The Use of Exogenous Testosterone in Elite Female Competitions

Introduction

Accepted, evidence-based medical indications for the therapeutic use of testosterone in females is extremely limited, although there is off-label prescribing in some countries [e.g., to treat postmenopausal women with Hypoactive Sexual Desire Disorder (HSDD)*(1). In response to requests from stakeholders, WADA has created this guidance document for Anti-Doping Organizations (ADOs) and their Therapeutic Use Exemption (TUE) Committees. It provides an overview of androgen structure, physiology, regulation, and measurement to support ADOs in gaining a comprehensive understanding of the various aspects of testosterone, facilitating the evaluation of TUE applications and the application of the International Standard of TUEs (ISTUE) Article 4.2 conditions (2).

Eligibility criteria in elite female sport, whether for transgender athletes or those with differences of sexual development (DSD), are not doping issues, but the responsibility of international sport federations. To clarify, issues such as naturally high levels of testosterone or potential retained advantages following gender transition are not the remit of the anti-doping community and thus will not be discussed in this document. There is a brief mention of transgender athletes from a TUE perspective; further information is available in the TUE Physician Guideline for Transgender Athletes (3).

The issue of circulating testosterone concentrations and therapeutic use of testosterone in females has long been a subject of controversy. Opinions vary regarding medical indications and appropriateness, but there is little doubt that exogenous testosterone is performance enhancing in males and females (4–8), and thus the administration of testosterone and its precursors have long been prohibited in sport, both in- and out-of-competition.

1. Androgens – Structures

Androgens are of two types: natural and synthetic. Natural androgens are represented primarily by testosterone, the dominant mammalian androgen, together with its more potent, pure (non-aromatizable) metabolite, dihydrotestosterone (DHT). In addition, pro-androgen precursors of adrenal origin, such as androstenedione (A4) and dehydroepiandrosterone (DHEA), are weak androgens that may be converted to potent androgens (testosterone, DHT). Additional pro-androgens of adrenal origin, 11-oxo androgens 11-hydroxy A4 (11OH A4) and 11-hydro testosterone (11OH T), lack androgenic bioactivity but can be converted in the body to androgens 11-keto A4 and 11-keto T, respectively.

*Note that this document uses HSDD throughout although the DSM-V describes Female Sexual Interest/Arousal Disorder (FSIAD), a combination of 2 formerly separate disorders which includes HSDD. Most of the literature refers to HSDD, as does ICD-11 (1)

2. Testosterone Physiology

a. Production

Testosterone production differs markedly between males and females. Prior to male puberty, but after male mini puberty (the first six months of postnatal life), circulating testosterone does not differ between males and females. Male puberty creates a 20-30-fold increase in testicular testosterone secretion leading to a 15-20-fold higher circulating testosterone in males than in children or females at any age (9–11) (***Table 1***).

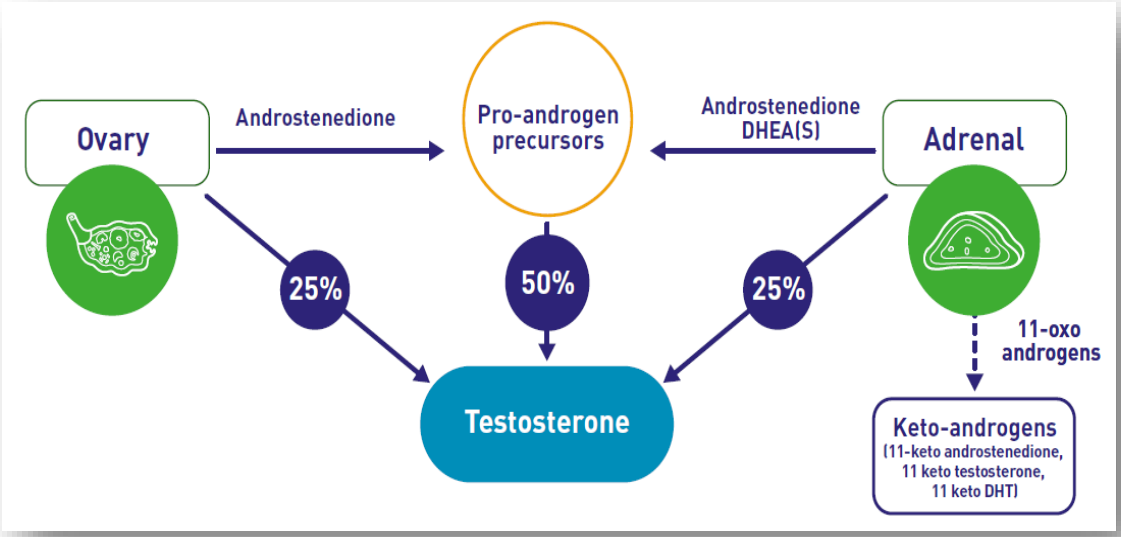
Table 1.
Testosterone: Production, clearance rates and typical circulating (blood) concentrations

