



Dehydroepiandrosterone Supplement- The Marvel Drug Used for the Treatment of Women with a Diminished Ovarian Reserve and Poor Ovarian Response to Fertility Treatment: A traditional Review

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ABSTRACT

Backgrounds: Poor ovarian reserve and poor ovarian response present a challenge to fertility doctors and in vitro fertilization (IVF) centers. Delaying childbearing is rising nowadays, contributing considerably to an increase in age-related infertility and the demand for assisted reproductive technologies (ART) treatment. This brings to the infertility clinics many women with a diminished ovarian reserve (DOR) and poor ovarian response (POR) Dehydroepiandrosterone (DHEA) is presented as a miracle-drug and has been reported to improve pregnancy chances in patients with a diminished ovarian reserve and poor ovarian response to fertility treatment. Additionally, DHEA is now utilized by approximately one-third of all IVF centers worldwide.

Aim: Our objective was to assess DHEA supplementation's effect on women with a diminished ovarian reserve and poor ovarian response to fertility treatment and to find out potential mechanisms of action of DHEA in infertile women. Therefore, we examined the rationale for using DHEA in poor responders and diminished ovarian reserve patients, selected the relevant studies, presented the data, and addressed its potential action mechanisms.

Methods: A literature search in PMC, PubMed, Google, and Google Scholar was carried out using the following keywords: "ovarian reserve," "DHEA and infertility," "DHEA and low ovarian reserve," "DHEA mechanism of action in low ovarian reserve." Study selection was in the language (English only), model (humans only), open accesses, and all types of studies were included as long as they were relevant to our study.

Limitations: While we were gathering the information for this review, there were some limitations. Our data was primarily obtained from articles with free full access and written in English language only; thus, relevant articles of closed access and written in other languages may have been skipped. This review article is a traditional review and, therefore, does not follow the standard Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for systematic reviews.

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Keywords: DHEA supplement and infertility, DHEA and low ovarian reserve, DHEA supplement in IVF, diminished ovarian reserve.

1. Introduction:

Female fertility decreases dramatically with age. The delay in having children is no longer a simple trend but a reality among women today (Narkwichean et al., 2013). Around 20% of women choose to establish their families after the age of 35. This is mainly due to the modern woman's expectation to build their professional and

financial stability and waiting for a stable relationship that would give her security (Narkwichean et al., 2013).

The physiological function of the ovary is to generate mature oocytes and produce steroid hormones that create a favorable environment for fertilization and embryonic implantation (Narkwichean et al., 2013). The aging of the ovaries is demonstrated by reduced oocyte



reserve, decreased fertility, and unfavorable reproductive events, such as pregnancy loss and aneuploidy. With age, the remaining eggs become less able to be fertilized by sperm (Narkwichean et al., 2013).

1.1. What is ovarian reserve?

Ovarian reserve is defined as the quantity of oocytes remaining in the ovary (American Society for Reproductive Medicine, 2020). Ovarian reserve, or oocyte quantity, is different from oocyte quality, which relates to the potential of a fertilized oocyte to result in a live-born infant. Ovarian reserve corresponds with age, but there is a considerable variation in ovarian reserve among women of the same age (American Society for Reproductive Medicine, 2020).

1.2. What is the average egg count by age?

The eggs are formed while a woman is still in utero (What Is Diminished Ovarian Reserve and What Can You Do About It?2021). This means that woman is born with all the eggs that will decrease over time. As reported by the American College of Obstetricians and Gynecologists, and demonstrated in Figure 1, the average number of eggs at each age are: at 20 weeks of gestation: 6 to 7 million oocytes; at birth: 1 to 2 million oocytes; at puberty: 300,000 to 500,000 oocytes; around age 37: approximately 25,000 oocytes; and around age 51, around 1000 oocytes (What Is Diminished Ovarian Reserve and What Can You Do About It? 2021).

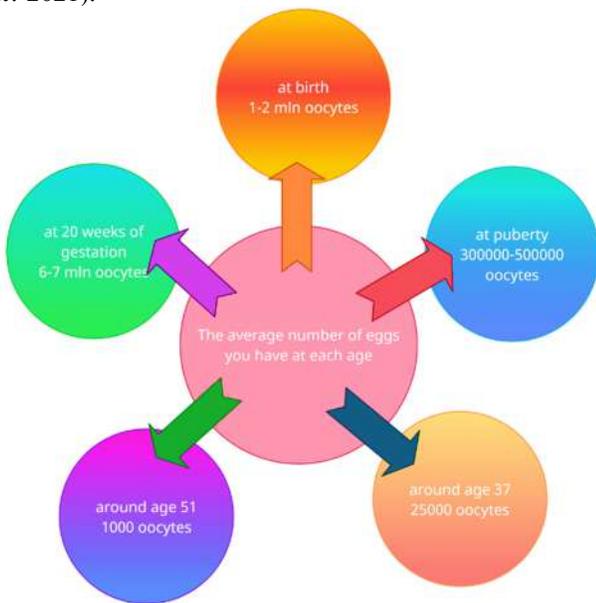


Figure 1. The average number of eggs that have women at each age.

1.3 Causes of diminished ovarian reserve

Aging naturally reduces egg reserves. However, as demonstrated in Table 1, numerous other factors can cause a diminished ovarian reserve (What Is Diminished Ovarian

Reserve and What Can You Do About It?2021, Kaur et al., 2013). These include:

Table 1. Factors which can cause a diminished ovarian reserve.

