Chapter 4

Effects of Dehydroepiandrosterone (DHEA) Supplementation to Improve Ovarian Response and IVF Outcomes on Women with Poor Ovarian Response

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.79320

Abstract

There is still no clear consensus on the poor responder (PR) definition, however, the European Society of Human Reproduction and Embryology (ESHRE) suggested, in 2011, the Bologna criteria, which includes, for a poor ovarian response definition, at least two of the following three characteristics: age > 40 years, the number of oocytes previously recovered equal to or less than three, and low ovarian reserve tests score. It is noticed that, despite the use of different effective ovulation stimulation protocols, clinical pregnancy rates remain low in PR. In recent years, however, many authors, including Casson et al., reported the beneficial of DHEA supplementation on ovarian response in this group. Dehydroepiandrosterone (DHEA), a precursor of estradiol (E2) and testosterone (T), originates from the reticularis adrenal zone and from ovarian theca cell. In this chapter, we intend to demonstrate the potential benefits of DHEA supplementation in women with poor response in IVF outcomes.

Keywords: dehydroepiandrosterone, poor ovarian response, in vitro fertilization, clinical pregnancy rate, ovulation stimulation protocol

1. Introduction

Female infertility increases dramatically with age. The delay in the decision of having children is no longer a simple trend, but a reality among women today [1, 2]. At least 20% of women choose to establish their families after the age of 35. This is mainly due to the expectation of the

modern woman to wish for, in the foreground, professional and financial stability, waiting for a stable relationship that would give her security [1–4].

Under the physiological aspect, the function of the ovary is to generate mature oocytes and produce steroid hormones that create a conducive environment to fertilization and embryonic implantation, and the aging of the ovaries is demonstrated by reduced oocyte reserve, decreased fertility as well as adverse reproductive events, such as gestational losses and pregnancy with aneuploidy. With age, the remaining eggs age and become less able to be fertilized by sperm [5].

2. Poor responder patients

The clinical management of the poor responders in the in vitro fertilization (IVF) processes is still a challenge for specialists in the field, since there is a lack of standardization in the definition of these patients classified as "poor responders." It is found that in such patients, a small number of follicles are developed during treatment and, as a consequence, a small number of oocytes are recovered through IVF [6–8].

The European Society for Human Reproduction and Embryology (ESHRE) [9] proposed in 2011 the so-called Bologna criteria that establish as a poor ovarian response, that is, a decrease in the quantity of eggs available for fertilization available in the ovaries to stimulation in IVF cycles, with at least two of the following three characteristics:

- Age above 40.
- The number of oocytes previously recovered in previous cycles of IVF less than or equal to three.
- Low ovarian reserve test scores.

According to different studies, 9–24% of patients who have undergone IVF and embryo transfer (IVF-ET) have been poor responders, resulting in low pregnancy rates, or between 2 and 4% [4, 10, 11].

The main causes are numerical and structural chromosomal changes, as well as mutations or variability in specific genes of reproductive aging, pelvic infections, chlamydia trachomatis infections, endometriosis, chemotherapy, and other factors that may lead to the reduction of ovarian reserve [12, 13].

In addition, there is an evident lack of data to identify the best intervention to achieve treatment success in poor responders, due to the heterogeneity of this group of women. Old age is considered the most relevant risk factor, but on the other hand, young women are not free of this condition and may also have a diminished ovarian reserve [3, 4, 14].

Thus, different protocols have been suggested to improve outcomes in those patients, such as: the use of nitric oxide, formed in vivo from L-arginine, which may play a role in follicular maturation and ovulation. Growth hormone is also employed to regulate the effect of FSH,

http://dx.doi.org/10.5772/intechopen.79320

increasing the synthesis of insulin-like growth factor and consequently ovarian function, quality, and embryo implantation [15–17].

In this way, the purpose of this chapter is to describe the effect of dehydroepiandrosterone supplementation (DHEA) as an adjunct in ovarian stimulation procedures.

3. Steroidogenesis

Steroidogenesis occurs through a cascade of events in the adrenal, ovary, and peripheral tissues. The set of reactions is triggered by hormonal stimuli specific for each organ, such as adrenocorticotrophic hormone (ACTH) that acts on the adrenal and luteinizing (LH) in the ovaries [12].

