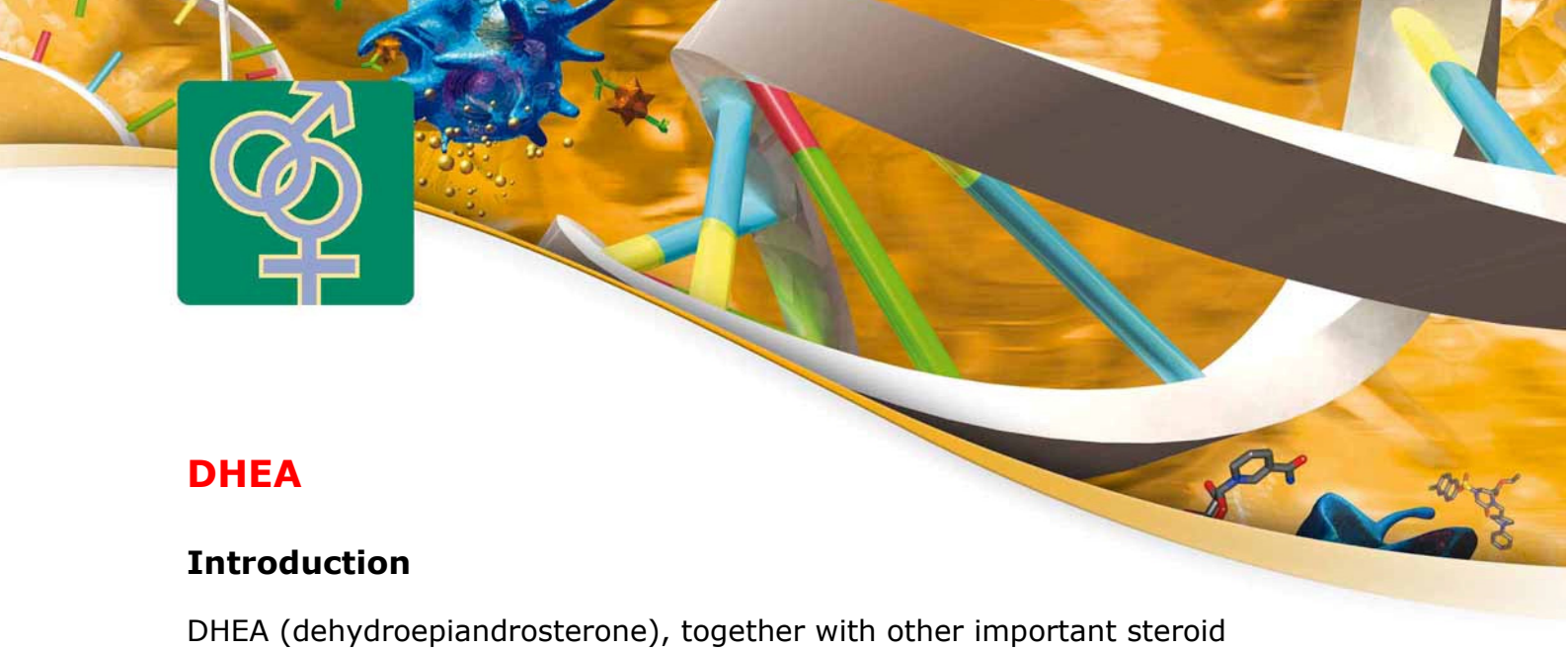
Reproductive

DHEA

Analyte Information

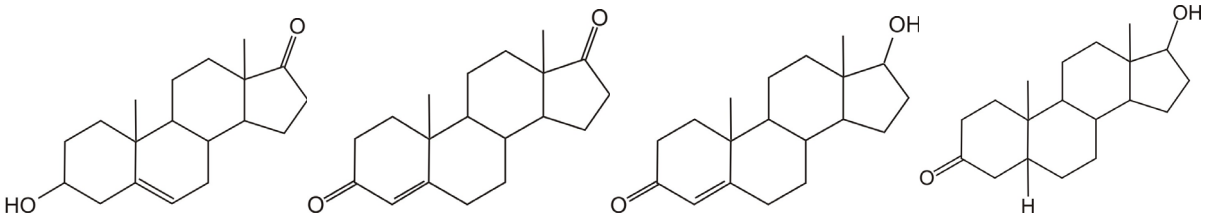


DHEA

Introduction

DHEA (dehydroepiandrosterone), together with other important steroid hormones such as testosterone, DHT (dihydrotestosterone) and androstenedione, belongs to the group of androgens. Androgens are a group of C_{19} steroids that stimulate or control the development and maintenance of male characteristics. This includes the activity of the male sex organs and the development of secondary sex characteristics. Androgens are also precursors of all estrogens, the female sex hormones.
DHEA (dehydroepiandrosterone) is the aromatic C_{19}-steroid composed of a 10,13-dimethyl, 3-hydroxy group and 17-ketone. Its chemical name is 3β-hydroxy-5-androsten-17-one, its summary formula is $C_{19}H_{28}O_2$, and its molecular weight (Mr) is 288.4 Da. The structural formulas of DHEA and related androgens are shown in Fig.1

Fig.1: Structural formulas of the most important androgens



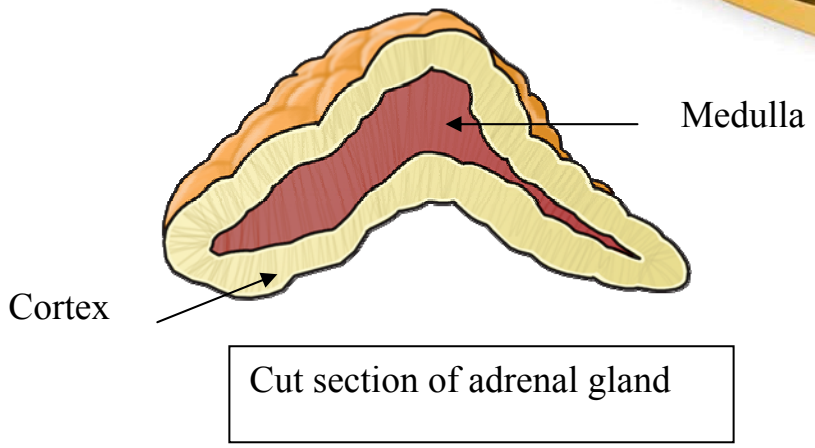
DHEA **Androstenedione** **Testosterone** **Dihydrotestosterone**

There are more than 40 other names used for DHEA, including: (+)-Dehydroisoandrosterone; (3beta, 16alpha)-3,16-dihydroxy-androst-5-en-17-one; 5,6-Dehydroisoandrosterone; 17-Chetovis, 17-Hormoforin, Andrestenol, Diandron, Prasterone and so on.
As DHEA is very closely connected with its sulfate form DHEA-S, both hormones are mentioned together in the following text.

