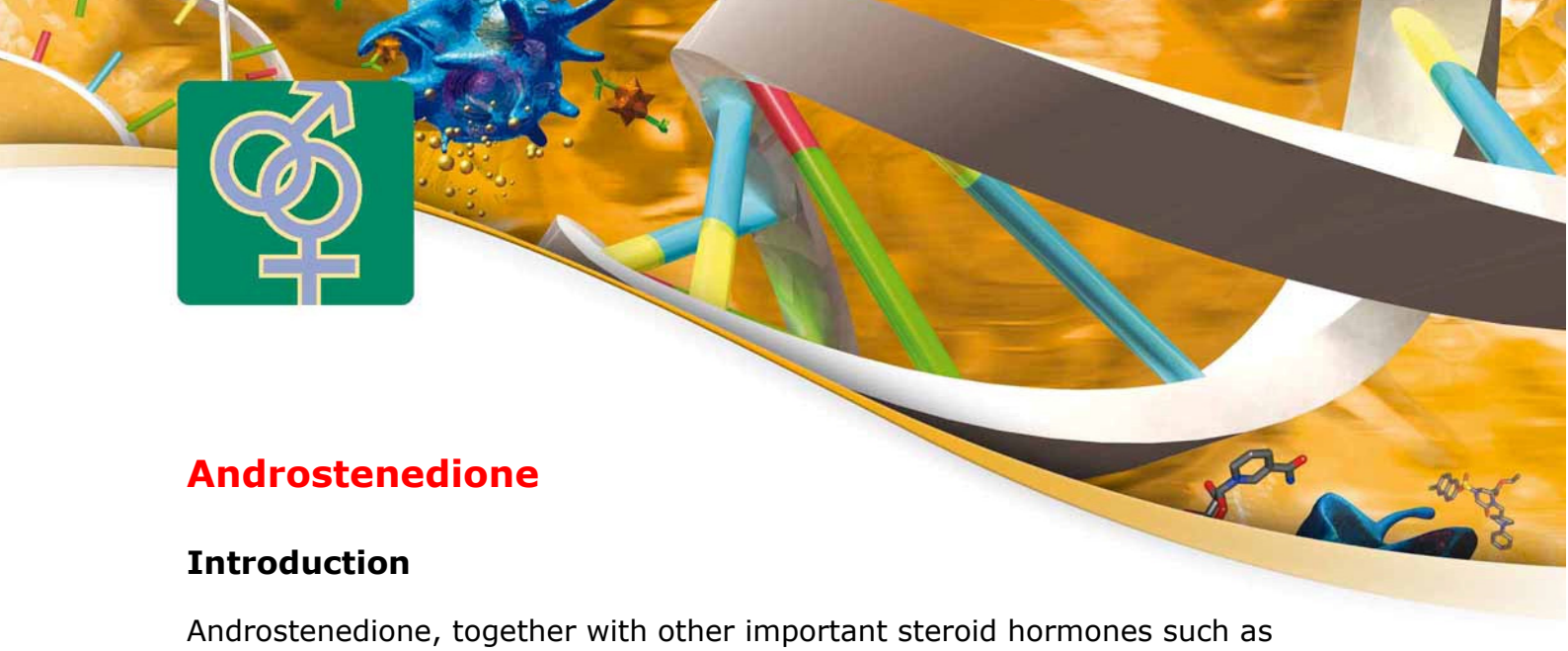
Reproductive

Androstenedione

Analyte Information

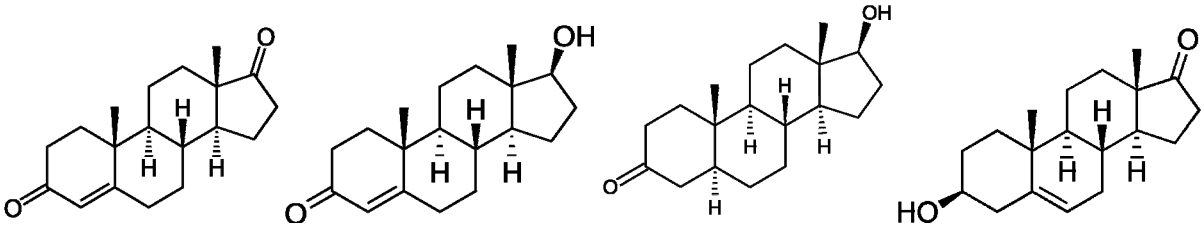


Androstenedione

Introduction

Androstenedione, together with other important steroid hormones such as Testosterone, DHT (Dihydrotestosterone) and DHEA (Dehydroepiandrosterone) belongs to the group of Androgens. It is is the common precursor of both male and female sex hormones.

