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Review Article

Dehydroepiandrosterone: A panacea for the ageing ovary?

Lt Col Nikita Naredi [a,*], Lt Col K. Sandeep [b], Lt Col V.D.S. Jamwal [c], Lt Col N. Nagraj [d], Lt Col Seema Rai [d]

[a] IVF Specialist, Assisted Reproductive Technology Centre, Army Hospital (R&R), New Delhi 110 010, India
[b] IVF Specialist, Assisted Reproductive Technology Centre, INHS Asvini, Mumbai, India
[c] Graded Specialist (Anatomy), Military Hospital Ahmedabad, Gujarat, India
[d] Senior Resident, Assisted Reproductive Technology Centre, Army Hospital (R&R), New Delhi 110 010, India

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ABSTRACT

Considerable improvements and advancements have been made in the treatment of infertility but poor ovarian reserve whether due to prematurely or a physiologically ageing ovary, continues to be one of the few unresolved problems of modern infertility care. Fertility researchers had been active for quite some time to find a way to help reverse the effects of ageing on the ovaries but none made an impact till the introduction of Dehydroepiandrosterone [DHEA]. DHEA a mild, and therapeutically well tolerated, male hormone has emerged as a real potential candidate to reverse the effects of ageing on ovaries. Apart from this, DHEA has also been postulated to improve egg and embryo quality, pregnancy rates and time to conception and reduces miscarriage rates. This review attempts to highlight the mechanism of action of this drug, its indications and its current status for treating women with decreased ovarian reserve.

Introduction

Menopause, the culmination of a woman's reproductive life, occurs when women experience a dramatic loss in ovarian function around the age of 50.[1] It is a consequence of the age-related decrease in the follicle number which dictates the onset of cycle irregularity and the final cessation of menses. This final occurrence of natural sterility is preceded by a process known as "Ovarian Ageing" in which there is a parallel decay in both the quantity and the quality of oocytes.[2] However in approximately 10% of women the decline of ovarian function occurs much earlier than others because of a phenomenon called premature ovarian ageing [POA].[3]

The follicular pool of the ovary of a woman, which she is endowed with is known as ovarian reserve [OR] and the ovarian reserve keeps declining with advancing female age. A good OR gives a lady the ability to produce high-quality eggs and thus achieve pregnancy. When this ovarian reserve becomes low or poor relative to what is expected at any given age it is known as premature ovarian ageing.[2] POA was one of the major often overlooked causes of female infertility.

Fertility researchers were thus active for quite some time to find a method to help reverse the effects of ageing on the ovaries and help women with poor ovarian reserve. Many drugs made their appearance in the arena of reproductive medicine to resolve the issue of physiologically and prematurely ageing ovaries but none made an impact till 2000.

* *Corresponding author*. Tel.: +91 (0) 8800504222 (mobile).
E-mail address: nikitanaredi@gmail.com (N. Naredi).
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Casson et al first reported the beneficial effects of dehydroepiandrosterone [DHEA] on ovaries with diminished reserve.[4] They reported that DHEA supplementation of women with diminished ovarian reserve [DOR] may bring about a positive impact on ovarian function by increasing the oocyte yield after stimulation with gonadotropins. Thereafter, since the beginning of this decade this drug is being administered at various Fertility centres to overcome the challenge of poor ovarian reserve in both, the ageing population of sub fertile women and the poorly responding young women.

What is DHEA?

Dehydroepiandrosterone [DHEA] and dehydroepiandrosterone sulphate [DHEA-S] are natural steroid hormones, which are the major secretory products primarily from the zona reticularis of the human adrenal cortex and to a lesser extent from the ovarian theca cells.[4] These hormones circulate in high amounts during female reproductive life however, concentrations fall progressively with age.[5] The age-related decrease in DHEA secretion inevitably raised the question that if ageing is a consequence of DHEA deficiency, it could be reversed by DHEA treatment.[6]

How does DHEA act?