	Females, Children	**Adult Males**
Production rate (mg/day)	0.2 (0.15 – 0.25)	7.0 (3-10)
Clearance rate (L/day)	600	1000
Circulating (Blood) concentration	0.06-1.68 nmol/L	7.7-29.4 nmol/L

Females, without underlying medical conditions, are reported to have a daily testosterone production rate of about 0.15-0.25 mg per day (12–14) based on original 1970's studies using tritiated tracer infusions, (15–17) but significantly lower estimates are reported using modern non-ionizing (deuterated) tracers (18,19). Circulating testosterone in females originates from three sources, with the adrenals and ovaries making roughly equal contributions (25% each) (13,20,21) and extra-glandular conversion of pro-androgen precursors of adrenal or ovarian origin into testosterone, contributing to about 50% of the circulating testosterone.

The non-ovarian contributions include weak pro-androgens of adrenal origin, including DHEA and androstenedione, which can be converted into potent androgens (T, DHT). Adrenal production of DHEA-sulfate (DHEA-S) provides a large, circulating potential reservoir of DHEA capable of conversion to potent androgens (13) (***Figure 1***). Additionally, the 11-oxy pro-androgens 11-hydroxy androstenedione and 11-hydroxy testosterone, although not active androgens, may be converted to androgens of modest potency, 11-keto A4 and 11-keto testosterone respectively (22,23), which are sufficiently androgenic to influence reproductive physiology of females (23–26). The pro-androgen precursors of adrenal origin may contribute to net androgen action in females, especially in the presence of steroidogenic disorders. (23,24).

Figure 1. Testosterone Synthesis and Metabolism in Females



The dual steroidogenic organ contributions to circulating testosterone in females means that loss of either ovarian or adrenal production alone leaves circulating testosterone within the female reference range. In theory, females can become androgen (testosterone) deficient only if both adrenal and ovarian steroid secretion are completely lost, as in panhypopituitarism or in post-menopausal women after complete adrenal failure or suppression.

An additional dimension of testosterone production in the body includes the within-tissue metabolism of androgen precursors into testosterone, known as the intracrine pathway (27,28). This intracrine pathway may contribute to tissue-specific androgen action, but without contributing to circulating testosterone concentration (27,29).

b. Ergogenic effects of testosterone

The majority of studies investigating testosterone and its ergogenic effect in athletes come from male populations. The male physical advantages for elite sport in which strength, speed, or endurance are crucial to success arise from the cumulative effects of sustained exposure to adult male circulating testosterone since male puberty (21). This is reflected in clear sex differences between male and female sport performances, a divergence that begins when males enter early puberty (30). There are ergogenic effects of male puberty predominantly on muscle, but also on cardiorespiratory function and blood hemoglobin. These effects, relevant to sports performance, occur only when circulating testosterone concentrations rise above those of pre-puberty from mid-male puberty onwards. Striking differences are evident with early to mid-pubertal median circulating testosterone concentrations of ~11.0 nmol/L (9,10), even when not yet at full adult male concentrations. In females, circulating testosterone

concentrations exert ergogenic effects on muscle proportionate to exposure to circulating levels above the female range. For example, administering testosterone to healthy females (without underlying medical conditions) to achieve mildly hyperandrogenic concentrations that remain lower than the bottom of the male range, 7.7 nmol/L, would be ergogenic (7,8).

c. Regulation

An important feature of the physiological regulation of circulating testosterone is the influence of negative testosterone feedback. In males, the single source of testosterone production (testes) is subject to strong negative feedback at the hypothalamus so that exogenous testosterone strongly suppresses endogenous testosterone production. By contrast, in females, the three sources of circulating testosterone are not subject to strong negative feedback.