Androstenedione is a C_{19} steroid hormone (chemical name 4-Androsten-3,17-dione, summary formula $C_{19}H_{26}O_2$, molecular weight (Mr) 286.4 Da. The structural formulas of androstenedione and related adrogens are shown below:



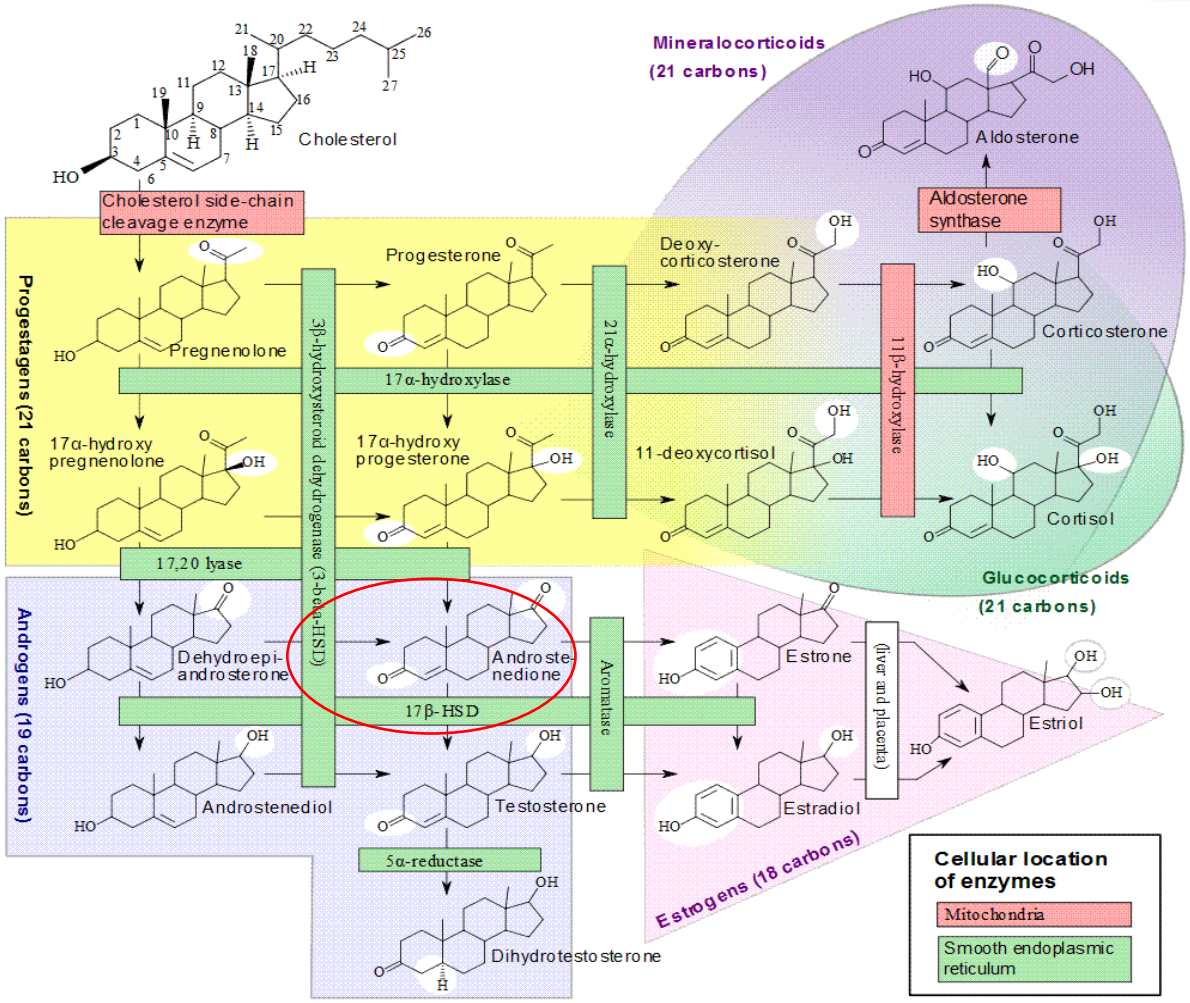
Androstenedione Testosterone Dihydrotestosterone Dehydroepiandrosterone

