII oocytes 3.25±2.31 to 4.53±3.27 (p=0.04) before DHEA and after DHEA, respectively.
Conclusions: DHEA or prasterone supplementation can be used as an adjuvant treatment in women of the POSEIDON IV group one month before the ovarian stimulation to improve their reproductive outcome.

Keywords: Dehydroepiandrosterone, DHEA supplementation, ICSI, Prasterone, Poor ovarian response

INTRODUCTION

The decrease in ovarian reserves is an important cause of infertility, it affects 9-24% of patients undergoing assisted reproduction treatment.[1] There's a close link between said decrease and a low response to stimulation treatment.[2] In spite of their being different strategies to address this problem, satisfactory results to increase the pregnancy rate haven't been obtained. In 2000, Dehydroepiandrosterone (DHEA) supplementation was first introduced for women with low ovarian reserve.[3] DHEA is a 19-carbon endogenous steroid produced in the suprarenal cortex (85%) and the ovarian theca cells (15%). It turns into sulfated dehydroepiandrosterone (DHEAS) in the target tissues and is then metabolized into androstenediol, androstenedione, and testosterone.[4] The administration of DHEA has been associated with a significative increase in testosterone levels.[5]

Recent studies support the use of DHEA in patients with deficient ovarian response in previous reproductive assistance treatments. Nevertheless, there is still a need for further evidence to support its routine use.[2,3,6,7] In 2016,

patient centric strategies liked POSEIDON emerged to classify patients and give them an individual prognosis.[8] Even though this staging has been applied, there are no studies that support the effectiveness of DHEA.

Therefore, the objective of this study was to evaluate the antral follicle count (AFC) and the number of oocytes in metaphase II after having administered 100 mg of DHEA over a month before controlled ovarian stimulation, specifically in women with low ovarian reserve classified into POSEIDON group IV.

METHODS

A quasi-experimental quantitative study was carried out in the clinical setting of assisted reproduction, previously approved by the ethics committee of the Hisparep Clinic and in accordance with the principles of the Declaration of Helsinki, with the informed consent of the patients. The study included women who attended between August 2021 and March 2022 with primary or secondary infertility, and a diagnosis of low ovarian reserve categorized into POSEIDON group IV with the following characteristics: over 35 years of age, Anti-Müllerian hormone (HAM) below 1.2 ng/ml, and/or antral follicle count (AFC) below 5.

The study excluded women who didn't accept participating in the study that had a previous endometriosis diagnosis, medical history of pelvic surgery or oophorectomy, medical history of polycystic ovary syndrome, or the use of androgens. The suspension criteria included the cancellation of the stimulation cycle or non-compliance with supplementation treatment.

The AFC evaluation was done through a transvaginal ultrasound within the first three days of the menstrual cycle. The administration of 100 mg of DHEA (BIOLAIF®, Medix) was done the prior to ovarian stimulation, which was done randomly in each patient with different doses of Recombinant Follicle Stimulating Hormone (rFSH, Gonal-F, 150 UI, Merck Serono S.p.A.), rFSH and Recombinant Luteinizing Hormone (rFSH/rLH, Pergoveris, 150/75 UI, Merck Serono S.p.A.), and human menopausal gonadotropin (Merional, 75 to 150 UI, IBSA Corne).

All the patients followed a flexible protocol with the use of with the use of gonadotropin-releasing hormone antagonist (GnRH, Cetrotide 0.25 mg, Merck Serono S.p.A.), starting when finding 14 mm follicles, administered subcutaneously. When detecting follicles above 18 mm, follicular maturing was programmed with human chorionic gonadotropin (hCG, 10,000 UI, Choriomon, IBSA, Corne), followed by follicular capture after 34 to 36 hours.

In the embryology laboratory, the number of obtained oocytes in metaphase II were analyzed, and after their fertilization by intracytoplasmic sperm injection, the embryos were monitored to evaluate the number of blastocysts that developed in the fifth and sixth day. All embryos were vitrified and a trophectoderm biopsy was performed for preimplantation genetic diagnosis of aneuploidy (PGT-A).

Statistical analysis

An analysis was carried out with descriptive and inferential statistics. For the descriptive analysis frequencies and proportions were used for categoric variables, as well as measures of central tendency and dispersion for numeric variables. Depending on normality and homoscedasticity, parametric or non-parametric tests were used to compare before and after.

RESULTS

The study included 24 women who started supplementation of 100 mg DHEA (BIOLAIF®, Medix) during the month prior to the assisted reproduction treatment. Out of those, 22 were given controlled ovarian stimulation for highly complex treatment for different causes of infertility, as well as low ovarian reserve, including neuroendocrine factor n=8 (36.3%), uterine factor n=7 (31.8%), masculine factor n=3 (13.6%), and tubeperitoneal factor n=3 (13.6%). The average age of the women was 41.3 years±3.08, with an average HAM of 0.61±0.71, and an average AFC of 5±2.1. Of all the women included in the study, 52% (n=11), this was their first time undergoing ovarian stimulation, while the other 48% (n=10) were going through their second one (Table 1).