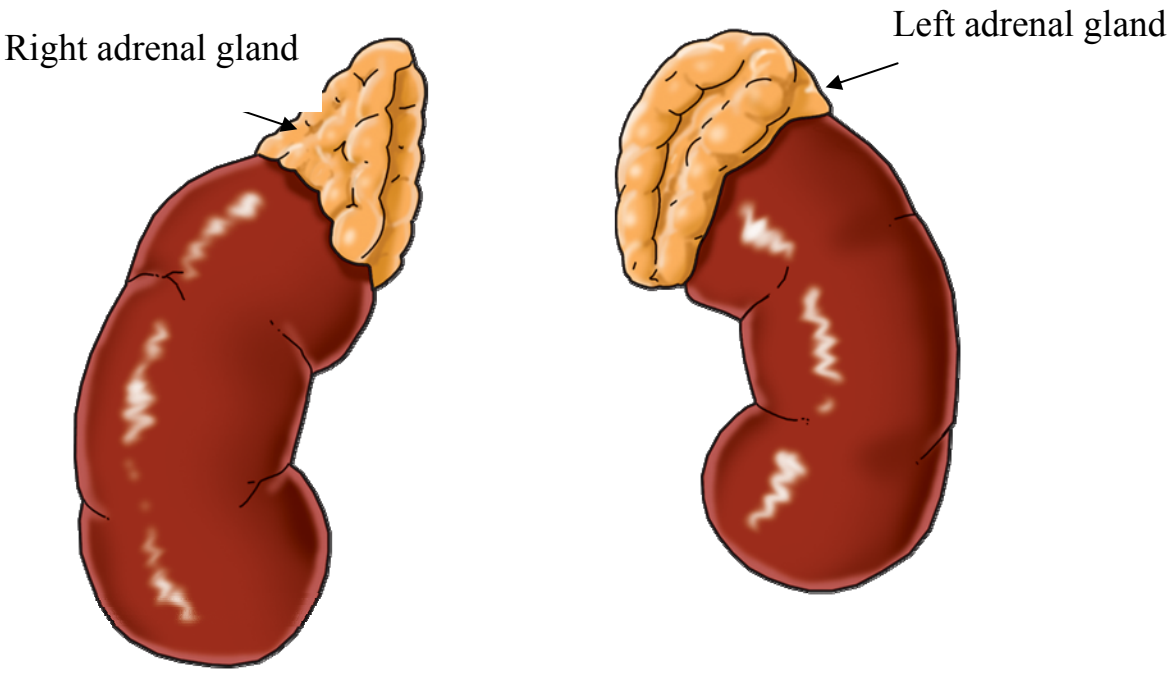
Biosynthesis

DHEA is the steroid hormone belonging to the weak androgens. DHEA and DHEA-S are the major C_{19} steroids produced from cholesterol by the zona reticularis of the adrenal cortex (Fig.2). DHEA is also produced in small quantities in the gonads (testis and ovary[3,8,14]), in adipose tissue and in the brain. From this point of view DHEA belongs to the neurosteroids[22].

Fig.2: Adrenal glands



Cut section of adrenal gland



DHEA is produced from cholesterol with the help of two cytochrome P450 enzymes. Cholesterol is converted into pregnenolone by the enzyme P450scc (side chain cleavage). Another enzyme, P450c17 (17α-hydroxylase, 17,20 lyase), then converts pregnenolone to17α-hydroxypregnenolone and finally to DHEA[1] (Fig.3).
DHEA is structurally similar to, and is a precursor of androstenedione, testosterone, etradiol and estrone.