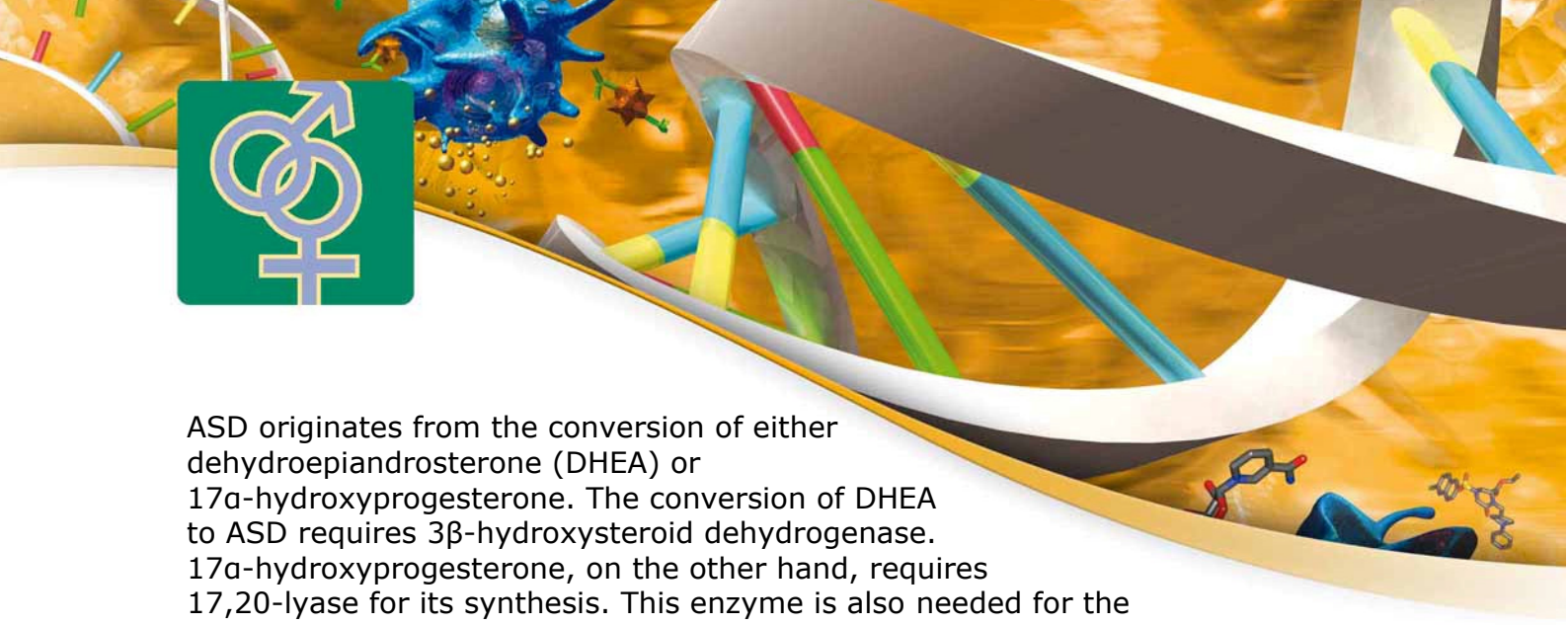
Androstenedione can be found under the following names: ASD, 4-Androstenedione, delta-4-Androstenedione, 3,17-Dioxoandrost-4-ene, 17-Ketotestosterone, Soft-ANST.

Biosynthesis

ASD is produced by the adrenals and gonads as the intermediate step in the biochemical pathway that produces the androgen testosterone and the estrogens estrone and estradiol.

Fig. 1 – Steroidogenesis



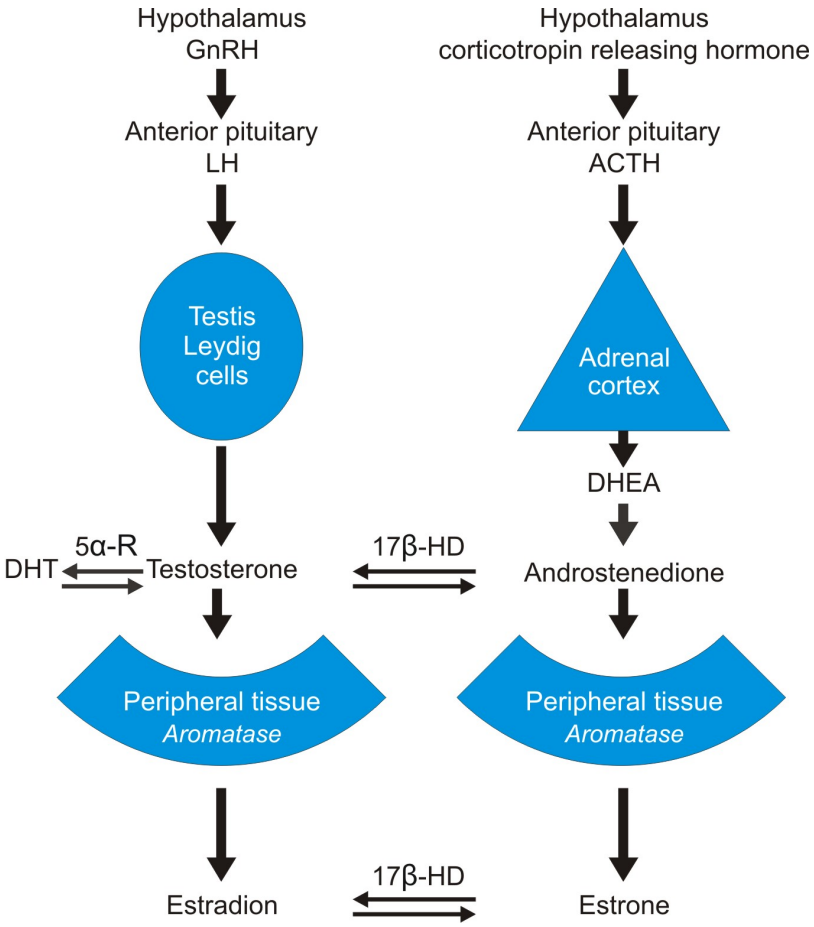


ASD originates from the conversion of either dehydroepiandrosterone (DHEA) or 17α-hydroxyprogesterone. The conversion of DHEA to ASD requires 3β-hydroxysteroid dehydrogenase. 17α-hydroxyprogesterone, on the other hand, requires 17,20-lyase for its synthesis. This enzyme is also needed for the synthesis of DHEA from 17α-hydroxypregnenolone. Thus both reactions that produce ASD directly or indirectly depend on 17,20-lyase.