Table 1: Demographic characteristics.

Characteristics	
Age (years) (n=24)	41.25±3.08
Infertility of type N (%)	n=22
Primary	12 (54.5)
Secondary	10 (45.5)
Infertility factor, N (%)	n=22
Uterine	7 (31.8)
Tube peritoneal	3 (13.6)
Neuroendocrine	8 (36.3)
Male	3 (13.6)
Antral follicle count	5±2.1
Anti müllerian hormone (ng/ml)	0.61±0.71
Previous stimulation, N (%)	10 (45.5)

The analysis included 10 women that had already presented previous ovarian stimulation, along with 16 women that were treated after supplementation. The count difference of antral follicles was 5±2.1 DE at 8.23±4.29 DE (p 0.004). After follicular aspiration, preDHEA 0.16± 0.40 DE of MI oocytes and 0.93±1.80 postDHEA (p 0.25); MII occytes preDHEA 3.25±2.31 and 4.53±3.27 postDHEA (p 0.04). Of the oocytes that were fertilized in vitro, through an intracytoplasmic sperm injection with subsequent development into blastocysts, a biopsy was

done of the trophectoderm for PGT-A obtaining, preDHEA 0.71±1,25 of the normal embryos and postDHEA 0.50 ±0.83 (p 0.66). For anormal embryos 0.71±0.48 preDHEA and a postDHEA 2.42±1.27 (p 0.06).

Table 2: Differences between stimulations before and after DHEA supplementation (n=24).

	Pre DHEA n=10	Post DHEA n=16	P value
Antral follicle count, X ± DE	5±2.1	8.23±4.29	0.004
Metaphase I oocytes, X ± DE	0.16±0.40	0.93±1.80	0.25
Metaphase II oocytes, X±DE	3.25±2.31	4.53±3.27	0.04
Preimplantational genetic test, X±DE			
Normal embryos	0.71±1.25	0.50±0.83	0.66
Abnormal embryos	0.71±0.48	2.42±1.27	0.06

DISCUSSION

Androgens play a crucial role in follicle genesis. The improvement in ovarian stimulation treatment with exogenous gonadotropins, because of DHEA regulation, is due to an increase in the action of follicle-stimulating hormone (FSH) on the ovary. In 1998, Casson observed a significant increase of serum testosterone and IGF-1 levels when administering 25 mg/day of DHEA to postmenopausal woman for three months, which returned their basal levels after six months.[9] DHEA promotes the function of androgen signalling pathways, increasing the expression of androgen receptors, and participating in follicular recruitment and growth. This while regulating the increate of serum concentration of IGF-1, induces the follicle differentiation and eases the transition of inactive follicles to earlier maturing stages, thus, generating an increase to the number of primary and antral follicles, resulting in a positive impact of oocyte quality.[10]

The DHEA positively modifies HAM levels as it's a precursor on the androgens within the follicles, which can potentially lead to a secondary increase of the pregnancy rate. Furthermore, the DHEA regulates the key biogenesis transcription factors which affect the metabolic route of intracellular energy, thus reducing the programmed cellular rate and apoptosis associated to aging.[11]

In 2000, Casson reused DHEA in women with low ovary response, managing to double the response to the use of gonadotropins.[3,11] Then in 2005, Barad informed of an improved ovary response when using 80 mg per day throughout two months during the intrauterine insemination cycle.[12] In 2006, Barad and Gleicher proved a significative increase in the number of fertilized oocytes and normal embryos, along with an improvement in embryonic scores, as well as pregnancy rates after DHEA supplementation in cases with low ovarian reserve.[13]

Throughout our cases, we were able to observe a significant increase in the antral follicular count and metaphase II oocytes with a higher dose during a previous month.[14] Nevertheless, we did not find significant differences pre and post treatment in the rate of euploid and aneuploid embryos, and this is possibly attributable to the age of the women in the study. We did however document an increase in the sensibility of the granulosa cells to FSH, with an increase in the expression of the FSH receptors, therefore resulting in an increase of the steroidogenesis.[6,11,15,16]

Regarding adverse effects, Rangel's 2021 study reported that the administration of 100mg of DHEA for 16 weeks is safe, as there are no observable metabolic modifications, nor any changes in the menstrual cycle, nor hyperandrogenism indicators. Our study corroborates the absence of adverse effects with the aforementioned dose for a month, suggesting this for safety.[17]

The metanalysis has shown that there are no significant differences in the pregnancy rate, cycle cancellation, total duration in the use of gonadotropins, oocytes recovered nor live birth rate between patients treated with and without androgens.[18] However, more evidence is needed to back up the use of DHEA supplementation in POSEIDON group IV in highly complex assisted reproduction treatments, which underlines the need for more randomized clinical trials.