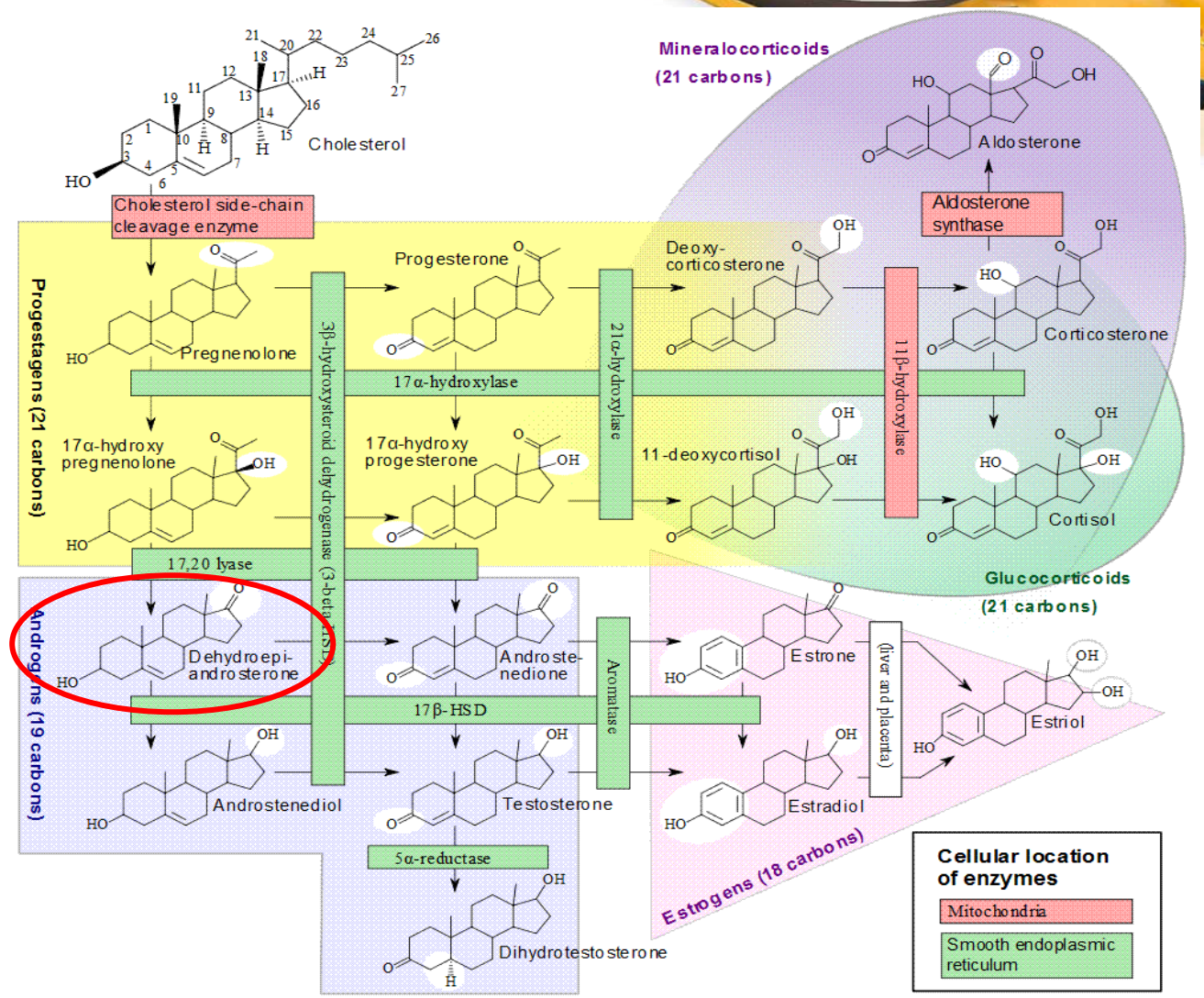


Fig.3: Steroidogenesis

The production of DHEA and DHEA-S is regulated by adrenocorticotropin (ACTH). Corticotropin-releasing hormone (CRH), and to a lesser extent arginine vasopressin (AVP), stimulate the release of ACTH from the anterior pituitary gland (Fig.4). In turn, ACTH stimulates the adrenal cortex to secrete DHEA and DHEA-S, in addition to cortisol. Negative feedback on CRH, AVP, and ACTH production is provided by cortisol. However there is no evidence that DHEA and DHEA-S use feedback on the hypothalamic-pituitary-adrenal (HPA) axis.

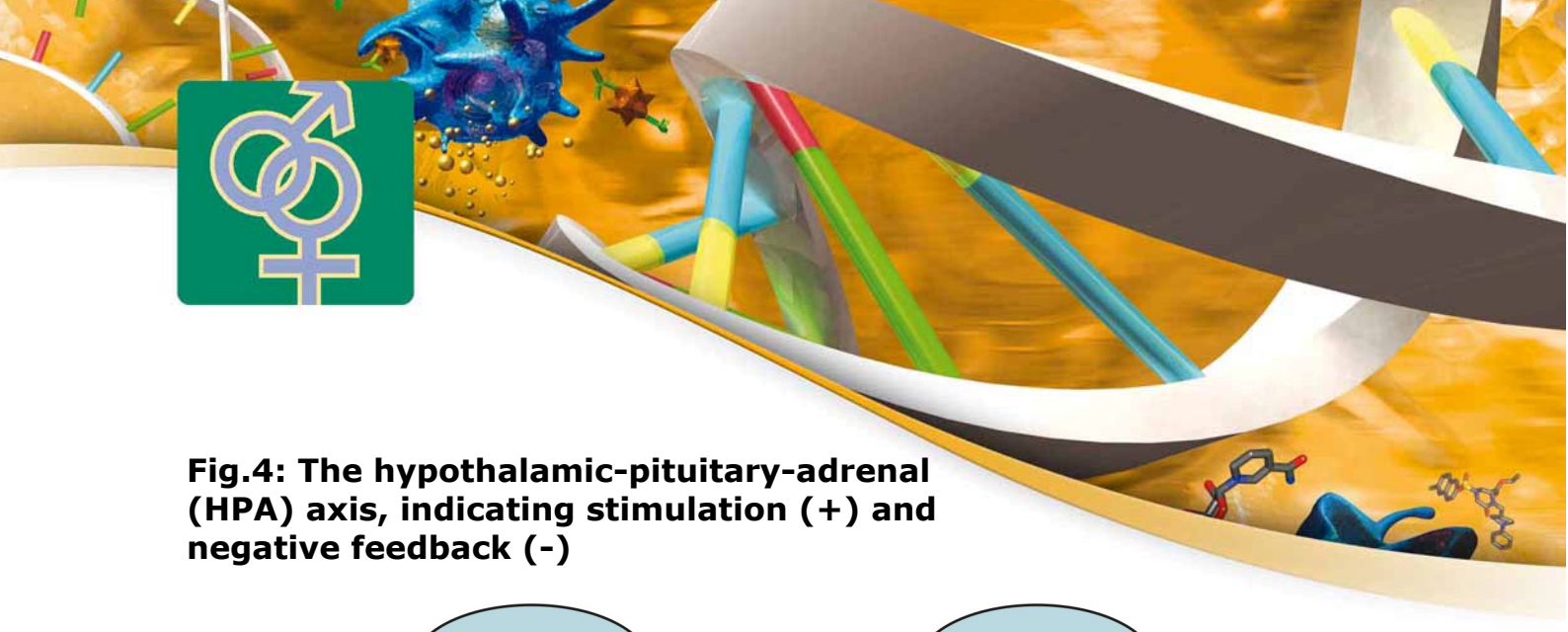
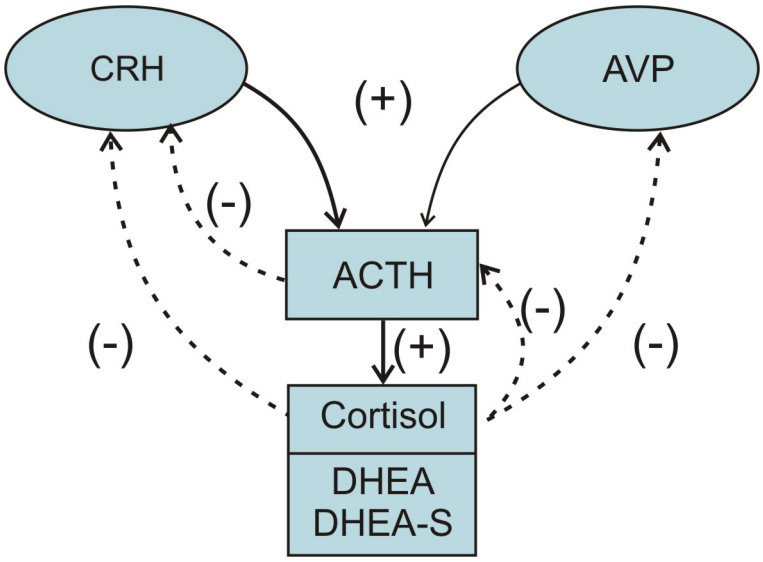