These hormones bind to a specific receptor on the cell membrane of the effector organ, activating an intracellular enzyme, the adenylyl cyclase, responsible for converting adenosine triphosphate (ATP) into cyclic adenosine monophosphate (cAMP). The cAMP, in turn, binds to a cytoplasmic protein (guanine nucleotide binding proteins—G protein), and this newly formed complex is responsible for the activation of the enzymes involved in steroidogenesis [17, 18].

The action of specific enzymes, which are distinct in the steroidogenic organs, is what determines the pathway to be followed. Thus, the combined action of two groups of enzymes on steroidogenesis is: enzymes of the superfamily cytochrome P450 and the hydroxysteroid dehydrogenases. The ovary undergoes the action of the 17α-hydroxylase or 17,20-lyase that guides the estrogen production pathway and in the adrenal, the 21-hydroxylase which is responsible for the production of glucocorticoids and mineralocorticoids [18–21].

3.1 Stages of steroidogenesis from cholesterol

According to Geber, Valle, and Sampaio [20], the raw material of steroidogenesis is cholesterol. Virtually, all cells of steroid-producing organs, with the exception of the placenta, are able to produce cholesterol from acetates in the smooth endoplasmic reticulum. However, this production is insufficient, and most of this precursor hormone is of serum origin. Cholesterol is transported in the bloodstream by low-density lipoproteins (LDL) which bind to specific receptors on the cell membrane of the steroid-opioid organs, allowing cholesterol to enter the cell.

After its entry into the cell, the cholesterol has its side chain broken in C20-C22, by the action of oxidizing desmolase, originating pregnenolone, which in turn, undergoes the action of the enzyme 3β-hydroxysteroid dehydrogenase converting it into progesterone.

Pregnenolone and progesterone then pass two parallel pathways: delta 5 and delta 4, respectively. Immediate reactions are common to both sequences, originating different products.

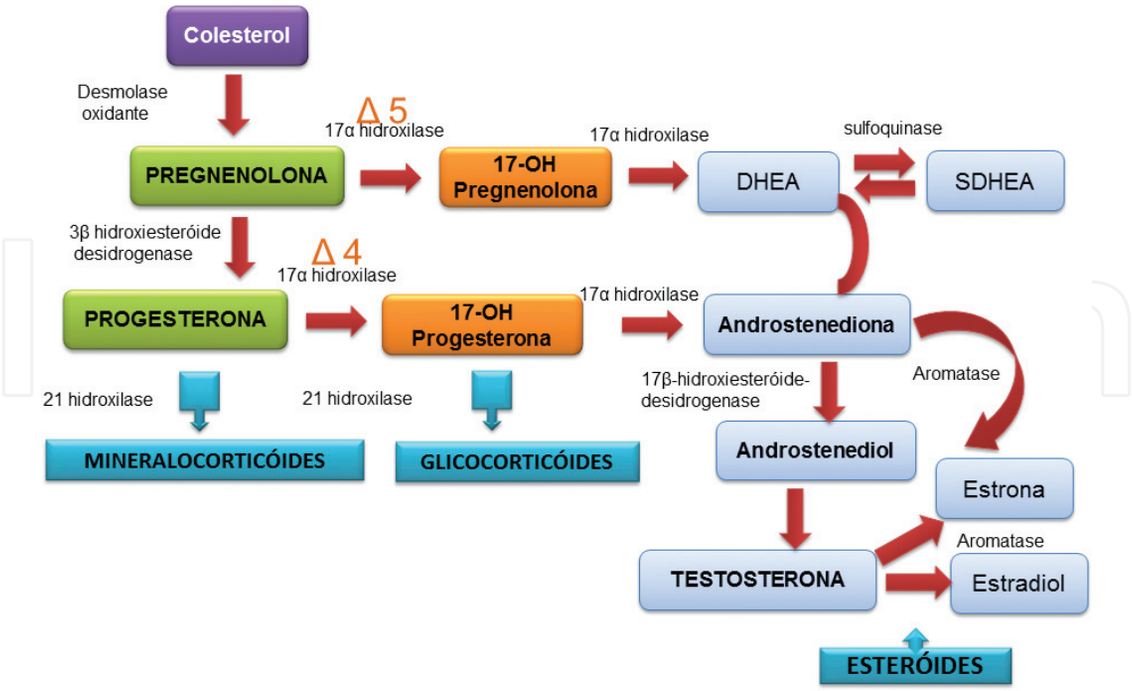

Figure 1. Steroidogenesis biochemical pathways.