Factors which can cause a diminished ovarian reserve
1. Smoking
2. Exposure to chemotherapy
3. Aging
4. Exposure to radiotherapy
5. Genetic abnormalities (45X, fragile X syndrome)
6. Previous ovarian surgery
7. Uterine artery embolization or ligation
8. Autoimmune disorders (like Addison disease)
9. Mumps oophoritis
10. Galactosemia
11. Pelvic infections (like tuberculosis)
12. Environmental factors
13. Idiopathic

1.4. Assessment of ovarian reserve

Hormonal markers and ultrasound measurements have been used to evaluate the ovarian reserve and prognosticate success in assisted reproductive techniques (Coccia et al. 2008, Parry et al. 2019]. Other parameters used are age, concentrations of follicle-stimulating hormone (FSH), estradiol, inhibin B, anti-Müllerian hormone (AMH), ovarian volume, ovarian antral follicle count (Kaur et al. 2013, Coccia et al. 2008).

Additional studies are dynamic tests using gonadotropin-releasing hormone agonist, clomiphene citrate-to assess ovarian response, and exogeneous FSH ovarian test (Kaur et al., 2013, Coccia et al.,2008). However, no single test provides a satisfactory accurate result, but the simultaneous assessment of a combination of tests can be used as a marker of diminished ovarian reserve and a good predictor of response to ovarian stimulation in patients who go through in vitro fertilization treatment (Coccia et al., 2008). Figure 2 demonstrate the tests used to check ovarian reserve.

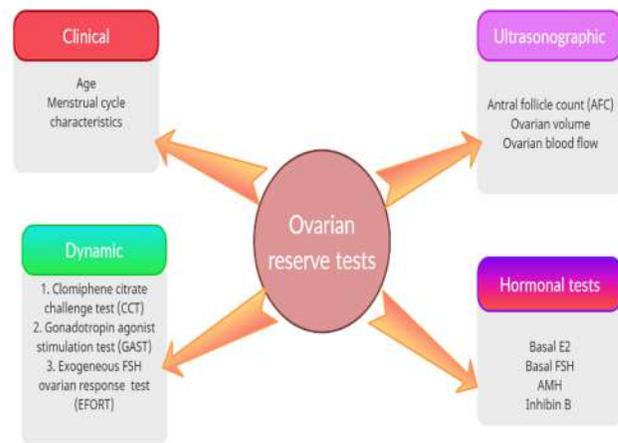


Figure 2. The tests used to check ovarian reserve.



1.4.1. Clinical Characteristics

Female age remains the predictor of the first choice in estimating the quantity and quality of ovarian reserve, as the number of follicles decreases with age (Parry et al., 2019). Menstrual cycle length is primarily determined by the rate and quality of follicular growth (the follicular phase duration), which determines the duration of the menstrual cycle (Parry et al., 2019).

A gradual shortening of the menstrual cycle begins in the late 30s, parallel with increasing FSH and decreasing of Inhibin B, produced by a low quantity of antral follicles (Parry et al. 2019).

1.4.2. Ultrasonographic Characteristics

Ultrasonographic measures of the ovarian reserve include antral follicles count and ovarian volume, ovarian blood flow (American Society for Reproductive Medicine, 2020), Kaur et al., 2013). Ovarian volume decreases with age and is, therefore, a potential indicator of ovarian reserve; however, this is uncommonly used for clinical prediction given the high menstrual cycle variability and general lack of sensitivity (American Society for Reproductive Medicine, 2020).

1.4.3. Blood Tests: FSH, Estradiol, AMH, Inhibin B

Basal serum FSH concentrations are elevated on days 2, 3, and 4 of the menstrual cycle in women with diminished ovarian reserve (DOR) (American Society for Reproductive Medicine, 2020). Elevated serum FSH is a specific but not sensitive test for DOR (American Society for Reproductive Medicine, 2020). Based on the World Health Organization (WHO) Second International Standard, FSH levels of >16.7 reflecting high level, >11.4 moderately high, and <10 mIU/mL normal level (Kaur et al. 2013). However, FSH levels have significant cycle variability that limits the reliability of a single measurement. A premature rise in serum Estradiol concentrations is a classic characteristic of reproductive aging. When the basal FSH concentration is normal, but the Estradiol level is elevated (>60 – 80 pg/mL), this may indicate ovarian dysfunction related to DOR (American Society for Reproductive Medicine, 2020).

Serum concentrations of AMH, which is produced by granulosa cells, are gonadotropin independent and, therefore, remain relatively consistent within and between menstrual cycles. AMH levels may be decreased in women while using hormonal contraceptives and, therefore, should be interpreted with caution in those patients (American Society for Reproductive Medicine, 2020) AMH being the most sensitive measure of the ovarian reserve, has replaced basal FSH and Estradiol level testing as a biomarker of ovarian reserve (American Society for Reproductive Medicine, 2020). Normal AMH values often exceed 2 ng/mL at 30, 1.5 ng/mL at 35, and 1 ng/mL at 40 (Parry et al. 2019)]. The AMH level associated with diminished

ovarian reserve is typically below 1 ng/mL (Parry et al., 2019).

Similar to AMH, Inhibin B is a glycoprotein secreted by preantral follicles, with levels declining with age (Parry et al., 2019). Inhibin B level is useful but overall remains suboptimal predictive because it is a late finding for diminished ovarian reserve and typically starts falling around four years before menopause (Parry et al., 2019). Inhibin B level fluctuates over the menstrual cycle, with peaks in the early to mid-follicular phase and ovulation. Therefore, Inhibin B is measured on the third day of the menstrual cycle in ovulatory women (Parry et al., 2019).