Fig.4: The hypothalamic-pituitary-adrenal (HPA) axis, indicating stimulation (+) and negative feedback (-)

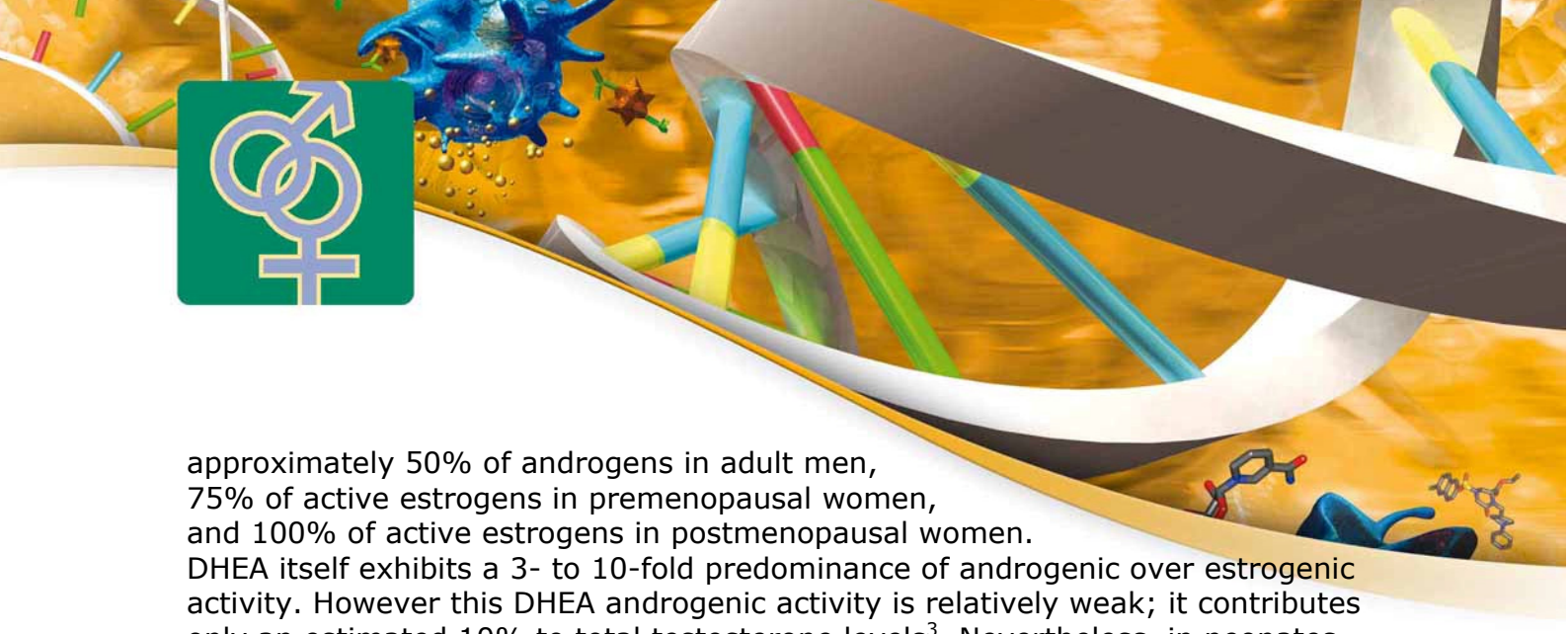


Metabolism

DHEA serves as a major precursor in testosterone and estrogen synthesis. DHEA is converted into potent androgens and/or estrogens in peripheral tissues[2,4,5].
DHEA can be converted into DHEA-S and DHEA-S back to DHEA. The sulfation is reversibly catalyzed by sulfotransferase (SULT2A1) primarily in the adrenals, the liver, and the small intestine. DHEA-S can be back-converted to DHEA through the action of steroid sulfatase.
DHEA is partially metabolized into 7β-hydroxydehydroepiandrosterone (7β-OH-DHEA) and its 7α-hydroxyisomer (7α-OH-DHEA).
DHEA has relatively low affinity for albumin and sex-hormone binding globulin (SHBG).
The half-life of DHEA is 15–30 min, with a metabolic clearance rate (MCR) of 2,000 L/day.
DHEA is excreted in urine mainly as sulfate, one of three most common 17-ketosteroides.

Physiological Function

The physiological role of DHEA has not been conclusively defined[15,16]. DHEA can be understood as the prohormone for the sex steroids (testosterone and estrogens). Together, DHEA and DHEA-S serve as the precursors to