One consequence of the absence of strong negative testosterone feedback in females is that exogenous testosterone is additive to endogenous testosterone concentrations. Hence, testosterone products that aim to replicate testosterone delivery at a rate considered equivalent to endogenous testosterone production of healthy pre-menopausal females, will have an additive effect, likely resulting in supraphysiological testosterone concentrations. For example, in a study of 265 females treated with testosterone or placebo transdermal patches for one year, median baseline testosterone [measured by solvent extraction/chromatography immunoassay method equivalent to Liquid Chromatography Mass Spectrometry (LC-MS)] increased from 0.5 nmol/L to 2.2 nmol/L (note: female reference range median = 1.0 nmol/L) (31). Similar supraphysiological circulating testosterone concentrations were reported using 5 or 10 mg daily 1% transdermal testosterone cream for 21 days (8,32), where the median pre-treatment testosterone concentration of 0.6 nmol/L increased to 1.9 nmol/L (5 mg) and 3.1 nmol/L (10mg) (32). The latter finding was confirmed by a separate study using 10 mg daily in which median testosterone concentration rose from 0.9 nmol/L (baseline) to 4.3 nmol/L (after 10 weeks daily treatment) (8). Currently there are very few female-oriented testosterone products, and it remains questionable if they can maintain circulating testosterone concentrations within the female reference range (33).

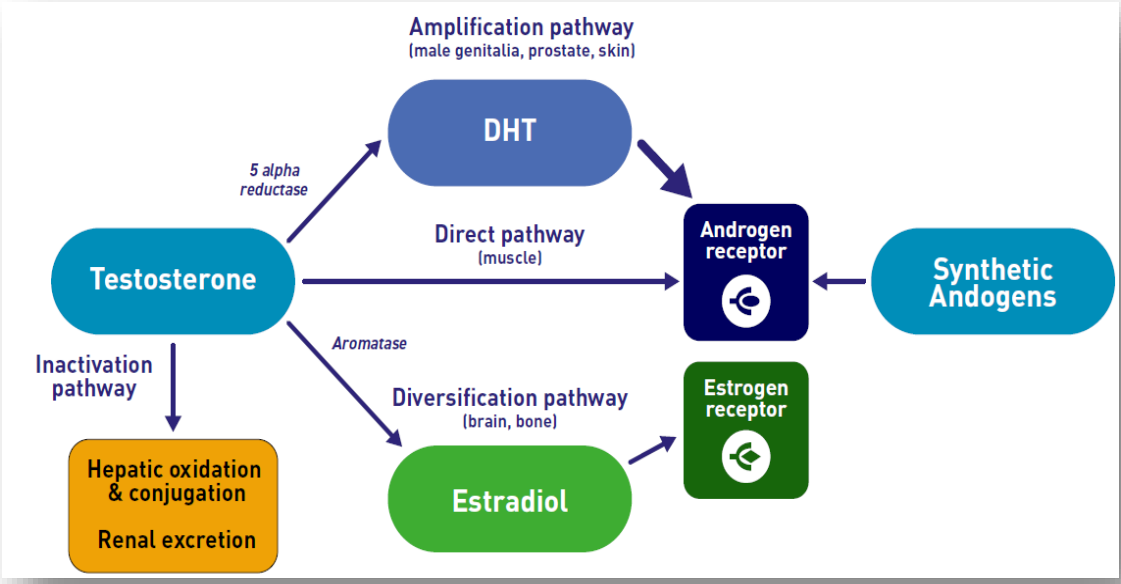
Consequently, although a comprehensive meta-analysis of placebo-controlled clinical trials demonstrated that testosterone has proven benefits on sexual function in some post-menopausal women with sexual dysfunction (34), such efficacy coincides with supraphysiological circulating testosterone concentrations. Hence, such pharmacologic testosterone dosing in females would likely exert ergogenic effects (8).

d. Mode of action

Testosterone exerts its bioactivity via one direct and two indirect pathways (**Figure 2**). The direct pathway involves testosterone binding to, and activating, the androgen receptor (AR) a mechanism characteristic of muscle. The two indirect mechanisms comprise an amplification and diversification pathway. The amplification pathway involves testosterone being converted in target tissues by the 5α-reductase enzyme into the more potent pure (non-aromatisable) androgen DHT. In adults, the amplification pathway is most strongly expressed in the skin

(and prostate in males), but also in other tissues such as liver, kidney, pancreas, and brain. The second indirect pathway, the diversification pathway, involves testosterone's conversion to estradiol by the enzyme aromatase, CYP19A1 (i.e., aromatization), which then acts via the estrogen receptor (ER). The diversification pathway is prominently active in regional brain areas, and in bone, fat and skin.