ASD is further converted to either testosterone or estrogens. Conversion of ASD to testosterone requires the enzyme 17β-hydroxysteroid dehydrogenase (17β-HSD), while conversion of ASD to estrogens (e.g. estrone and estradiol) requires the enzyme aromatase.

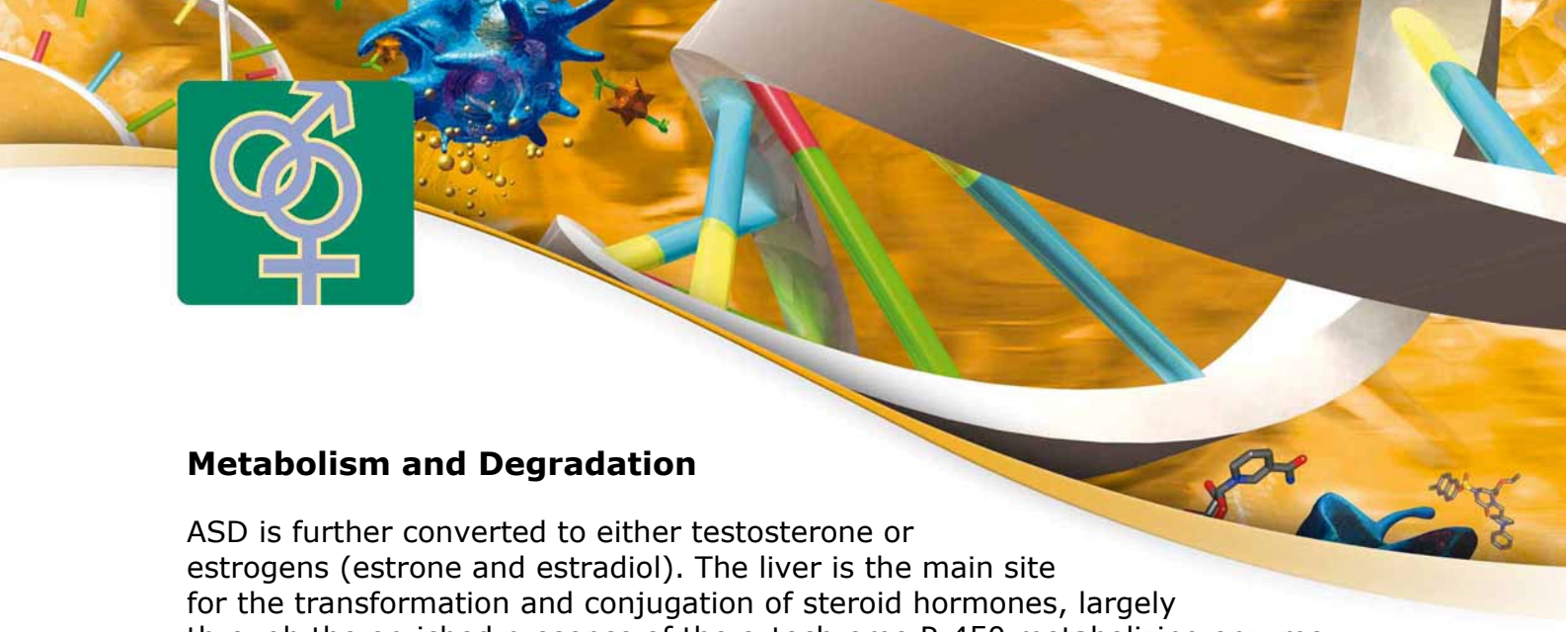
The production of adrenal ASD is governed by the adrenocorticotropic hormone (ACTH), whereas production of gonadal ASD is controlled by gonadotropins. In males, ASD is secreted primarily by the testes, and to some extent (about 2% of total production) in the adrenal cortex. The enzyme 17β-HSD regulates the balance between androstenedione and testosterone. The luteinizing hormone (LH) binds to Leydig cells and stimulates the production of testosterone. The follicle-stimulating hormone (FSH) increases the response of Leydig cells to LH by increasing the number of LH receptors expressed on Leydig cells. Leydig cells are found adjacent to the seminiferous tubules in the testes and they secrete testosterone, ASD and DHEA, when stimulated by the pituitary hormone LH. LH increases cholesterol 20,22-desmolase activity (a mitochondrial enzyme associated with the conversion of cholesterol to pregnenolone and known also as cytochrome P-450scc , where ”scc” refers to side-chain cleavage), leading to testosterone synthesis and secretion by Leydig cells.