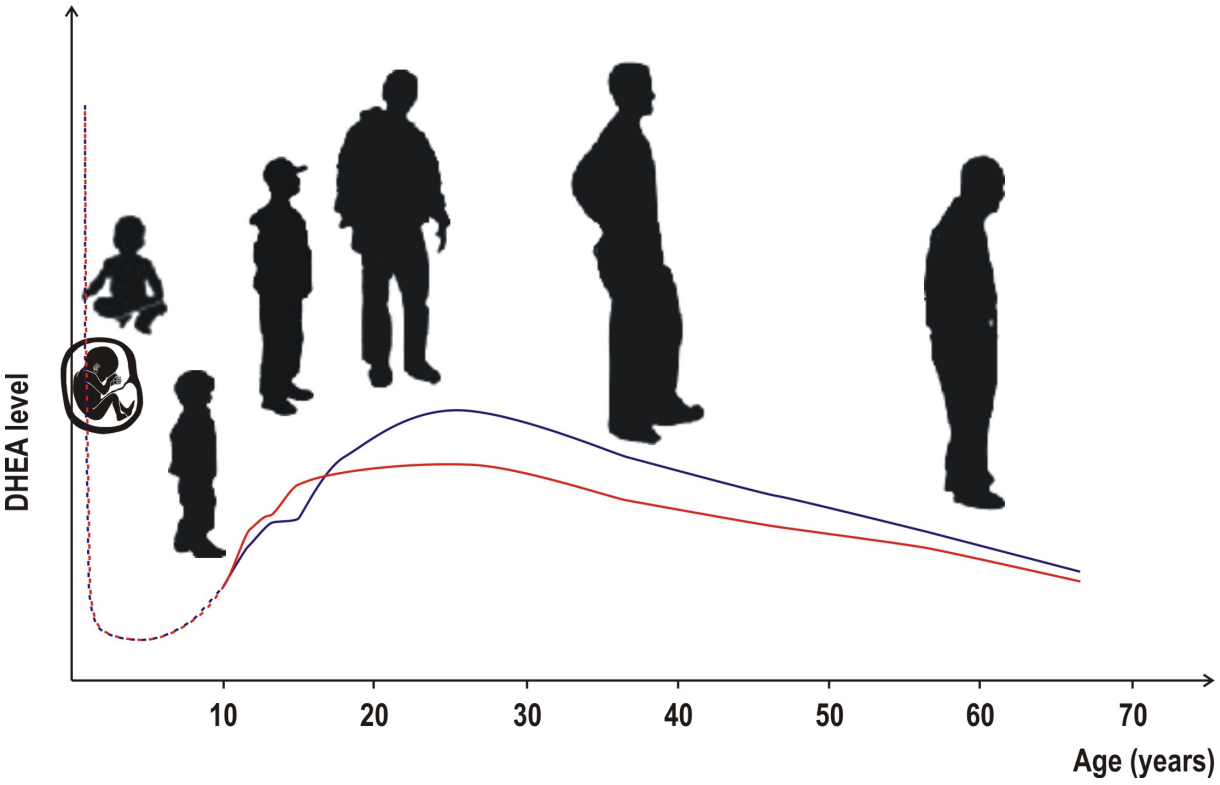
approximately 50% of androgens in adult men,
75% of active estrogens in premenopausal women,
and 100% of active estrogens in postmenopausal women.
DHEA itself exhibits a 3- to 10-fold predominance of androgenic over estrogenic activity. However this DHEA androgenic activity is relatively weak; it contributes only an estimated 10% to total testosterone levels[3]. Nevertheless, in neonates, children and adult women, circulating DHEA levels may be several times higher than those of testosterone, and rapid peripheral tissue conversion to more potent androgens (androstenedione and testosterone) and estrogens may occur. In addition, DHEA has a relatively low affinity for sex-hormone binding globulin. These factors may increase the physiologic biopotency of DHEA.
DHEA may have either estrogenic or androgenic effects depending on the organism surroundings. For example, in male androgenic surroundings, DHEA functions as estrogen, protecting the cardiovascular system. DHEA becomes involved in lipid production, mitochondrial respiration and protein synthesis, and influences the functioning of thyroidal hormones[9,11]. DHEA has an anti-ageing effect, increases immunity[10,11]. Its retarding effect on various diseases has been described (e.g. diabetes mellitus, some cancerous tumors and circulatory system diseases)[9]. Immune-system stimulation is caused by some DHEA metabolites[12]. From this point of view, the beneficial effects of DHEA may be characterized as anticancerotic, antisclerotic, antidiabetic, antiobese and immunostimulatory or immunoprotective.
DHEA is used as a supplement to mitigate symptoms of menopause in some countries.