Figure 2. Testosterone and Synthetic Androgen Pathways of Action



Synthetic androgens are either steroidal or non-steroidal and have the common characteristics of activating the androgen receptor (AR) and being structurally incapable of aromatization or 5α-reduction. Hence, synthetic androgens cannot replicate the full spectrum of testosterone's biological effects, with their inability to convert to the potent metabolites estradiol and DHT locally within tissues.

e. Circulating testosterone levels in females

Females at any age have circulating testosterone concentrations comparable with those before puberty with the reference range (by LC-MS) for adult pre-menopausal females being 0.06 to 1.68 nmol/L from aggregating multiple studies (21). Circulating testosterone concentrations are influenced by ovulation and age whilst remaining within the female reference range. Ovulation produces a small mid-cycle peak (~50%) (35–37). Age influences circulating testosterone concentrations in healthy females, with a peak in the 3rd decade of life and a gradual decline with age, paralleling reduction in adrenal pro-androgen precursor DHEA-S concentrations (38). In women with intact adrenal function, the menopausal transition

(or bilateral oophorectomy or premature ovarian insufficiency) produces no specific change in circulating testosterone by immunoassay (38) or by LC-MS (36,37).

As above, the loss of either or both major organ sources of testosterone and its precursor steroids may slightly reduce circulating testosterone. For example, loss or suppression of ovarian function such as bilateral oophorectomy (38) or premature ovarian insufficiency (39) causes some reduction in circulating testosterone (by immunoassay). Loss of adrenal function alone (20,40,41) or loss of both adrenal and ovarian function due to panhypopituitarism (42) or adrenal insufficiency in females after natural or premature menopause (41), reduces circulating testosterone in females. But all of these reductions in circulating testosterone concentrations do not reduce levels below the normal female reference range.

Notably, due to its hydrophobicity, most circulating testosterone is bound to sex hormone-binding globulin (SHBG), with the remainder loosely bound to albumin or unbound (43). Consequently, the concentration of SHBG determines the blood concentration of testosterone. The “free testosterone” hypothesis proposes that unbound testosterone in the circulation is more bioactive than bound testosterone because it is more accessible to sites of testosterone action; however, this fraction is also more accessible to sites of degradation (44). It is therefore logically impossible to determine whether unbound (“free”) or loosely bound (“bioavailable”) testosterone is the most or least bioactive fraction of circulating testosterone. Direct laboratory measurement of unbound or loosely bound testosterone is laborious, costly, and relies on non-robust methodologies that are rarely available. Instead, various formulae are substituted to calculate the unbound or loosely bound fractions of testosterone. These include calculated free testosterone (45–47) and the free androgen index (48). However, such formulae do not create valid analytes, as they lack any certified reference standard or measures of quality control. They are therefore unsuitable for pooling (to derive consensus reference ranges) or comparison between different laboratories or centers and are not considered valid or acceptable evidence in anti-doping science.

f. Testosterone measurement

It should be noted that the Global Consensus on Testosterone Use in Women and the guidelines from the International Society for the Study of Women’s Sexual Health (ISSWSH) agree that testing testosterone levels in women is not meant for diagnosis, but rather to monitor therapy. Similarly, the North American Menopause Society (NAMS) acknowledges that hormone testing during menopause has limited use and is primarily for assessing absorption issues when symptoms persist (34,49,50).

When measured in clinical practice, serum testosterone concentrations are usually measured by immunoassays that provide quick, inexpensive results. However, these results are not reliable for low circulating concentrations such as in females at any age, children or hypogonadal males.

Due to the lack of accuracy and specificity of these steroid immunoassays, they are not used for antidoping purposes; more accurate mass spectrometry-based methods are required. The current generation of commercial “direct” (one-step, non-extraction) testosterone

immunoassays are employed in routine pathology laboratories to adapt those measurements into high throughput, multiplex automated immunoassay platforms. Introduced in the 1990s, these simplified “direct” assays discarded crucial pre-assay steps required for valid blood steroid measurements, thus resulting in method-specific bias and marked inaccuracy, especially at the low circulating levels in females and children (37-39). For example, “undetectable” serum testosterone levels, (i.e., concentrations below the detection limit of that immunoassay), occur at levels where reproducibility is suboptimal, and blood testosterone can still be measured by more sensitive and accurate LC-MS measurement.