Both pregnenolone and progesterone will undergo 17α-hydroxylase or 17,20-lyase action, resulting in 17-hydroxypregnenolone and 17-hydroxyprogesterone, respectively. These substances may be followed by a biochemical pathway that will originate the androgens and estrogens or the one that will give rise to the hormones of the adrenal cortex. 17-hydroxypregnenolone and 17-hydroxyprogesterone under the action of 17α-hydroxylase will give origin to dehydroepiandrosterone (DHEA) and androstenedione, respectively.

Subsequently, DHEA and androstenedione by the stimulation of the enzyme 17β-hydroxysteroid dehydrogenase will transform into androstenediol and testosterone, which are the terminal androgens. Androstenedione and testosterone undergo the action of a set of enzymatic reactions called aromatization and give rise to estrone and estradiol.

Figure 1 briefly describes the biochemical pathways of steroidogenesis [18, 20].

The action of all these hormones is on the general metabolism, thus, they participate in the glucose regulation and ionic balance of sodium and potassium in the body, among others [18].

4. Dehydroepiandrosterone (DHEA)

Dehydroepiandrosterone (DHEA) and its sulfated form (SDHEA) are androgenic hormones mainly produced by the reticular zone of the adrenal glands, from cholesterol. This gland accounts for 90% of DHEA production and 100% of SDHEA production. Other sites of production of this hormone are testicles, ovaries, adipose tissue, brain, and skin [1, 12, 21].

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In addition to precursors of the sex hormones, they act on the secretion of all other hormones secreted by the adrenal (**Figure 2**).

It is worth mentioning that DHEA is converted peripherally into its sulfate and vice versa. SDHEA is the most abundant C19 steroid, being an excellent marker of cortical adrenal function [12].

According to Rosenthal and Glew [18], DHEA plays an important role in protein metabolism, since it is considered the main anabolic agent, but has an androgenic activity, considered to be weak, representing less than 10% of testosterone potency. On the other hand, the production of weak androgens, such as DHEA and androstenedione, cannot be deprecated because more than about 50% of testosterone levels result from the peripheral transformation of these weak androgens. The daily secretion of the hormone DHEA is about 30 mg in the young man and 20 mg in the young woman, considering both in the resting condition. Food factors such as the consumption of proteins and fats have increased production, while carbohydrates interfere reducing production.

During female reproductive life, the two hormones circulate in the human body in large quantities, with SDHEA having a longer serum half-life than DHEA [18, 20].

DHEA is secreted by the adrenal in a pulsatile way, accompanying the diurnal rhythm similar to that of cortisol, being stimulated by corticotrophin releasing hormone (CRH) and adreno-corticotrophic hormone (ACTH) [22].

Throughout the life of man and woman, adrenal cortisol production increases, and conversely, DHEA, Melatonin, and Growth Hormone (GH) decrease. During the first year of life, the adrenals produce little DHEA. Around 6–7 years of age, there is an increase in levels of this hormone, so that at the age of 20, it is the most abundant hormone in circulating blood [1, 20].

From 30 to 40 years of age, a drop-in level of this hormone begins, and by the age of 70, there is only 25% or less of the amount of the hormone present at age 20. **Table 1** shows the levels of DHEA found in the human body over the years distributed by gender and age group [1, 23].

Due to their higher bioavailability, serum levels of SDHEA are used as a benchmark in clinical exams. Most DHEA, before it is released into circulation, is converted into DHEA sulfate, and that sulfated form can be transformed back into DHEA as the body needs it. In turn, DHEA is rapidly transformed into testosterone and estrogen.