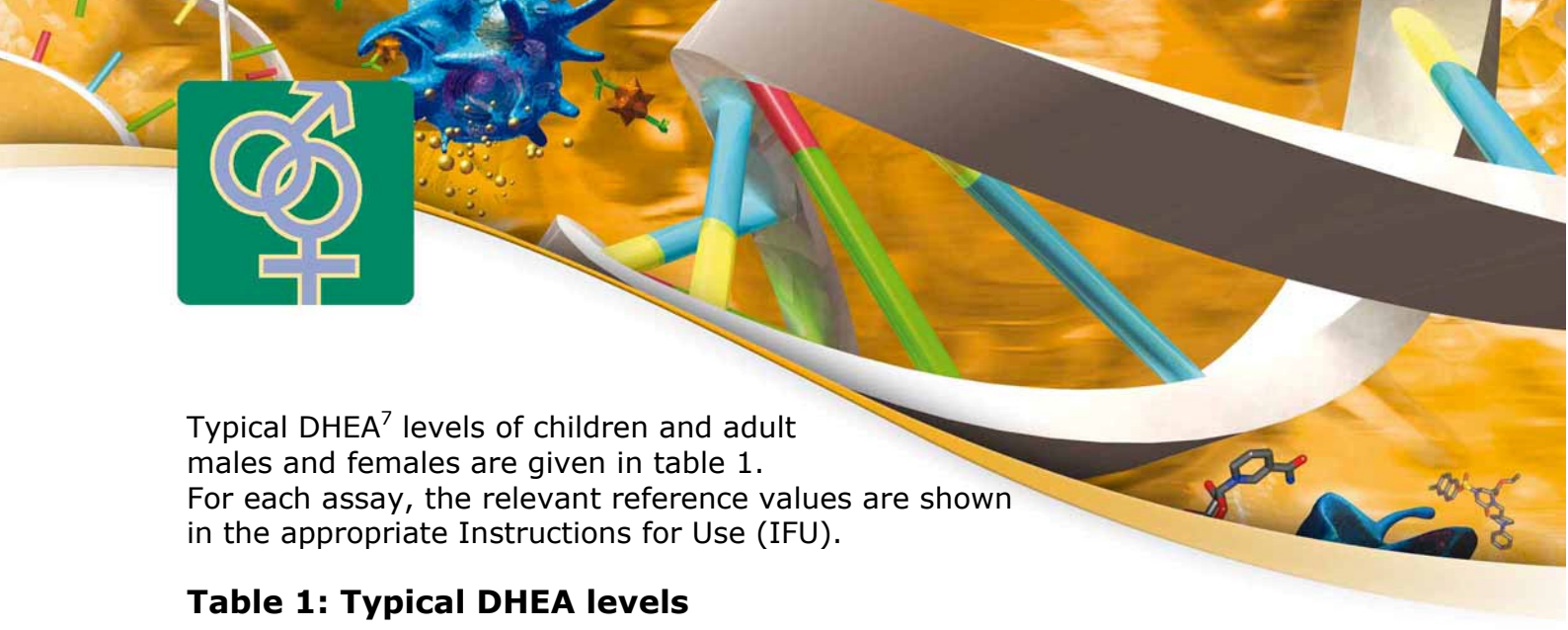
Levels

DHEA, together with DHEA-S, is the most abundant steroid in humans. The typical feature of DHEA is a decline in levels with age.
Serum DHEA levels are relatively high in the fetus and neonates, are low during childhood, and increase during puberty[17,18]. The fetal adrenal glands secretes DHEA in large quantities. This serves as a precursor in placental production of the dominant pregnancy estrogen – estriol. In the weeks after birth, DHEA levels fall by 80% or more and remain low until the onset of adrenarche at age 7 - 8 (in girls) or age 8 - 9 (in boys). At the onset of adrenarche, the adrenal glands gradually resume DHEA production, which accelerates through puberty. The adrenal cortex secretes approximately 4 mg of DHEA and 25 mg of DHEA-S per day in young adults. Maximal values of circulating DHEA are reached between the ages of 20 and 30 years. Thereafter serum DHEA levels decrease markedly[4,6,20] at a rate of 2% per year. By the eighth or ninth decade of life, serum levels are at 10 – 20% of those during peak production years. This age-associated decrease in DHEA secretion has been named adrenopause, despite the fact that only DHEA production declines, whereas glucocorticoids and mineralocorticoids continue to be secreted without considerable variance.

DHEA has a metabolic clearance rate approximately
100 times higher than that of DHEA-S. Because of this,
serum DHEA levels are 250 - 500 times lower than DHEA-S levels.
In addition, serum DHEA levels exhibit significant diurnal variation, with the highest concentrations in the morning, and are dependent on adrenocorticotropic hormone (ACTH)[15,19].
The menstruation cycle does not significantly affect DHEA production.

Fig.5: Changes of DHEA levels during the life cycle



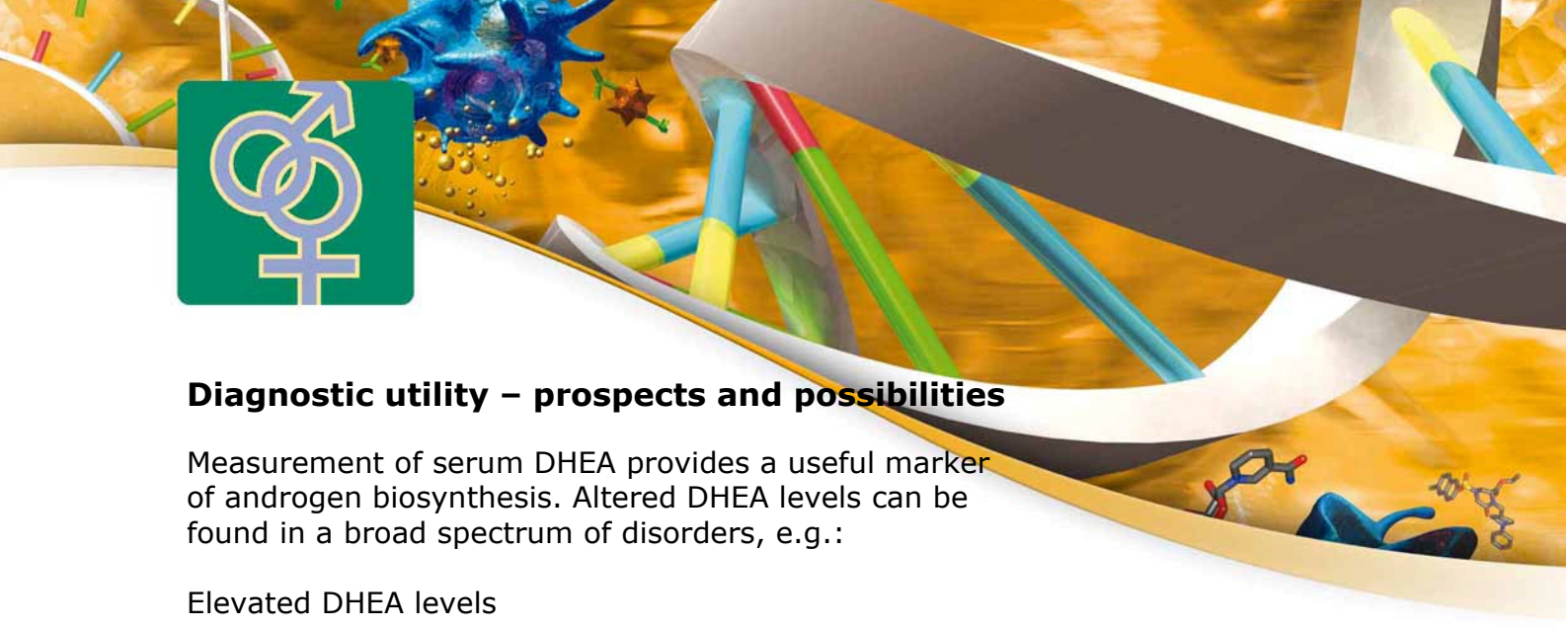


Typical DHEA[7] levels of children and adult males and females are given in table 1.
For each assay, the relevant reference values are shown in the appropriate Instructions for Use (IFU).

Table 1: Typical DHEA levels

Specimen (serum)	**Reference interval** (ng/mL)
Cord:	2.00 – 15.9
Premature:	0.80 – 31.5
New born (3 days):	0.65 – 12.5
1-30 days:	0.50 – 7.60
1 -6 months:	0.26 – 3.85
6 – 12 month:	0.18 – 0.95
1 – 6 years:	0.29
6 – 8 years:	0.93
Puberty Tanner stage:	
Stage I	
male, female:	0.31 – 3.45
Stage II	
male:	1.10 – 4.95
female:	1.50 – 5.70
Stage III	
male:	1.70 – 5.85
female:	2.00 – 6.00
Stage IV	
male:	1.60 – 6.40
female:	2.00 – 7.80
Stage V	
male:	2.50 – 9.00
female:	2.15 – 8.50
Adult	
male:	1.80 – 12.5
female:	1.30 – 9.80

Equation for the conversion of units: 1 ng/mLx3.47 = nmol/L



Diagnostic utility – prospects and possibilities

Measurement of serum DHEA provides a useful marker of androgen biosynthesis. Altered DHEA levels can be found in a broad spectrum of disorders, e.g.:

Elevated DHEA levels

- Congenital adrenal hyperplasia due to deficiency of 3β-dehydrogenase, 21-hydroxylase, or 11β-hydroxylase
- PCOS in women (Polycystic Ovary Syndrome)
- hirsutism
- virilizing adrenal tumors
- ectopic ACTH-producing tumor
- premature adrenarche
- Cushing's syndrome
- schizophrenia[21]
- obesity[13]

Decreased DHEA levels

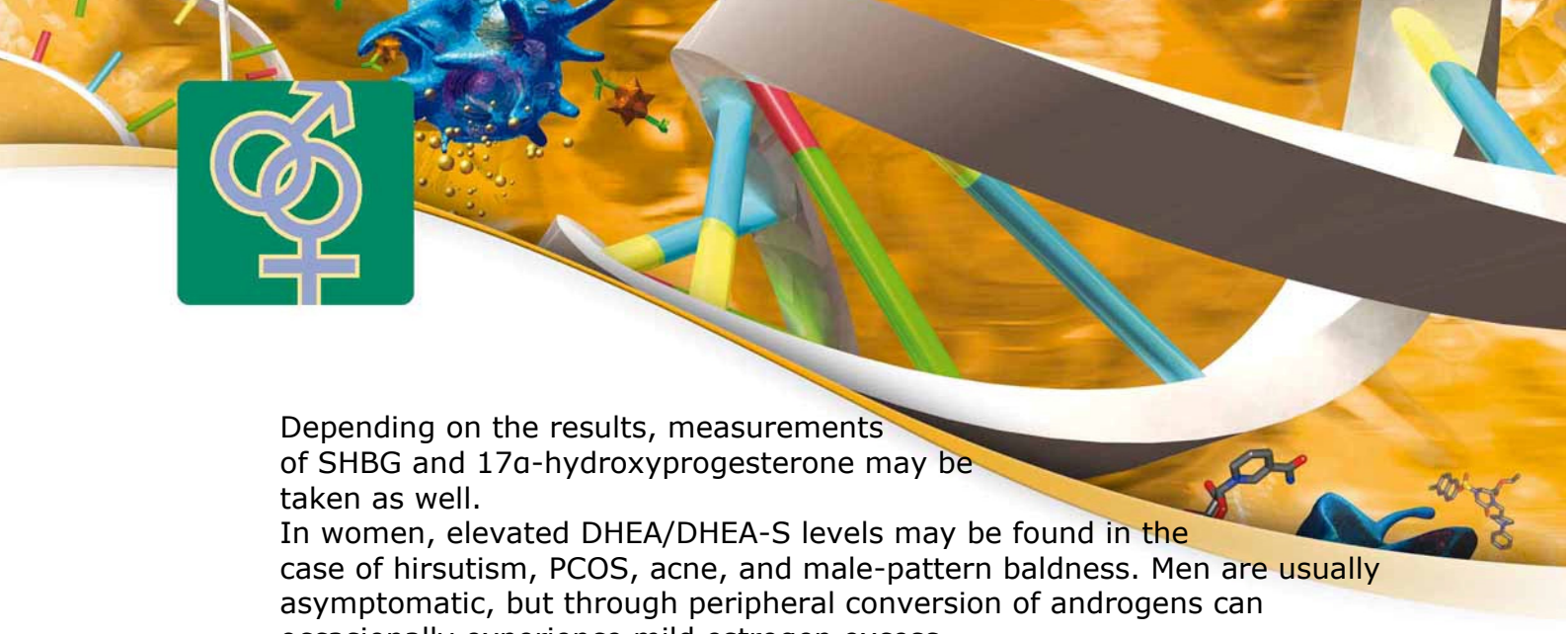
- hypoadrenalism (abnormally decreased activity of the adrenal glands)
- delayed puberty
- hyperlipidemia
- psychosis
- psoriasis

Diagnostic utility – Practical applications

Measurement of serum DHEA/DHEA-S levels is the useful marker of adrenal androgen synthesis. **Elevated DHEA-S/DHEA levels indicate increased adrenal androgen production.**

Diagnosing and differential diagnosis of hyperandrogenism

DHEA is measured in conjunction with other sex steroids. An initial screen in adults might include DHEA/DHEA-S and free testosterone measurement.



Depending on the results, measurements of SHBG and 17α-hydroxyprogesterone may be taken as well.
In women, elevated DHEA/DHEA-S levels may be found in the case of hirsutism, PCOS, acne, and male-pattern baldness. Men are usually asymptomatic, but through peripheral conversion of androgens can occasionally experience mild estrogen excess.

In the diagnosis of congenital adrenal hyperplasia (CAH)

DHEA is measured together with cortisol, 17α-hydroxyprogesterone and androstenedione.

Monitoring of Congenital adrenal hyperplasia (CAH) treatment

DHEA is measured in conjunction with testosterone, 17-OHP, androstenedione and DHEA-S. Congenital adrenal hyperplasia (CAH) due to 3β-dehydrogenase deficiency is associated with excessive DHEA/DHEA-S production. Lesser elevations may be observed in 21-hydroxylase deficiency (the most common form of CAH) and 11β-hydroxylase deficiency.