3. Treatment with Testosterone and DHEA

Evidence-based pharmacological treatment of females with testosterone is limited to post-menopausal females with sexual dysfunction (Hypoactive Sexual Desire Disorder, HSDD). A comprehensive meta-analysis of placebo-controlled randomized controlled trials (RCTs) of at least three months’ duration found that testosterone treatment using doses intended for females (based on intended daily delivery of 300 µg of testosterone) improves multiple aspects of sexual dysfunction in postmenopausal females with HSDD with adequate safety for up to two years (51,52). However, the meta-analysis did not support the use of testosterone for pre-menopausal females with HSDD or other conditions or for disease prevention (34,51). These meta-analysis findings are endorsed by multiple professional medical societies and organizations. Yet, most testosterone products have been developed for use by males, with very few designed specifically for the 10-15-fold lower doses more appropriate for females.

The available evidence suggests that delivering daily testosterone at the equivalent rate of endogenous testosterone production in females produces supraphysiological circulating testosterone concentrations (as discussed above in **Section 2c**.), which is likely ergogenic and therefore not acceptable under the Code and ISTUE (2,53)

The pro-androgen, DHEA, is widely recommended on the internet and social media to obtain androgen effects. This adrenal pro-androgen has minimal intrinsic androgenic activity, as it lacks any specific receptor (unlike testosterone) and must be converted to potent androgens (T, DHT) to exert androgenic effects. The available evidence from controlled clinical trials shows no specific benefit, and DHEA is not recommended for post-menopausal females with HSDD (51,54) or females with adrenal failure (54–56). One placebo-controlled RCT found that DHEA treatment (100mg daily for 6 months) did not increase muscular strength in an older, non-athletic population (57). However, because of its potential conversion to more potent androgens, like testosterone, DHEA is prohibited at all times for all athletes.

4. Testosterone and the Prohibited List

Testosterone and synthetic androgens are among the original substances prohibited at all times in elite sports by the International Olympic Committee (IOC) in the 1970s and remain so in the current WADA Prohibited List (58). The ergogenic effects of androgens are based on their ability to increase muscle size and strength in males (4,6) and females (7,8), as well as increase cardiac output, raise hemoglobin concentration, and enhance overall exercise performance. Consequently, use by elite athletes (male and female) of testosterone, as well

as its steroidal or non-steroidal synthetic androgen analogs and/or pro-androgens, is prohibited at all times.

5. Therapeutic Use Exemptions (TUE)

a. The TUE process and ISTUE Article 4.2 criteria

The TUE application process provides athletes with an opportunity to apply for a TUE when medical treatment that involves the use of a prohibited substance or prohibited method is required. This process, protecting all clean athletes, promotes competition on a level playing field. An athlete applying for a TUE must have a diagnosed medical condition and must satisfy all four of the International Standard of TUEs (ISTUE) Article 4.2 criteria for the grant of a TUE:

a) The Prohibited Substance or Prohibited Method in question is needed to treat a diagnosed medical condition supported by relevant clinical evidence.

b) The Therapeutic Use of the Prohibited Substance or Prohibited Method will not, on the balance of probabilities, produce any additional enhancement of performance beyond what might be anticipated by a return to the Athlete's normal state of health following the treatment of the medical condition.

c) The Prohibited Substance or Prohibited Method is an indicated treatment for the medical condition, and there is no reasonable permitted Therapeutic alternative.

d) The necessity for the Use of the Prohibited Substance or Prohibited Method is not a consequence, wholly or in part, of the prior Use (without a TUE) of a substance or method which was prohibited at the time of such Use.

b. Consideration of ISTUE criteria when evaluating TUEs

When considering ISTUE Article 4.2(a), note there is no universal consensus on the biochemical diagnostic criteria for androgen insufficiency/deficiency in females, as the lower limit of the reference range is almost indistinguishable from zero (0.06 nmol/L) (**Section 2a & 2e**). Consequently, reference ranges of blood testosterone in females are not helpful other than for diagnosing conditions of androgen excess (34). HSDD in a naturally or surgically menopausal female is an off-label indication for testosterone treatment (**Section 3**). DHEA treatment has been recommended for females with adrenal insufficiency and low libido, decreased energy, or depression (59), but this conflicts with consensus recommendations (54–56). Thus, it would be challenging for females with these conditions to meet the ISTUE criterion 4.2(a) for treatment with testosterone (or DHEA).