1.4.4. Dynamic Tests

The Clomiphene citrate challenge test involves measurements of serum FSH before and after treatment with clomiphene citrate (100 mg daily, cycle days five to ninth) (American Society for Reproductive Medicine, 2020). Whereas rising Inhibin B and Estradiol levels derived from growing ovarian follicles will suppress FSH in women with responsive ovaries, the smaller follicular cohorts in women with DOR will generate less Inhibin B and Estradiol. Therefore, an elevated FSH concentration after clomiphene stimulation suggests DOR (American Society for Reproductive Medicine, 2020).

Gonadotropin agonist stimulation test evaluates the change in Estradiol level on days two and three of the menstrual cycle following subcutaneous injection of gonadotropin agonist such as leuprolide acetate (Parry et al., 2019). This will induce a massive, temporary release of FSH and LH, which in turn will increase the production of Estradiol within 24 hours (Parry et al., 2019). Significant positive correlations between ovarian response and the rise in Estradiol level after the stimulus have been demonstrated (Parry et al., 2019).

Exogenous FSH ovarian reserve test is based on an increase of Estradiol and Inhibin B 24 hours after administration of 300 IU of recombinant FSH on cycle day three (Parry et al., 2019).

1.5. How to improve or treat diminished ovarian reserve?

If DOR is early diagnosed, then adequate action can be taken to resolve this challenge (Kaur et al., 2013). Prevention of further ovarian damage in women with DOR can be achieved by smoking cessation, careful surgical technique during ovarian surgeries, avoiding ovarian drilling, and diathermy (Kaur et al., 2013). Patients undergoing radiotherapy or chemotherapy should be explained about existing options for fertility preservation (Kaur et al., 2013). Lack of definitive treatment options makes challenging the management of DOR. However, oocytes cryopreservation and the use of stem cells are promising options for the future (Kaur et al., 2013).

Additionally, one of the most commonly used treatments for diminished ovarian reserve is supplements like dehydroepiandrosterone (DHEA), a mild androgen

produced in the adrenal glands' zona reticularis and ovaries (De Macedo et al., 2018). In 1939 a German scientist Butenandt received the Nobel Prize in Chemistry for identifying and isolating DHEA. While in 1996, DHEA's anti-aging effects were described. This motivated scientists to study the role of DHEA in reproduction and specifically in diminished ovarian reserve (De Macedo et al., 2018).

Therefore, our study aim is to review the published literature on the use and the results after using DHEA in infertile women and specifically in women with diminished ovarian reserve and poor ovarian response to fertility treatment.

2. Results of the Review and Discussion of Findings:

DHEA and its sulfate ester (DHEAS) are sex steroids in women that work as precursors for estrogen and androgens' intracellular production. Serum levels of those hormones decline with age resulting in loss of well-being, lowered libido, and lower sexual function in premenopausal and postmenopausal women (De Macedo et al., 2018). Serum DHEAS and DHEA levels peak between ages 20 and 30 years, then drops by 2 % per year, and by the age of 70, serum levels of hormones are 20–23 % of their peak values nadirs of 10–20 % around age 80 (De Macedo et al., 2018).

The exact mechanism(s) by which DHEA improves ovarian reserve, pregnancy rate, IVF parameters, and the decreased miscarriage rate is still under investigation (Parry et al., 2019). The apparent improvement in miscarriage rate and in vitro fertilization (IVF) pregnancy rate may be explained by improving embryo ploidy, as DHEA supplementation results in an increased ovarian Insulin-like growth factor 1 (IGF-1) expression reduced in poor responders (De Macedo et al., 2018). Administration of this hormone also elevates the IGF-1 binding protein type 3 (IGFBP-3) levels, possibly mediated by increased androgens levels. Therefore, the IGF-1/IGFBP-3 ratio may be indicative of oocyte quality and maturity. Increasing intrafollicular androgens results in an increased AMH expression by the granulosa cells and Inhibin-B production (De Macedo et al., 2018).

DHEA supplementation can promote preantral follicle growth, suppress apoptosis, and rescue atretic follicles, thereby increasing ovarian reserve levels, which in turn increases AMH (De Macedo et al., 2018). When AMH levels were above 1.05 ng/ml, clinical pregnancy rate, live birth rate, and miscarriage rate were significantly improved as a result of DHEA utilization (De Macedo et al., 2018). AMH levels were observed to increase in parallel with DHEA supplementation duration, and this improvement is more noticeable in young patients with primary ovarian insufficiency compared to patients with age-related diminished ovarian reserve (De Macedo et al., 2018). Figure 3 shows potential mechanisms of action of DHEA in infertile women.