Fig. 2 – Androstenedione in males



GnRH	Gonadotropin releasing hormone
DHT	Dihydrotestosterone
5α-R	5-alpha reductase
17β-HD	17-beta hydroxysteroid dehydrogenase
LH	Lutenaizing hormone
DHEA	Dihydroepiandrosterone
ACTH	Adrenocorticotropin hormone

In premenopausal women, the adrenal glands and ovaries each produce about half of the total ASD (about 3 mg/day). After menopause, ASD production is decreased by approximately 50%, primarily due to a reduction in ovarian secretion. Nevertheless, ASD is the principal steroid produced by the postmenopausal ovary. Ovarian ASD production is stimulated by luteinizing hormone (LH) and thus serum ASD levels vary with the menstrual cycle[3]. Adrenal ASD production gradually declines with advanced age in both men and women.



Metabolism and Degradation

ASD is further converted to either testosterone or estrogens (estrone and estradiol). The liver is the main site for the transformation and conjugation of steroid hormones, largely through the enriched presence of the cytochrome P-450 metabolizing enzyme systems. Thus the liver is the major androgen-neutralizing organ, and it is there that the steroid hormones undergo the structural modifications generally regarded as prerequisites for their biological inactivation. Approximately 90% of conjugated steroids released by the liver are excreted by the kidney[13,14].

Physiological Function

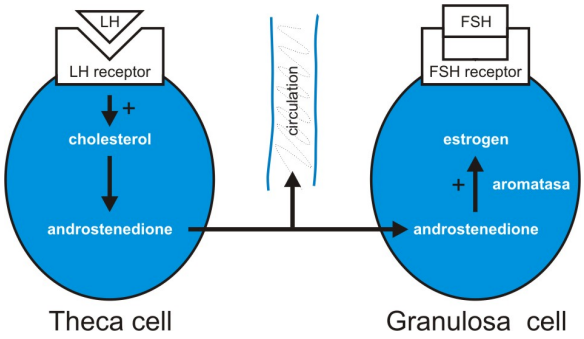
ASD is the immediate precursor to both testosterone and estrone, both of which may be subsequently converted to estradiol. Due to the presence of a 17-oxo (rather than hydroxyl) group, ASD has relatively weak androgenic activity, approximately less than 20% of testosterone activity[1]. Although it is a weak androgen, the serum ASD levels may exceed testosterone levels in both normal and disease states. ASD secretion and production rates exceed those of testosterone in women, and significant extra-adrenal conversion of ASD to testosterone occurs. Androstenedion, like other steroids, can be bound to carrier proteins. In circulation it can be found weakly bound to albumin. The affinity of sex hormone-binding globulin (SHBG) for ASD is much less than for testosterone or estradiol[1-3]. The physiologic role of ASD is not well defined.

In normal pubertal and adult men, the major portion of ASD is produced in the testis, either directly or by the conversion of testosterone, while in normal adult women essentially equivalent amounts of ASD are produced by the adrenal gland and ovary[2,3]. Increased ASD levels may play a role in the development of secondary sexual hair during adrenarche.

The side effects experienced by males taking (supplementary) ASD are enlarged breasts, enlarged prostate and increased risk of prostate cancer[5,15].

In females, androstenedione is released into the blood by theca cells of ovarian follicles. This serves to provide an androstenedione substrate for production of estrogen in granulosa cells, since these cells lack the 17,20-lyase required for androstenedione. Similarly theca cells lack the enzyme aromatase required to make estrogens themselves. Thus, theca cells and granulosa cells work together to form estrogen[10].

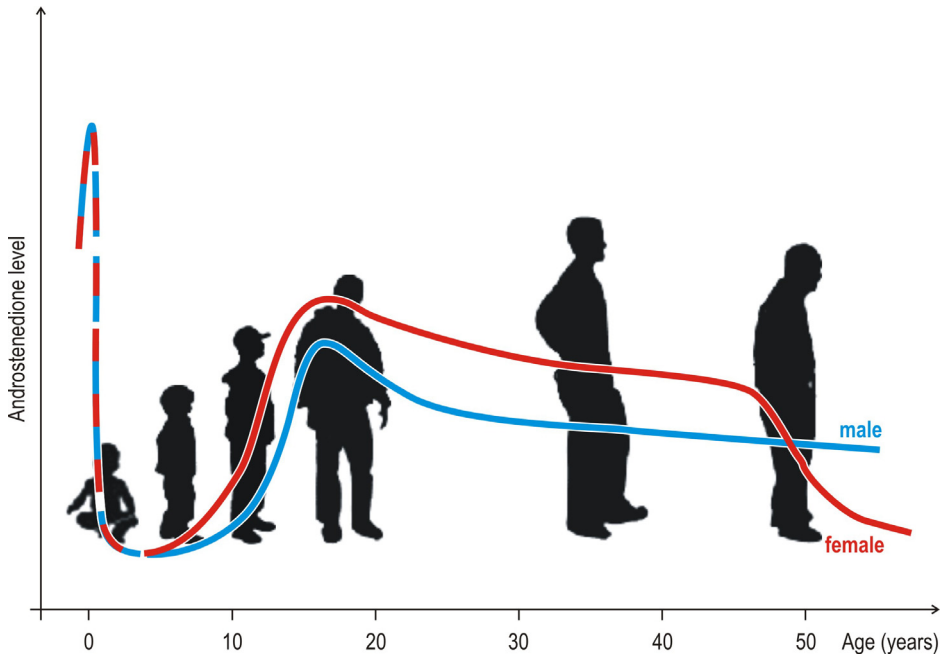
Fig. 3 – Androstenedione as a substrate for estriol production in females