Diagnosis and differential diagnosis of premature adrenarche

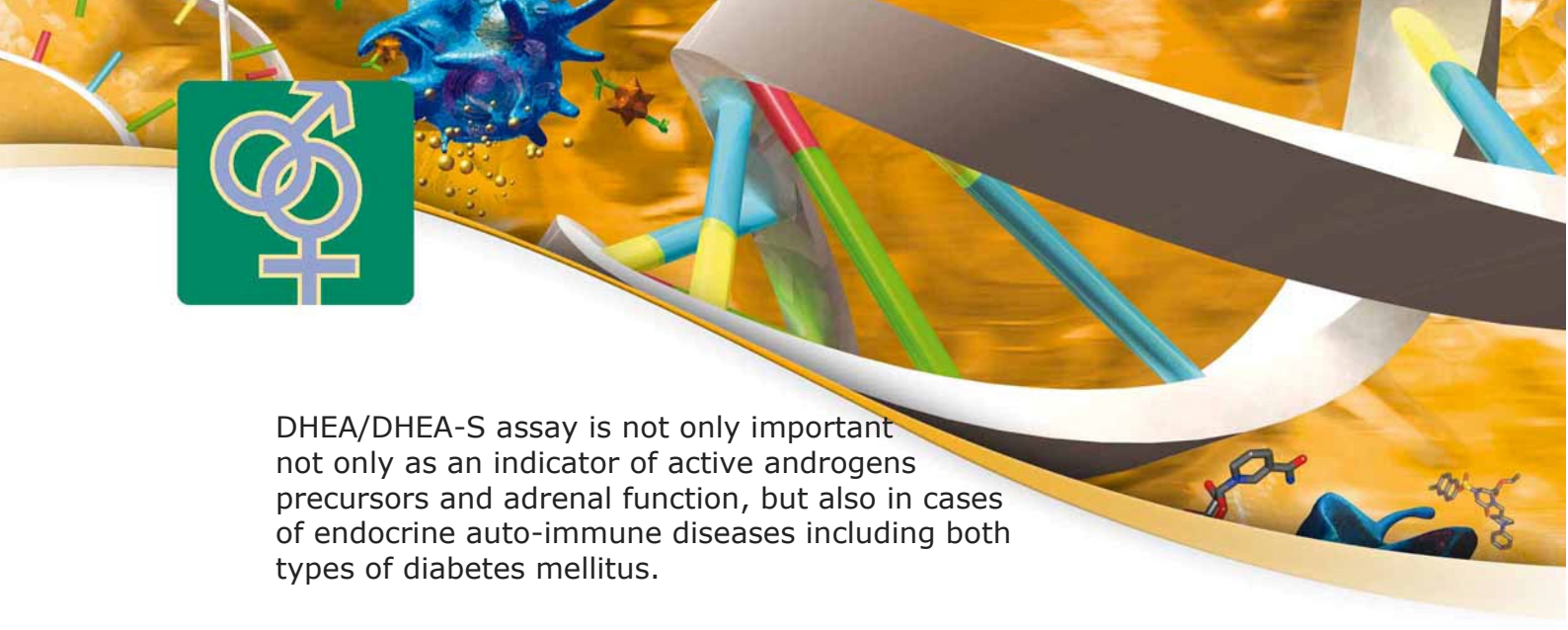
DHEA is measured in conjunction with FSH, LH, testosterone, free testosterone, 17-OHP, estradiol, DHEA-S, androstenedione and SHBG. Increased levels of DHEA/DHEA-S during adrenarche may indicate increased risks. In girls, early adrenarche may increase the risk of later polycystic ovary syndrome. In boys, early penile enlargement may develop.

Diagnosis of androgen-secreting adrenal tumor

Elevated DHEA/DHEA-S levels indicate increased adrenal androgen production. Mild elevations in adults are usually idiopathic, but levels five or more times higher than normal may suggest the presence of an androgen-secreting adrenal tumor. DHEA/DHEA-S levels are elevated in more than 90% of patients with such tumors. Carcinomas typically lack the ability to produce downstream androgens, such as testosterone; by contrast, androgen-secreting adrenal adenomas may also produce excess testosterone and secrete lesser amounts of DHEA/DHEA-S.

Others

Low DHEA/DHEA-S levels may be found in cases of deficiency of steroidogenic acute regulatory protein (StAR – a transport protein that regulates cholesterol transfer within the mitochondria) or of 17α-hydroxylase.



DHEA/DHEA-S assay is not only important not only as an indicator of active androgens precursors and adrenal function, but also in cases of endocrine auto-immune diseases including both types of diabetes mellitus.

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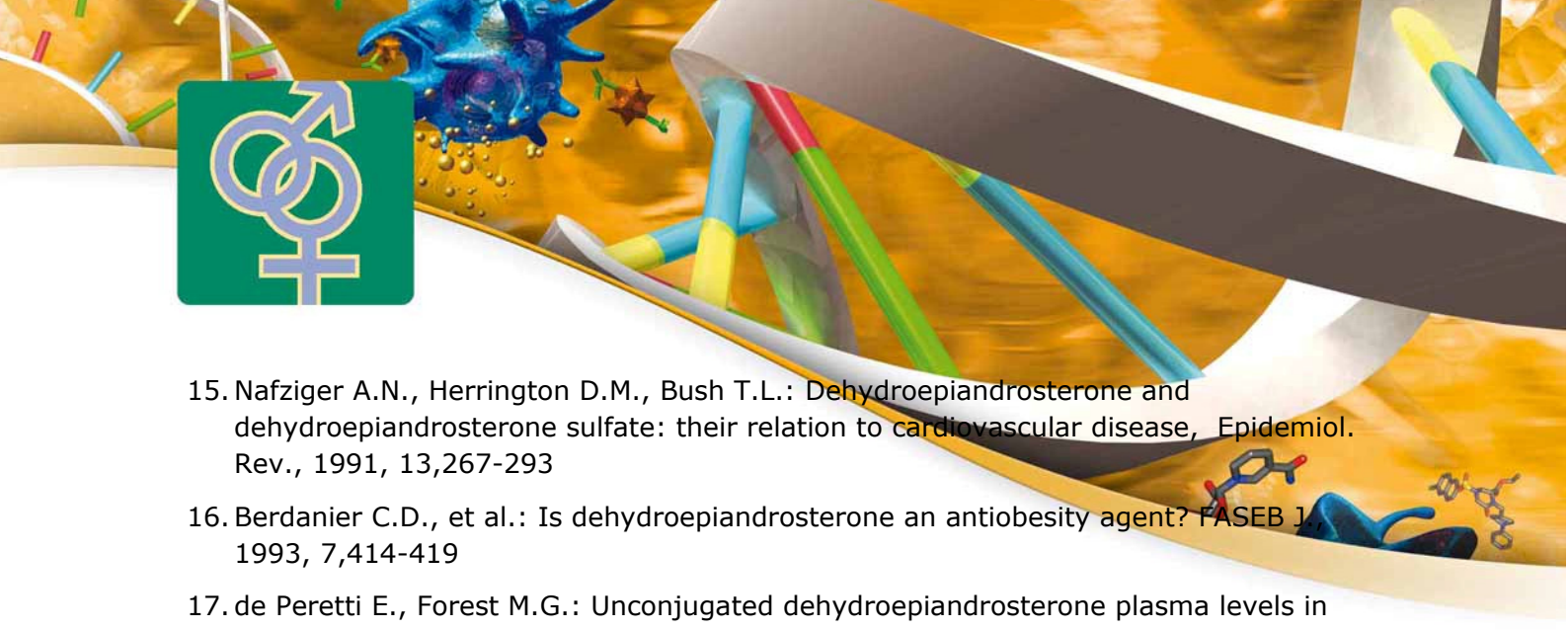

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