CONCLUSION

As we understand the physiology of steroidogenesis and oocyte development, we have managed to develop techniques to improve the reproductive outcome of women with low ovarian response. Therefore, prasterone could be used as a supplement in this group of women, however, more evidence is needed to support its routine use.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Ulug U, Ben-Shlomo I, Turan E, Erden HF, Ali Akman M, Bahceci M. Conception rates following assisted reproduction in poor responder patients: A retrospective study in 300 consecutive cycles. Reprod Biomed Online. 2003;6(4):439-43.
2. Drakopoulos P, Bardhi E, Boudry L, et al. Update on the management of poor ovarian response in IVF: the shift from Bologna criteria to the Poseidon concept. Ther Adv Reprod Heal. 2020;14:263349412094148.
3. Casson PR, Lindsay MS, Pisarska, Carson SA, Buster JE. Dehydroepiandrosterone supplementation augments ovarian stimulation in poor responders: a case series technology depends on ovarian stimulation and concurrent multiple oocyte development, induced

by administration of. Hum Reprod. 2000;15(10):2129-32.
4. Traish AM, Kang HP, Saad F, Guay AT. Dehydroepiandrosterone (DHEA)-A precursor steroid or an active hormone in human physiology (CME). J Sex Med. 2011;8(11):2960-82.
5. Palacios S. Hypoactive sexual desire disorder and current pharmacotherapeutic options in women. Women's Heal. 2011;7(1):95-107.
6. Noventa M, Vitagliano A, Andrisani A, Blaganje M, Viganò P, Papaelo E, et al. Testosterone therapy for women with poor ovarian response undergoing IVF: a meta-analysis of randomized controlled trials. J Assist Reprod Genet. 2019;36(4):673-83.
7. Triantafyllidou O, Sigalos G, Vlahos N. Dehydroepiandrosterone (DHEA) supplementation and IVF outcome in poor responders. Hum Fertil. 2017;20(2):80-7.
8. Alviggi C, Andersen CY, Buehler K, Conforti A, De Placido G, Esteves SC, Fischer R, et al. A new more detailed stratification of low responders to ovarian stimulation: from a poor ovarian response to a low prognosis concept. Fertil Steril. 2016;105(6):1452-3.
9. Casson PR, Santoro N, Elkind-Hirsch K, et al. Postmenopausal dehydroepiandrosterone administration increases free insulin-like growth factor-I and decreases high-density lipoprotein: A six-month trial. Fertil Steril. 1998;70(1):107-10.
10. Sönmezer M, Oezmen BA, Cil AP, Özkavukçu S, Taşçı T, Olmuş H, et al. Dehydroepiandrosterone supplementation improves ovarian response and cycle outcome in poor responders. Reprod Biomed Online. 2009;19(4):508-13.
11. Li CJ, Lin L Te, Tsui KH. Dehydroepiandrosterone shifts energy metabolism to increase mitochondrial biogenesis in female fertility with advancing age. Nutrients. 2021;13(7).
12. Barad DH, Gleicher N. Increased oocyte production after treatment with dehydroepiandrosterone. Fertil Steril. 2005;84(3):756.e1-756.e3.
13. Gleicher N, Weghofer A, Barad DH. Improvement in diminished ovarian reserve after dehydroepiandrosterone supplementation. Reprod Biomed Online. 2010;21(3):360-5.
14. Gleicher N, Weghofer A, Barad D. Increased euploid embryos after supplementation with dehydroepiandrosterone (DHEA) in women with premature ovarian aging. Fertil Steril. 2007;88(September):S232.
15. Nielsen ME, Rasmussen IA, Kristensen SG, Christensen ST, Møllgård K, Wreford Andersen E, et al. In human granulosa cells from small antral follicles, androgen receptor mRNA and androgen levels in follicular fluid correlate with FSH receptor mRNA. Mol Hum Reprod. 2011;17(1):63-70.
16. De Leo V. Hormonal effects of flutamide in young women with polycystic ovary syndrome. J Clin Endocrinol Metab. 1998;83(1):99-102.
17. Rangel M. Metabolic, reproductive outcomes and side effects after the administration of 100 mg dehydroepiandrosterone (DHEA) in women with an adequate ovarian reserve. Fertil Steril. 2021;116(3):e316.
18. Sunkara SK, Pundir J, Khalaf Y. Effect of androgen supplementation or modulation on ovarian stimulation outcome in poor responders: A meta-analysis. Reprod Biomed Online. 2011;22(6):545-55.

Cite this article as: Morán-Orozco EI, Lezama-Ruvalcaba JL, Paladino-Barquera GA, Salazar-Trujillo JC, Laguna-Pérez DA, Salazar López-Ortiz CG, et al. Dehydroepiandrosterone supplementation improves reproductive outcomes in women of the POSEIDON IV group. Int J Reprod Contracept Obstet Gynecol 2024;13:1117-20.