Levels

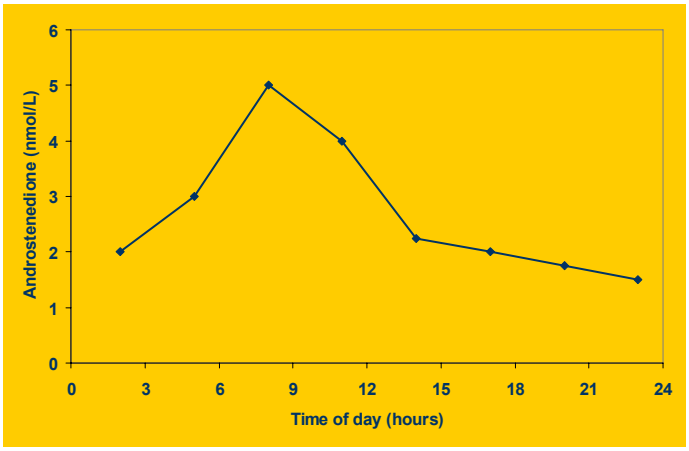
Serum ASD levels are high in fetal and neonatal serum, decrease during childhood, and increase during puberty.

Fig.4 – Changes of ASD levels during the life cycle



Serum ASD levels show significant diurnal variation dependent on the secretion of ACTH, peaking in the morning. ADS serum levels vary cyclically during the menstrual cycle as well, peaking near midcycle[3]. During pregnancy an increase in plasma levels occures[16].

Fig.5. – Circadian variations of ASD levels[17]