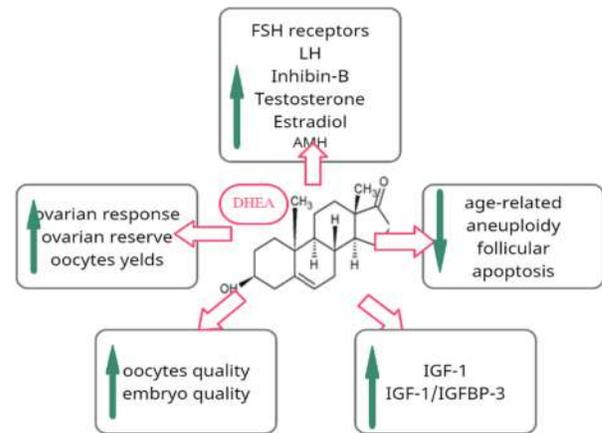


Figure 3. Potential mechanisms of action of DHEA in infertile women

In 1992, Buster et al. investigated the bioavailability of oral micronized dehydroepiandrosterone, anticipating its adjunctive use in postmenopausal steroid replacement (Buster et al., 1992). Eight postmenopausal women participating in a clinical trial received either a placebo or 150 or 300 mg of oral micronized dehydroepiandrosterone in a lipid matrix. Estradiol concentrations remained less than 20 pg/ml, but androgen concentrations rose by one hour and remained elevated through the twelfth hour after last dose of DHEA supplement (Buster et al., 1992). DHEA raised by 7 (11.5)-fold above placebo; dehydroepiandrosterone S by 14 (20)-fold above placebo, and testosterone by 4 (7)-fold above placebo (Buster et al., 1992).

In 2000, Casson et al. first described the therapeutic benefits of DHEA supplementation in women with diminished ovarian reserve. They conducted a case series in which five healthy non-smoking women <41 years old were given 80 mg/day of oral micronized DHEA for two months. All had normal FSH concentrations but had a poor response to ovarian stimulation with gonadotropins in ovulation induction, followed by intrauterine insemination cycles (Casson et al., 2000). While taking DHEA, they underwent ovarian stimulation with FSH, which was given intramuscular twice a day, and HCG (10 000 IU) at follicular maturity, followed by intrauterine insemination. After two months of DHEA treatment, DHEA-S, testosterone, and peak Estradiol concentrations increased. One patient conceived and delivered a twin pregnancy (Casson et al., 2000). The mechanism by which DHEA operates its effects is uncertain; however, the authors believe it might have a role in increasing the serum concentrations of IGF-1, which may improve the response to gonadotropins (Casson et al., 2000).

However, in 2001, Casson's paper was criticized for methodological errors, as he was changing the stimulation regimen and the choice and type of gonadotrophins used (Van Weering et al., 2001).

After Casson's original paper, there was no follow up studies until 2005, when was described a case of significantly improved ovarian reserve in a 42.7-year-old woman who was using the dietary supplement dehydroepiandrosterone (DHEA) along with acupuncture (Barad et al., 2005). After her first cycle, before starting the DHEA supplement, she produced one egg and one embryo; therefore, she was advised to consider the option of egg donation. The patient declined the option and decided to start an oral DHEA supplementation (75 mg per day of micronized DHEA), which was unknown to her physician (Barad et al., 2005). Following nine consecutive freeze IVF cycles, her oocyte and embryo yields increased from cycle to cycle (Barad et al., 2005).

Ovulation induction was achieved by using norethindrone acetate tablets (10 mg) for ten days, starting on day two of menses, followed three days later by 40 µg of leuprolide acetate twice a day, and after other three days, by either (cycle 1) 600 IU of FSH, (cycle 2–8) 450 IU of FSH and 150 IU of hMG, or (cycle 9) 300 IU of FSH plus 150 IU human menopause gonadotrophins (hMG) (Barad et al., 2005). When the follicle diameter was 18 to 20 mm, follicular maturation was triggered by an injection of 10,000 IU hCG, with oocyte retrieval 34 hours later. Peak Estradiol in cycle one was 1,211 pmol/L, in cycle eight was 18,557 pmol/L, and in cycle nine, after decreasing the dose of gonadotropin to 300 IU FSH and 150 IU hMG, peak Estradiol was 9,178 pmol/L and 17 oocytes were retrieved, from which 16 were cryopreserved (Barad et al., 2005).

The change in her ovarian function following DHEA supplementation resulted in the initiation of a prospective investigation of the role of DHEA in patients with diminished ovarian reserve.

Then Barad et al. in 2006, investigated the effect of treatment with DHEA on fertility outcomes among women with diminished ovarian reserve (Barad et al., 2006). In a case-control study, 25 women with significantly DOR had one IVF cycle before and after DHEA treatment. Women received 75 mg of DHEA daily for an average of 16 weeks (Barad et al., 2006). Ovulation induction was achieved by using norethindrone acetate tablets (10 mg) for ten days, starting on day two of menses, followed three days later by 50 µg of leuprolide acetate, twice daily, and, after another three days, by 450 IU of recombinant FSH and 150 IU of HMG (Barad et al., 2006). When at least two follicle diameters reached 18 mm, follicular maturation was triggered by 10 000 IU HCG injection. After treatment with DHEA, patients produced more oocytes, higher peak Estradiol level, higher fertilization rates, higher average day three blastomere counts, and had higher grade embryos on day three (Barad et al., 2006).

In 2007, Barad et al. performed a case-control study of 190 women with diminished ovarian function (Barad et al., 2007). The study group included 89 patients who used supplementation with 75 mg daily of oral micronized DHEA for up to four months before entering into IVF

(Barad et al., 2007). The control group was composed of 101 couples who received only infertility treatment. DHEA supplementation resulted in significantly higher pregnancy rates; in the study group, 25 pregnancies (28.4%) vs. 11 pregnancies (11.9%) in the control group (Barad et al., 2007).