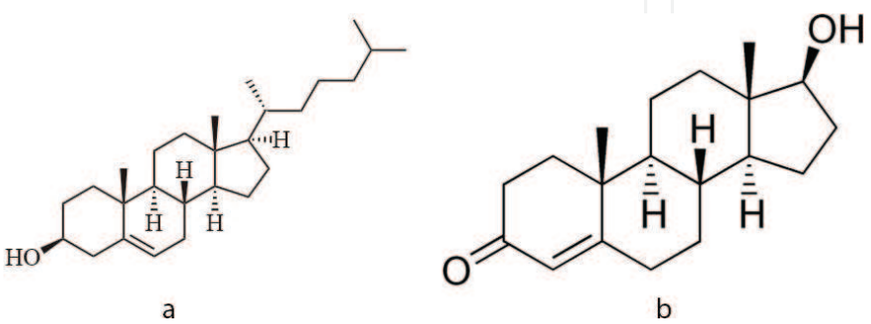

Figure 2. Molecular structure of cholesterol and DHEA, respectively.

Age	Women	Men
18–19	145–395 μg/dL (3.92–10.66 μmol/L)	108–441 μg/dL (2.92–11.91 μmol/L)
20–29	65–380 μg/dL (1.75–10.26 μmol/L)	280–640 μg/dL (7.56–17.28 μmol/L)
30–39	45–270 μg/dL (1.22–7.29 μmol/L)	120–520 μg/dL (3.24–14.04 μmol/L)
40–49	32–240 μg/dL (0.86–6.48 μmol/L)	95–530 μg/dL (2.56–14.31 μmol/L)
50–59	26–200 μg/dL (0.70–5.40 μmol/L)	70–310 μg/dL (1.89–8.37 μmol/L)
60–69	13–130 μg/dL (0.35–3.51 μmol/L)	42–290 μg/dL (1.13–7.83 μmol/L)
69 and older	17–90 μg/dL (0.46–2.43 μmol/L)	28–175 μg/dL (0.76–4.72 μmol/L)

Compiled from: Medical Encyclopedia DHEA-sulfate test.

Table 1. The DHEA-sulfate test measures the amount of DHEA-sulfate in the blood.

The decline of DHEA observed after 30 years leads to a decrease in peripheral production of sex hormones in both sexes. This fact coincides with the appearance of age-related diseases such as obesity, cardiovascular disease, cancer, diabetes mellitus, immune system disorders, rheumatic diseases, viral infections, and depression [1].

Like this, Antonio et al. [1] related that several studies indicate that a replacement of these hormones could have anti-aging effect as well, and some scientific evidence indicates that DHEA also plays other beneficial functions in the body as: increased insulin sensitivity, aiding in the improvement of glucose uptake, mainly by skeletal muscle, liver, and adipose tissue. There is also evidence of the positive effects of DHEA on bone density because low levels of this hormone have been found in patients with osteoporosis.

Researches have shown that DHEA reduces the levels of interleukin-6 and alpha tumor necrosis factor, decreasing proinflammatory cytokines and kappa-beta nuclear factor, which is the central factor of the inflammatory cascade. In relation to stress and exercise, it reduces the production of TNF-alpha, increases glucose tolerance, improves lipid profile, and has a complementary action to exercise, increasing the production of T lymphocytes [24].

Data from the literature report that the concentration of DHEA in Alzheimer's disease is lower when compared to the controls. There have been reports that showed an inverse relationship between DHEA levels and cardiovascular disease and mortality in men as well as breast tumors [1]. Therefore, DHEA is closely related to greater well-being and better physical fitness. In this approach, DHEA has also been used by athletes as a supplement to better muscle performance as a substitute for classic anabolic steroids used for this purpose [24].

Synthetic DHEA is produced from diosgenin, which is found and extracted from wild yam and soya. The dose of DHEA indicated for men is between 50 and 100 mg/day, but there is a danger of aromatization when the dose is close to 100 mg. In women, the dose ranges from 12.5 to 25 mg. Thus, testosterone and estrogen levels need to be monitored regularly in patients who are using DHEA supplements [6, 25].

In women, several side effects have been reported even with the use of physiological doses of DHEA, including acne, hair loss, hirsutism, and alteration of voice tone, the latter two of which

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may be irreversible processes. In the short term, in addition to its virilizing effects, the use of DHEA may result in the reduction of high density lipoprotein (HDL), interfering with the uptake of cholesterol. Other side effects such as hepatic dysfunction, hypertension, psychotic symptoms, seizures, and palpitations have also been described. In vitro, DHEA inhibits cytochrome p450 3A4 and may therefore increase the serum concentrations of many drugs metabolized by this isoenzyme [26].