Dehydroepiandrosterone is an essential prohormone in ovarian follicular steroidogenesis[4] during the conversion of cholesterol to the two sex hormones, oestradiol and testosterone.[7] Another plausible mechanism postulated for the gonadotropin-augmentation effect secondary to DHEA supplementation is that it enhances the serum free IGF-I concentrations by ~150%, independently of changes in GH secretion.[8,9] Thus DHEA amplifies hepatic and end organ IGF-I response to GH which in the milieu of the ovarian follicle, may potentiate gonadotropin action.

Anti-Mullerian Hormone [AMH] an indicator of ovarian reserve is a dimeric glycoprotein and a member of the transforming growth factor super family. It is exclusively produced by the granulosa cells of early developing follicles from primary to antral follicle stages 10. Improvement in AMH concentrations as revealed by Gleicher et al suggested that DHEA increases the pool of follicles up to pre-antral stage.[3] This observation added to another of the possible mechanisms by which DHEA exerts its effects: it affects recruitment from the dormant primordial follicular pool, may reduce apoptosis which is the primary process of elimination for originally recruited follicles or may selectively and directly affect granulosa cells.[10]

Who would be benefitted?

The indications for institution of DHEA supplementation has progressively changed since its first use in 2004 by The Centre for Human Reproduction [CHR] in New York City, the torch bearers in the usage of this wonder drug till date.[4,7,11,12] Initially only older women above age 42 were supplemented with a prerequisite of one failed IVF cycle and retrieval of less than 4 oocytes. By mid-2005 DHEA was instituted to all women above age 40 with evidence of poor ovarian reserve and a history of one failed prior IVF cycle. By early 2006 indications were further extended to women under age 40 if they demonstrated elevated baseline follicle stimulating hormone [FSH] levels above 10 mIU/ml and had shown ovarian resistance in at least one failed IVF cycle. After mid-2006 FSH baseline criteria was changed from absolute FSH elevations to elevations in age-specific FSH levels.[13] At present all women above age 40 are being offered routine supplementation in many centres since January 2007, while younger women under age 40 are continuing to be only selectively supplemented if demonstrating elevated age-specific baseline FSH levels and have had inappropriately low oocyte yield in at least one IVF cycle.[2]

How much and for how long?

DHEA supplementation is carried out with oral, pharmaceutical grade micronized medication at a dosage of 25 mg, three times daily. The morbidly obese women require a daily dosage of 100 mg. This supplementation dosage was adopted in practice since it represented the amount of medication the index patient had used, as inspired by the report by Casson et al[4,11] and has therefore remained the only standard treatment dosage. Patients should receive at least two months of DHEA supplementation prior to oocyte retrieval however maximal DHEA effects increases over time, reaching peaks after approximately four to five months of supplementation.[14] Women may conceive spontaneously while on DHEA[7] in which case, it is discontinued after confirmation of pregnancy by the second positive pregnancy test.

How to monitor DHEA effect?

Ovarian reserve has traditionally been measured by FSH concentrations on cycle days 2 or 3[13] but of late Anti-Mullerian hormone [AMH] has attracted more attention and has, been suggested as a more specific reflector of ovarian activity.[13,15] Its utilization for investigation of prematurely diminished ovarian reserve has also been documented.[16] Thus AMH levels may be utilised to assess ovarian reserve following DHEA supplementation.

Gleicher et al in their study for the first time by assessing changes in AMH concentration presented that DHEA supplementation positively affected the diminished ovarian pool with a steady increase in AMH concentration after initiation of DHEA.[3] This DHEA effect was visible not only in older ovaries, but found to be more pronounced in younger women with premature ovarian ageing.

What are the side effects?

Side effects at the dosages being prescribed for DOR are small and rare, and primarily relate to androgen effects. Women using DHEA may experience possible adverse effects like acne, hair loss, deepening of the voice, and facial hair growth however most of them are reversible. DHEA in a dosage of