Further, in 2007 Gleicher et al., in a retrospective case-control study, investigated estradiol levels, oocyte and embryo numbers, and aneuploidy rates after DHEA supplementation (Gleicher et al., 2007). Amongst 27 women with premature ovarian aging, eight had received at least one month of supplementation with DHEA (micronized, 75 mg/day) before oocyte retrieval, and 19 had not received such substitution. Patients in both groups received a microdose gonadotropin-releasing hormone (GnRH) agonist protocol for ovarian stimulation (Gleicher et al., 2007). The results showed that peak estradiol levels, oocyte, embryo numbers, and aneuploidy rates all demonstrated improvement after DHEA supplementation (Gleicher et al., 2007).

Bedaiwy et al. in 2009, presented a retrospective case-control study to investigate the effect of DHEA pre- and co-treatment on improving the outcome of IUI in 40 infertile women with a previous low ovarian response but with normal basal FSH (Bedaiwy et al., 2009). The control group consisted of 99 infertile women matched for age and basal FSH. They were treated with 75 mg oral DHEA/day for at least 60 days prior to and during controlled ovarian stimulation (COS) by FSH together with IUI. Both groups were treated with the same controlled ovarian stimulation together with intrauterine insemination (IUI) (Bedaiwy et al., 2009). The pregnancy rate was significantly higher in the DHEA group (14/30) compared with controls (9/99). DHEA treatment resulted in significantly more basal antral follicles, progesterone, estradiol, and Estradiol level compared with controls (Bedaiwy et al., 2009).

Sönmezer et al. assessed the effect of DHEA supplementation on cycle outcome in 19 patients with poor ovarian response scheduled to undergo a second intracytoplasmic sperm injection (ICSI)/embryo transfer cycle were enrolled, while first ICSI/embryo transfer cycles were taken as the control group (Sönmezer et al., 2009). All subjects were given DHEA supplementation (75 mg/day) for at least three months (90-180 days) prior to their second ICSI/embryo transfer cycle (Sönmezer et al., 2009). In both cycles, a fixed dose of recombinant FSH (rFSH) and human menopausal gonadotrophin (HMG) along with a flexible gonadotrophin-releasing hormone (GnRH) antagonist protocol was administered (Sönmezer et al., 2009). A favorable decrease of serum Estradiol concentrations was noted in mean day three, increased number of >17 mm follicles, oocytes, top quality day two, and day three embryos were achieved in DHEA-supplemented cycles (Sönmezer et al., 2009). Cycle cancellation rates were reduced (5.3% versus 42.1%), the pregnancy rate per patient (47.4% versus 10.5%) and

clinical pregnancy rate per embryo transfer (44.4% versus 0%) were achieved after DHEA supplementation (Sönmezer et al., 2009).

The first randomized controlled trial was published by Wisner et al. in 2010. Thirty-three women with significantly DOR were enrolled, 17 in the DHEA group and 16 in the control group, undergoing IVF cycles (Wisner et al., 2010). The study group received 75 mg/day of DHEA before starting the next IVF cycle and during treatment (Wisner et al., 2010). The DHEA group demonstrated a non-significant improvement in estradiol level along with improved embryo quality during treatment between the first and second cycles and also had a significantly higher live birth rate compared with controls (23.1% versus 4.0%) (Wisner et al., 2010).

Gleicher et al. performed a retrospective cross-sectional study and longitudinal analysis of 120 women with DOR, elevated age-specific FSH concentrations (on cycle days 2 or 3) of 11.0 mIU/ml AMH concentrations below 0.8 ng/ml (Gleicher et al., 2010). The women were supplemented for 30–120 days with DHEA (25 mg three times daily). AMH concentrations considerably improved after DHEA supplementation over time by approximately 60% (Gleicher et al., 2010). Women below 38 years demonstrated higher AMH concentrations, more than older females, and improved pregnancy rate by 23.64% via IVF (Gleicher et al., 2010).

In 2012 was published the results of a randomized controlled study performed by Moawad and Shaer. The patients were 133 women with a prior poor response to ovarian stimulation in IVF (Moawad and Shaer, 2012). The cases were into two groups: in the first group, patients were taking 75 mg/day of DHEA orally for at least 12 weeks before starting controlled ovarian hyperstimulation (COH), and in the second control group, patients started COH without DHEA priming (Moawad and Shaer, 2012). The results showed that the study group had statistically higher numbers of retrieved oocytes (5.9 ± 3.6) compared to the control group (3.5 ± 2.9), and a significant lower cancellation rate (13.4%) and a higher number of embryos transferred (2.8 ± 0.9) compared to the control group (28.8% and 1.7 ± 1.1 , respectively) (Moawad and Shaer, 2012). However, the pregnancy rate was higher in the study group (24.1%) compared to the control group (21.3%), no statistically significant difference was observed (Moawad and Shaer, 2012).

Additionally, in 2013 was published the results of a retrospective study of Kadam et al. (Kadam et al., 2013). The study involved 100 women with DOR, proven by low serum AMH levels (0 - 2.0 ng/ml) and reduced antral follicle count (AFC) on ultrasound (Kadam et al., 2013). The patients who were 25–45 years were administered DHEA 75 mg daily for three months to improve their ovarian reserve (Kadam et al., 2013). Patients with serum AMH levels between 1–2 ng/ml benefitted the most from the therapy. Their serum AMH levels, as well as the AFC,

were raised at the end of the treatment, and they also responded well to assisted reproductive techniques (ART), and got pregnant (30%) (Kadam et al., 2013). However, the group with low serum AMH levels (less than 1 ng/ml) did not show improvement in the levels of serum AMH as well as the AFC, and had low success rates with the assisted ART and were finally counseled for egg donation (Kadam et al., 2013).