5. Therapeutic effects of DHEA supplementation in patients with diminished ovarian response

The possible therapeutic effects of DHEA supplementation in poor responders were first reported in 2000 by Casson et al. [27]. From that date, up to now, about 26% of IVF clinics in different countries have used DHEA supplementation protocols in women with diminished ovarian reserve, and favorable results have been observed most of the time.

In studies with SDHEA, the authors report their performance as a pre-hormone testosterone, responsible for 48% of this hormone in circulating follicular fluid in patients treated with this androgen. That is, SDHEA acts as a prohormone relevant for ovarian follicular sexual steroidogenesis. Experimental investigations with laboratory animals revealed that androgens could potentiate the effect of FSH on folliculogenesis. The authors reported that the use of testosterone or dihydrotestosterone in these animals increased the number of FSH receptors in the plasma membranes of granulosa cells. There was then a stimulus for the initial growth of the follicles, recruiting the primordial follicles early, and consequently developing a greater number of preantral and antral follicles [3, 10, 21].

These findings corroborate the two-cell theory (**Figure 3**), which postulates that androgens play a critical role in the proper regulation of steroidogenesis [10, 21].

DHEA supplementation can rescue atresic follicles, promote preantral follicle growth, and suppress apoptosis, thereby increasing ovarian reserve levels [10, 21].

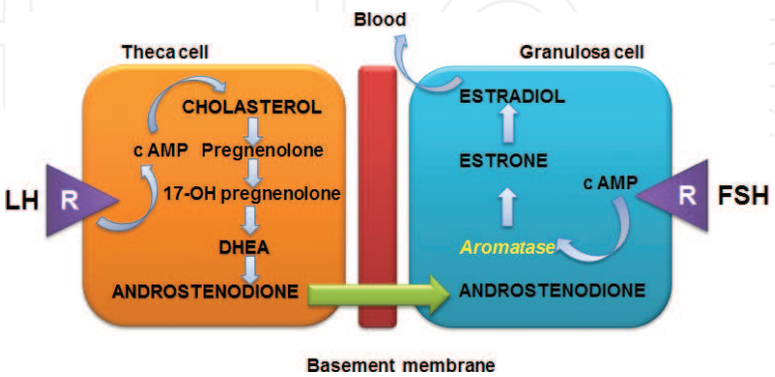

Figure 3. Teak cells have numerous (R) LH receptors and when binding occurs between them, results in the activation of cyclic AMP and androstenedione synthesis from cholesterol. Androstenedione crosses the basement membrane of the teak cells and enters the granulosa cells of the ovary. At this site, under activation of FSH and the enzyme aromatase, androstenedione is converted into estrone and estradiol.

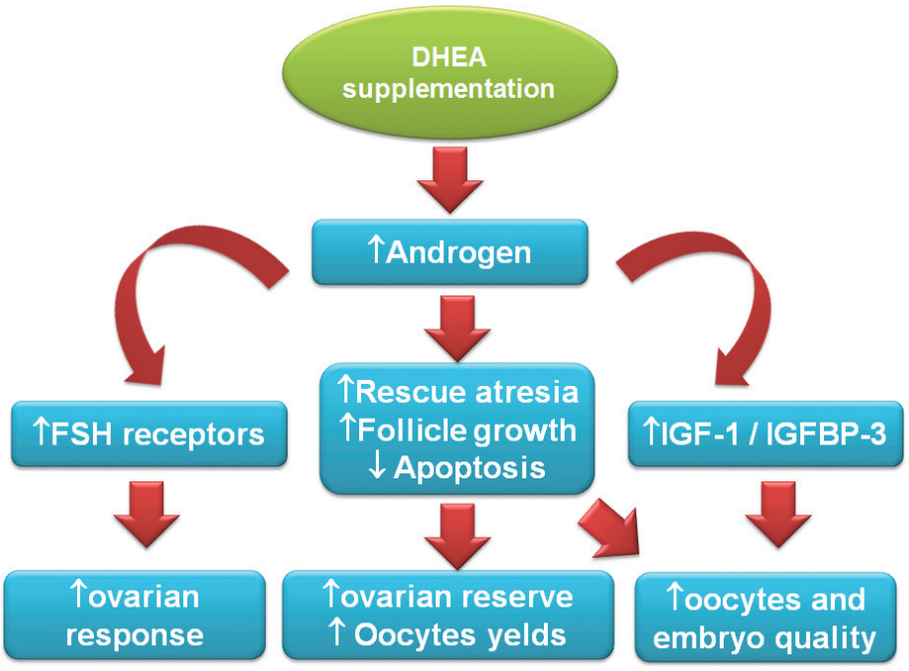

Figure 4. Schematic of the mechanism of possible effects of DHEA in patients with diminished ovarian reserve.