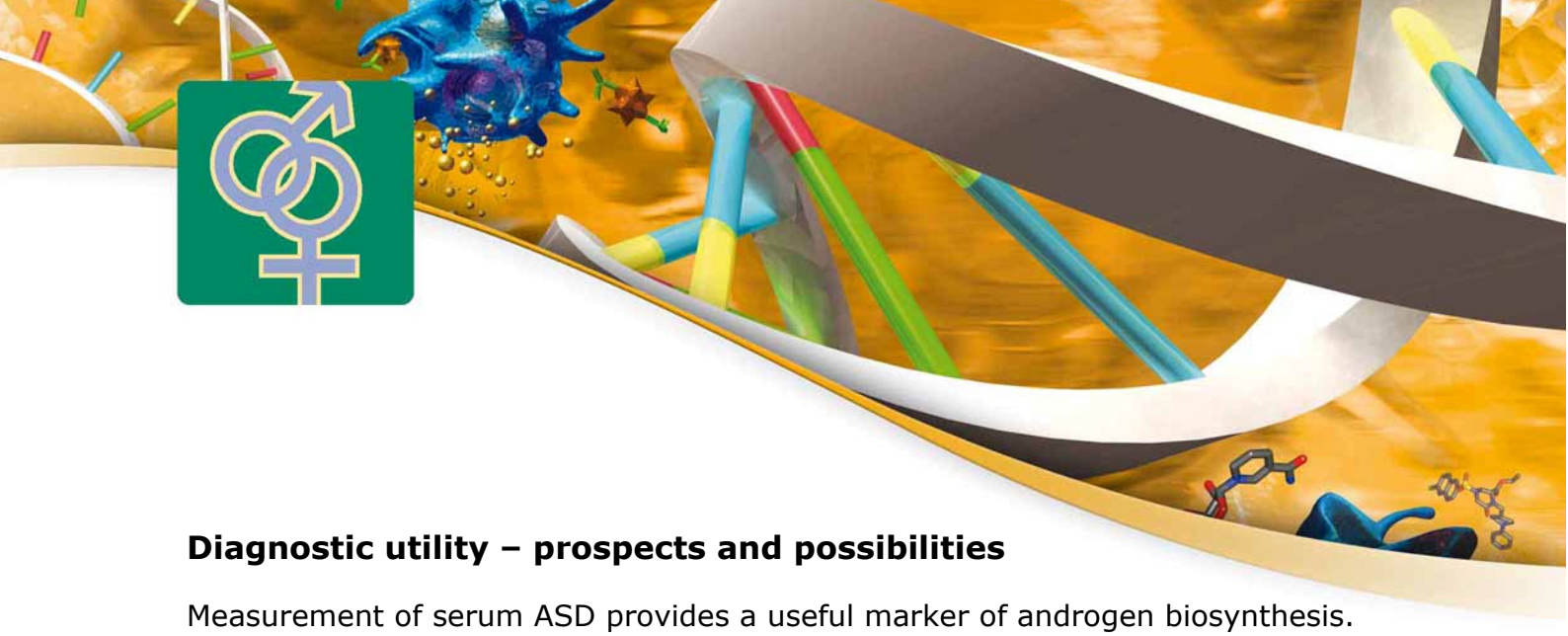


The following table shows sample reference intervals of ASD levels taken from the Tietz Textbook of Clinical Chemistry[13]. These are strictly for informational purposes, as appropriate reference levels vary according the assay used.

For each assay, the relevant reference values are shown in the appropriate Instructions for Use (IFU).

Specimen (serum)	**Reference interval** (ng/mL)
Cord:	0.30 – 1.50
Premature:	0.80 – 4.46
Newborn: (1-7 days):	0.20 – 2.90
1-12 months	0.06 – 0.68
Prepubertal (1-10 years):	0.08 – 0.50
Puberty (10-17 years): (varies with Tanner stage and sex)	0.08 – 2.40
Adult:	
Male:	0.75 – 2.05
Female (collected at least 1 week before or 1 week after menstrual period)	0.85 – 2.75

Equation for the conversion of units: 1 ng/dL = 0.0349 nmol/L



Diagnostic utility – prospects and possibilities

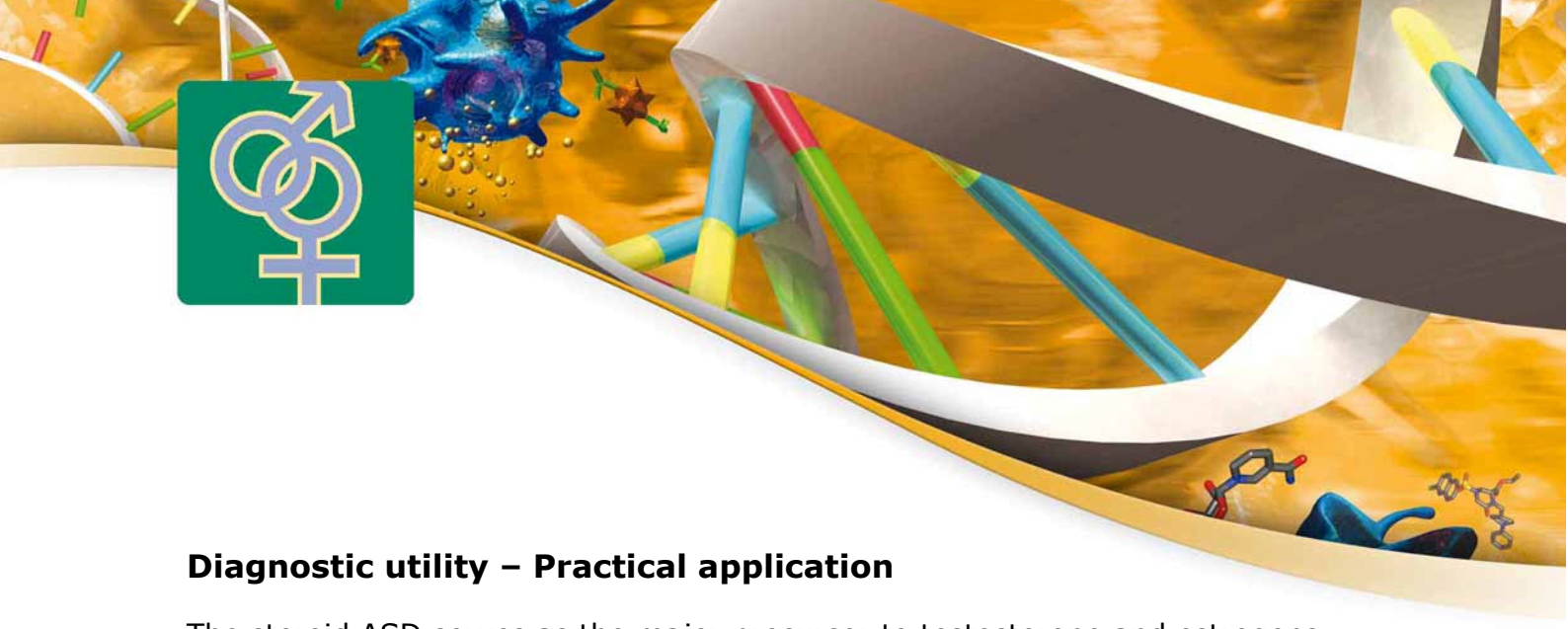
Measurement of serum ASD provides a useful marker of androgen biosynthesis. Abnormal ASD levels can be found throughout a broad spectrum of disorders, including:

Elevated androstenedione levels

- idiopathic increase of ASD
- PCOS in women (Polycystic Ovary Syndrome)
- hirsutism
- congenital adrenal hyperplasia – CAH (depends on cause)
- Cushing´s syndrome
- ACTH-producing tumor
- androgen-secreting adrenal tumor (benign/carcinoma)
- androgen-secreting gonadal tumor (benign/carcinoma)
- hyperplasia of ovarian stroma or tumor
- osteoporesis in females
- premature adrenarche
- premature puberty
- use of androstenedione supplements
- use of drugs such as corticotropine, clomiphene, cyproterone acetate, levonorgestrel, metyrapone

Decreased androstenedione levels

- 17-alpha hydroxylase deficiency
- sickle-cell anemia
- adrenal failure
- ovarian failure
- corticosteroids such as dexamethasone



Diagnostic utility – Practical application

The steroid ASD serves as the major precursor to testosterone and estrogens. Determination of serum ASD levels is important in the evaluation of the functional state of adrenals and gonads. Its clinical interest derives from the fact that it is often elevated in cases of abnormal hair growth (hirsutism)[6,7] and virilization.

Androstenedione determination is utilized particularly for:

Diagnosis and differential diagnosis of hyperandrogenism
in conjunction with measurement of free testosterone and testosterone and, if needed, with SHBG and androgenic steroids as DHEA-S

Diagnosis of CAH (Congenital Adrenal Hyperplasia)
in conjunction with 17-OHP (17-alpha-hydroxyprogesterone), DHEA-S and cortisol

Monitoring of CAH treatment
in conjunction with testosterone, 17-OHP, DHEA-S and DHEA

Diagnosis of premature adrenarche
in conjunction with FSH, LH, testosterone, free testosterone, 17-OHP, estradiol, DHEA-S, DHEA and SHBG

References

1. Dorfman R.I., Shipley R.A.: Androgens., John Wiley and Sons, New York, 1956, 116-128.
2. Horton R., Tait J.: Androstenedione production and interconversion rates measured in peripheral blood and studies on the possible site of its conversion to testosterone. J. Endocrinol. Invest., 1966, 45,301-313.
3. Pang S., Riddick L.: Hirsutism. IN Lifshitz F (ed): Pediatric Endocrinology, A Clinical Guide, second edition. Marcel Dekker, Inc., New York, 1990, 259-291.
4. Cavallo A., Corn C., Bryan G.T., Meyer W.J. III: The use of plasma androstenedione in monitoring therapy of patients with congenital adrenal hyperplasia. J. Pediatr., 1979, 95, 33-37.
5. Barrett-Connor E., Garland C., McPhillips J.B., Khaw K.-T., Wingard D.L.: A prospective, population-based study of androstenedione, estrogens, and prostate cancer. Canc. Res., 1990, 50, 169-173.
6. Rittmaster R.S., Thompson D.L.: Effects of leuprolide and dexamethasone on hair growth and hormone levels in hirsute women: The relative importance of the ovary and adrenal in the pathogenesis of hirsutism. J. Clin. Endocrinol. Metab., 1990, 70, 1096-1102.
7. Zwicker H., Rittmaster R.S.: Physiology and significance in hirsute women. J. Clin. Endocrinol. Metab.,1993, 76, 112-116.
8. Rosen M. Nouri N., Alexander L.: Evaluation of a direct assay for the measurement of androstenedione. Clin. Chem.,1987, 33, 891.
9. Yalow R., Berson S.: Odell WD and Daughaday WH, eds. Principles of Competitive Protein Binding Assays. J.B. Lippincott Co., Philadelphia, 1971, 1-19.
10. Medical Physiology, Boron & Boulpaep, ISBN 1-4160-2328-3, Elsevier Saunders 2005. Updated edition. Page 1155.
11. Leder, B., Longcope, C., Catlin, D., Ahrens, B. Shoenfeld, D., and Finkelstein, J.: Oral Androstenedione Administration and Serum Testosterone Concentrations in Young Men, JAMA, 283(6):779-782.
12. Brown G., Vukovich M., and King, D.: Testosterone Prohormone Supplements, Medicine and Science in Sports and Exercise, 38(8):1451-1461.
13. Burtis C.A., Ashwood E.R.: Tietz Textbook of Clinical Chemistry, 3rd edition. W.B. Saunders Company, Philadelphia, 1999.
14. Griffin J.E., Wilson J.D.: Textbook of Endocrinology, 8th ed.,1992, 799-852.
15. http://www.ehow.com/about_5256981_side-effects-androstenedione.html
16. Castracane V.D., Asch R.H.: Pregnancy: Testosterone and androstenedione in premature ovarian failure pregnancies: evidence for an ovarian source of androgens in early pregnancy. Human Reproduction, 1995, 10, 677-680.
17. Ostrowska Z., Zwirska-Korczala K., Pardela M., Drozdz M., Kos-Kudla B., Bontner B.: Circadian variations of androstanedione, DHEA-S, and free testosterone in obese women with menstrual disturbances. Endocrine Reg. 1998, 32, 169-176.