Yilmaz et al. evaluated the effect of DHEA supplementation on OR by measuring markers such as antral follicle count (AFC), serum AMH and inhibin B in patients with diminished ovarian reserve (Yilmaz et al., 2013). In a prospective study, participated 41 patients with diminished OR (Yilmaz et al., 2013). The patients received supplementation with DHEA 75mg/day, for at least six weeks. Serum AMH, inhibin B, FSH, Estradiol, and AFC were determined before and after DHEA supplementation. There were significant differences in day three of FSH, Estradiol, AFC, AMH, and inhibin B levels before and after DHEA supplementation in all patients. The study population was divided into two groups (<35 and ≥ 35 years), and significant differences were found in all of the parameters in both study groups (Yilmaz et al., 2013).

Vlahos et al. conducted a prospective study in which 48 women diagnosed with a poor ovarian response. Patients received DHEA supplementation of 75 mg/day for at least 12 weeks, and ovarian stimulation for IVF (Vlahos et al., 2014). They were compared to poor responders ($n = 113$) who did not receive supplementation (Vlahos et al., 2014). Supplementation with DHEA for at least 12 weeks resulted in a statistically significant increase in AMH levels and decreased baseline FSH (Vlahos et al., 2014). Administration of DHEA did not affect any of the stimulation parameters, nor was there any difference in pregnancy and live birth rates between the two groups (Vlahos et al., 2014).

Tsui et al. investigated the effect of DHEA supplementation on women with a poor ovarian response (POR) (Tsui et al., 2014). Ten patients with POR were treated with a daily GnRH antagonist for IVF. They were enrolled in a prospective study and treated with DHEA supplementation (30 mg, three times a day, orally) for three months before the next IVF cycle (Tsui et al., 2014). Parameters of treatment outcomes were compared before and after DHEA supplementation. As a result of DHEA supplementation, a significant increase in antral follicle count, from 2.8 ± 1.0 to 4.1) was observed, and AMH, from 0.4 ± 0.2 ng/mL to 0.84 ± 0.2 (Tsui et al., 2014). A significant decrease of the day-three FSH and Estradiol was noted. Increased numbers of retrieved oocytes, fertilized oocytes, day-three embryos, and transferred embryos were also seen in these women with POR after DHEA treatment. Additionally, three women became pregnant after DHEA treatment (Tsui et al., 2014).

Yeung et al. assessed the effect of DHEA on AFC, ovarian response to a standard low dose of gonadotrophin



stimulation, and the number of oocytes in anticipated normal responders undergoing in vitro fertilization (IVF) (Yeung et al., 2016). Seventy-two sub-fertile women with AFC of 5-15 scheduled for IVF were selected to participate in a randomized, double-blind, placebo-controlled study. In the study group (n= 36), women received DHEA 25 mg three times a day; in the placebo group (n = 36), they received a placebo, starting from 12 weeks before the scheduled IVF treatment (Yeung et al., 2016). After 12 weeks of treatment with DHEA, a significantly higher serum and follicular DHEA-S and testosterone relative to placebo were noted. However, no significant differences in AFC, AMH, FSH, and ovarian response to standard-dose ovarian stimulation and IVF cycle outcomes were detected (Yeung et al., 2016).

Hu et al. conducted a prospective cohort study from August 2014 to August 2016. In the study, 103 DOR women were divided into two groups; the DHEA group (n = 53), which received DHEA supplementation, and the control group (n = 50), which did not receive DHEA (Hu et al., 2018). The DHEA group received DHEA supplementation (25 mg three times a day) for 8 weeks before the IVF. DHEA supplementation resulted in significantly higher levels of serum Testosterone, DHEAS, and androgen receptor (AR) messenger ribonucleic acid (mRNA) expression in granulosa cells (GCs). However, no significant differences were found in OR, ovarian response, or IVF outcomes between the two groups (Hu et al., 2018).

Chern et al. conducted a retrospective cohort study between January 2015 and December 2017. A total of 151 patients with poor ovarian responders, divided into two groups and underwent IVF cycles with the gonadotropin-releasing hormone antagonist protocol (Chern et al., 2018). The study group (n = 67) received 90 mg/daily of DHEA for an average of three months before the IVF cycles, while

the control group (n = 84) underwent the IVF cycles without DHEA pretreatment. The study group demonstrated a greater number of retrieved oocytes, fertilized oocytes, day three embryos, and top-quality embryos at day three and a higher clinical pregnancy rate and live birth rate than the control group (Chern et al., 2018).

Dasari and Ali presented a case report published in 2018. A 32-year-old woman with primary infertility had an AMH of 0.63 ng/ml and an AFC of four (Dasari and Ali, 2018). She underwent ten cycles of ovulation induction with clomiphene citrate (CC) and laparoscopic ovarian drilling (LOD) two years before, which was unsuccessful. She had been treated with DHEA 75 mg once daily for three months. Her AMH increased to 1.2 ng/ml, AFC to seven, and conceived naturally after the fourth cycle of ovulation induction with gonadotropins without cycle monitoring (Dasari and Ali, 2018).