Some researchers reported a transient increase in Insulin-like growth factor 1 (IGF-1) in patients undergoing ovarian stimulation with gonadotropin after 8 weeks of pretreatment with DHEA. The hypothesis was that the effect of DHEA on ovulation induction may have been mediated by increased IGF-1. Thus, IGF-1 is shown to have positive effects on the embryos development, with an improvement in oocytes and embryo quality with DHEA therapy. Administration of this hormone also elevates the levels of the IGF-I binding protein type 3 (IGFBP-3), possibly mediated by increased levels of androgens. Thus, the IGF-I/IGFBP-3 ratio may be indicative of oocyte quality and maturity (**Figure 4**) [1, 4, 7, 8, 28].

Currently, androgens are often being used in assisted human reproduction as an option to improve the ovarian response of women considered to be more responsive. Thus, androgens have been given prior to ovarian induction in order to improve the response to stimulation with exogenous FSH in patients previously classified as having low ovarian reserve. Researches have described that treatments with moderate doses of androgens in patients with low antral follicle counts can increase both the quantity and quality of oocytes and embryos, leading to favorable results in assisted human reproduction treatments. However, it is important to observe that some studies have shown that DHEA supplementation for IVF in women with decreased ovarian reserve did not increase the clinical rate of pregnancy. It is therefore noted that the mechanism of action of this steroid hormone remains obscure and that there are several controversies about it [28–31, 33–35].

The data in **Table 2** show the reported results of using DHEA in more responding women.

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Author/Year	Sample size	Age	Study objectives	Results
Gibson [32]	16	44.7 ± 2.3	Use of DHEA in endometrial receptivity and embryo implantation	Increased pregnancy rate
Keane [17]	387	39.2 ± 4.1	To search for three groups of patients, who were given GH, DHEA and GH + DHEA as a supplement	The combination of GH and DHEA did not bring significant benefits in the birth rate
Lin [33]	72	39.4 ± 3.5	To evaluate the effect of DHEA administration on the improvement of ovarian intracellular function	It confirmed the beneficial effects of DHEA on mitochondrial function and on the reduction of apoptosis in cumullus cells
Tavares [11]				There was an increase in the number of recruited follicles, of selected oocytes; better embryo quality; lower risk of aneuploidies; higher rate of clinical pregnancy and live births.
Casare [10]	Systematic review		Effect of DHEA on assisted reproduction	DHEA did not contribute to significant differences in the studied parameters
Nearkwichean [4]				DHEA does not improve quantitatively the ovarian response nor the pregnancy rate
Gleicher [8]				Improves ovarian function; increases the pregnancy rate by reducing aneuploidies and the rate of gestational losses
Wiser [6]	17	36.9 ± 4.7	To analyze the peak of estradiol in the day of the HcG; the quality of the embryo; the birth rate after the use of DHEA	Confirmed the beneficial effects of DHEA on ovarian function
Barad [7]	89	41.6 ± 0.4	Clinical pregnancy rate	
Barad [2]	25	40.4 ± 0.8	To analyze the peak of estradiol in the day of the HcG; number and quality of oocytes and embryos; number of transfers using DHEA	

Table 2. Main results of DHEA use in more responding women.

6. Conclusion

The potential benefits of DHEA supplementation in poor responders with diminished ovarian reserve still require further large scale multicenter randomized controlled studies required to clarify such benefits.

The different methodologies and protocols of stimulation and the dose and duration of DHEA supplementation are varied in the evaluated studies. The small population sample and the different clinical interpretations of poor ovarian response may lead to the impairment of the analysis and the accuracy of the results on the use of DHEA.

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