Ozcil investigated the impact of DHEA supplementation on ovarian reserve parameters and pregnancy rates in patients with a poor ovarian reserve (POR) and primary ovarian insufficiency (POI) (Ozcil, 2020). A total of 34 people, six patients with POI and 28 patients with POR, were included in the study. Patients in the POI and POR group were taking 50 mg DHEA supplementation daily for five months (Ozcil, 2020). Following DHEA administration, the AFC increased in 30.8% of the patients, while AMH levels not significantly (Ozcil, 2020). The live birth rate and pregnancy rate per cycle were higher in POR patients than those with POI (Ozcil, 2020). the pregnancy rate was (36% vs. 29%), and pregnancy rates per cycle (8.5% vs. 6.35%), which were higher in the POR group. The rates of live birth were the same in the POI and POR groups (29% vs. 29%) (Ozcil, 2020).

Table 2, reviews the published literature in women using DHEA, and the results achieved after using DHEA supplementation

Authors	Year of publication	Type of study	Number of patients	The dosage of DHEA	The results
Casson et al.	2000	Case-series	Five cases <41 years old with DOR	80 mg/day oral micronized DHEA for two months (along with OI protocol)	After two months of DHEA treatment, DHEA-S, testosterone, and peak Estradiol concentrations increased. One patient conceived and delivered a twin pregnancy.
Barad and Gleicher	2005	Case-report	One case. A 42.7-year-old patient with DOR	75 mg per day of micronized DHEA from second to ninth cycle, (along OI)	Following nine consecutive freeze IVF cycles, her oocyte and embryo yields increased from cycle to cycle. The peak Estradiol level increased and 17 oocytes were retrieved, from which 16 were cryopreserved

Table 2, reviews the published literature in women using DHEA, and the results achieved after using DHEA supplementation

Authors	Year of publication	Type of study	Number of patients	The dosage of DHEA	The results
Barad and Gleicher	2006	Case-control study	25 women with significantly DOR had one IVF cycle before and after DHEA treatment.	75 mg of DHEA daily for an average of 16 weeks (along with OI)	After treatment with DHEA, patients produced more oocytes, higher peak Estradiol level, higher fertilization rates, higher average day three blastomere counts, and had higher grade embryos on day three
Barad et al.	2007	case-control study	190 women with DOR	The study group included 89 patients who used supplementation with 75 mg daily of oral micronized DHEA for up to four months before entering into IVF. The control group of 101 couples received only infertility treatment	DHEA supplementation resulted in significantly higher pregnancy rates; in the study group, 25 pregnancies (28.4%) vs. 11 pregnancies (11.9%) in the control group
Gleicher et al.	2007	Retrospective case-control study	27 women with premature ovarian aging	eight had received at least one month of supplementation with DHEA (micronized, 75 mg/day) before oocyte retrieval, and 19 had not received DHEA (along with OI)	The peak estradiol levels, oocyte, embryo numbers, and aneuploidy rates all demonstrated improvement after DHEA supplementation
Bedaiwy et al.	2009	Retrospective case-control study	40 infertile women with a previous POR with normal basal FSH, the control group consisted of 99 infertile women matched for age and basal FSH	Control group received 75 mg DHEA per day for at least 60 days prior to and during controlled ovarian stimulation (COS) by FSH together with IUI.	The pregnancy rate was significantly higher in the DHEA group (14/30) compared with controls (9/99), and significantly more basal antral follicles, progesterone, estradiol, and Estradiol level compared with controls

Table 2, reviews the published literature in women using DHEA, and the results achieved after using DHEA supplementation

Authors	Year of publication	Type of study	Number of patients	The dosage of DHEA	The results
Sönmezer et al.	2009	Case-control study	19 patients with POR scheduled to undergo a second intracytoplasmic sperm injection (ICSI)/embryo transfer cycle were enrolled, while first ICSI/embryo transfer cycles were taken as the control group	DHEA supplementation (75 mg/day) for at least three months (90-180 days) prior to their second ICSI/embryo transfer cycle (along with OI)	A decrease of serum Estradiol in mean day three, increased number of follicles, oocytes, top quality day two, and day three embryos were achieved in DHEA-supplemented cycles. Cycle cancellation rates were reduced (5.3% versus 42.1%), the pregnancy rate per patient (47.4% versus 10.5%) and clinical pregnancy rate per embryo transfer (44.4% versus 0%) were achieved
Wiser et al.	2010	Randomized controlled trial	33 women with DOR, 17 in the DHEA group and 16 in the control group, undergoing IVF cycles	75 mg/day of DHEA before starting the next IVF cycle	The DHEA group demonstrated a non-significant improvement in estradiol level along with improved embryo quality during treatment between the first and second cycles and also had a significantly higher live birth rate compared with controls (23.1% versus 4.0%)
Gleicher et al.	2010	Retrospective cross-sectional study and longitudinal analysis	120 women with DOR	The women were supplemented for 30–120 days with DHEA (25 mg three times daily), along with OI and IVF.	AMH concentrations considerably improved after DHEA supplementation by approximately 60%. Women below 38 years demonstrated higher AMH concentrations, more than older females, and improved pregnancy rate by 23.64% via IVF.
Moawad and Shaeer	2012	Randomized controlled study	133 women with a prior poor response to ovarian stimulation in IVF	The first group, patients were taking 75 mg/day of DHEA orally for at least 12 weeks before starting controlled ovarian hyperstimulation (COH), and in the second control group, patients started COS without DHEA priming	The study group had higher numbers of retrieved oocytes (5.9 ± 3.6) compared to the control group (3.5 ± 2.9), and lower cancellation rate (13.4%) and a higher number of embryos transferred (2.8 ± 0.9) compared to the control group (28.8% and 1.7 ± 1.1 , respectively), the pregnancy rate in the study group (24.1%) compared to the control group (21.3%)

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Authors	Year of publication	Type of study	Number of patients	The dosage of DHEA	The results
Kadam et al.	2013	Retrospective study	100 women with DOR	DHEA 75 mg daily for three months, along with assisted reproductive techniques (ART)	Serum AMH levels, as well as the antral follicle count (AFC), were raised at the end of the treatment, and they also responded well to ART, and got pregnant (30%). The group with low serum AMH levels (less than 1 ng/ml) did not show improvement in the levels of serum AMH as well as the AFC, and had low success rates with the assisted ART
Yilmaz et al.	2013	Prospective study	41 patients with DOR	DHEA 75mg/day, for at least six weeks	Significant differences in day three of FSH, Estradiol, AFC, AMH, and inhibin B levels after DHEA supplementation in all patients were noted
Vlahos et al.	2014	Prospective study	48 women with DOR, compared with poor responders ($n = 113$)	75 mg/day for at least 12 weeks (along with OI for IVF)	Significant increase in AMH levels and decreased baseline FSH, but did not affect any of the stimulation parameters, nor was there any difference in pregnancy and live birth rates between the two groups
Tsui et al.	2014	Prospective study	10 women with POR	30 mg three times/day, ≥ 3 months (mean 12.2 weeks). along with OI before next IVF	Improved Improvement in ovarian reserve markers (FSH, AMH, E2, AFC) Improvements in oocytes retrieved, fertilized oocytes, Day 3 embryos and transferred embryos
Yeung et al.	2016	Randomized, double-blind, placebo-controlled study	72 sub-fertile women	In the study group ($n= 36$), women received DHEA 75 mg/day; the placebo group ($n = 36$), starting from 12 weeks before the scheduled IVF treatment	A significantly higher serum and follicular DHEA-S and testosterone relative to placebo were noted. However, no significant differences in AFC, AMH, FSH, and ovarian response to standard-dose ovarian stimulation and IVF cycle outcomes were detected
Hu et al.	2017	Prospective cohort study from August 2014 to August 2016	103 DOR women	The DHEA group ($n = 53$), which received DHEA supplementation, 75 mg/day for 8 weeks before the IVF and the control group ($n = 50$), which did not receive DHEA	DHEA supplementation resulted in higher levels of serum Testosterone, DHEAS, and androgen receptor (AR) messenger ribonucleic acid (mRNA) expression in granulosa cells (GCs), no significant differences were found in OR, ovarian response, or IVF outcomes between two groups

Table 2, reviews the published literature in women using DHEA, and the results achieved after using DHEA supplementation

Authors	Year of publication	Type of study	Number of patients	The dosage of DHEA	The results
Cern et al.	2018	Retrospective cohort study between January 2015 and December 2017	151 patients with POR	The study group (n = 67) received 90 mg/daily of DHEA for an average of three months before the IVF cycles, while the control group (n = 84) underwent the IVF cycles without DHEA pretreatment	The study group demonstrated a greater number of retrieved oocytes, fertilized oocytes, day three embryos, and top-quality embryos at day three and a higher clinical pregnancy rate and live birth rate than the control group
Dasari and Ali	2018	Case-report	A 32-year-old woman with primary infertility, and DOR after laparoscopic ovarian drilling	DHEA 75 mg once daily for three months	AMH and AFC increased, and conceived naturally after the fourth cycle of ovulation induction with gonadotropins
Ozcil	2020	Prospective study	34 women, 6 patients with POI and 28 patients with DOR	Both groups were taking 50 mg DHEA supplementation daily for 5 months	AFC increased in 30.8% of the patients, while AMH levels not significantly. The live birth rate, pregnancy rate per cycle were higher in POR patients than those with POI, the pregnancy rate was (36% vs. 29%), and pregnancy rates per cycle (8.5% vs. 6.35%), higher in the POR group, live birth rate was the same in the POI and POR groups (29% vs. 29%)

DOR- diminished ovarian reserve, POR- poor ovarian response, COS-controlled ovarian stimulation, OI- ovulation induction, POI- primary ovarian insufficiency, AMH- anti-Mullerian hormone, AFC-antral follicle count, FSH- follicle stimulant hormone, E2- estradiol, ICSI- intracytoplasmic sperm injection, IVF- in vitro fertilization, IUI- intrauterine insemination.

3. Conclusion:

In conclusion, DHEA supplementation has beneficial effects on patients with diminished ovarian reserve and poor ovarian response. Several possible mechanisms of DHEA actions have been proposed and may be related to DHEA-enhanced levels of androgen; however, further research to explore how DHEA works is demanded. A potentially effective clinical approach such as DHEA supplementation is an attractive adjuvant therapy before ART, IVF, with increased spontaneous conceptions.

As described above, DHEA improves the pregnancy rate in young women with premature diminished ovarian reserve. Additionally, decreases the age-related aneuploidy

and eventually miscarriage rate in older women with age-related diminished ovarian reserve. However, it is important to note that all studies suffer from improper design, the low number of enrolled participants, and the lack of large, multicenter randomized controlled trials, which are needed to confirm the results.

We assume that DHEA supplementation is a novel concept in improving embryo/oocyte yields and possibly oocyte quality. However, much remains to be answered, such as who does and who does not benefit from DHEA supplementation, the appropriate duration and dose, and whether DHEA is of any use in women with undetectable or low AMH levels.

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