When considering ISTUE Article 4.2(b), even with what some may consider physiologic replacement, the desired psychosexual effects of testosterone in HSDD (34,51) are only achieved with supraphysiological measured testosterone concentrations (**Section 2b, 2c & Section 3**). The likely ergogenic effects of increased testosterone, principally on muscle, are evident when circulating testosterone concentrations rise above the female reference range

into levels comparable with those of mid male puberty (8) (**Section 2a**). Hence, these testosterone treatments are likely to provide ergogenic effects, making them unacceptable under the ISTUE criterion 4.2(b), which requires that any treatment for a known disease should "not provide additional performance enhancement beyond a return to the athlete's normal state of health".

Therefore, it is highly unlikely that there is a scenario in which an athlete competing in elite female competition would be able to meet all the ISTUE criteria necessary for the grant of a TUE.

It should be noted that in males with low circulating testosterone concentrations due to conditions such as aging, overtraining, malnutrition, sleep deprivation, are not valid indications for the grant of a TUE if competing in sports subject to anti-doping rules. However, because there is well-documented, accepted, and measurable lower limit of normal circulating testosterone concentration in males, there are circumstances, of organic hypogonadism (e.g., bilateral orchiectomy) in which a male could be granted a TUE for testosterone (60).

6. Considerations for Trans Athletes

As previously mentioned, the eligibility to compete in binary competitions is not a doping issue and is entirely the remit of sport federations and their constituents. Anti-doping regulations as they pertain to the TUE process for transgender athletes will be briefly discussed here.

Transgender women: Most gender-affirming treatment for transwomen centers on estrogen therapy for feminization. If estrogen is used consistently, this will reduce endogenous testosterone in non-orchiectomized individuals to the goal of <1.7 nmol/L (50 ng/dL) as recommended by the WPATH standards of practice and Endocrine Society clinical practice guidelines (61,62). No TUE is required for any estrogen treatment, although a TUE would be required and should be granted for the adjunctive uses of a gonadotropin-releasing hormone (GnRH) analog or spironolactone.

It would be rare for a transwoman to request testosterone treatment, although some may have a mistaken belief that they no longer have any testosterone. This is based on misunderstanding of the physiology and/or unreliable testosterone immunoassays. Even after medical or surgical castration, adrenal and extra-glandular sources of testosterone maintain circulating testosterone concentrations within the usual female reference range. However, at such circulating testosterone concentrations, testosterone immunoassays are highly inaccurate and may produce artefactual undetectable concentrations. More accurate LC-MS measurements will usually indicate residual circulating testosterone concentrations within the female reference range. Consequently, transwomen are unlikely to meet the TUE criteria for testosterone treatment as they meet neither the criteria of ISTUE Articles 4.2a) and b).

Transgender men: Testosterone is used for its intended masculinizing effects in transmen at doses up to standard male doses for hypogonadal men (see TUE Physician Guidelines - Transgender Athletes and TUE Physician Guidelines - Male Hypogonadism). In elite sport,

such treatment requires a TUE for testosterone, which is usually granted for transgender men with established female birth sex transitioning to and maintaining a gender identity of a transman. These TUEs should only be granted to transmen competing exclusively in open or male competitions. The TUE approval is for standard testosterone doses that are comparable to those for organic male hypogonadism.

7. Summary

In women, there are almost no evidence-based, accepted medical indications for testosterone; it is however being used in some countries to treat postmenopausal women with HSDD. Evidence to support off-label prescribing of testosterone for anti-aging, mood disorders, and as a general energy tonic, is lacking, and this practice is against United States Federal Drug Administration guidance and the international Endocrine Society's clinical practice guidelines. While some people may choose to seek medical treatment with testosterone, the ergogenic potential of testosterone precludes the granting of TUEs in most situations in elite sport.

It should be noted that the Prohibited List only applies to *Athletes*, as defined by Anti-Doping Organizations, and thus subject to WADA anti-doping rules. There are many individuals competing in lower level/recreational sports for whom these anti-doping rules would not apply.

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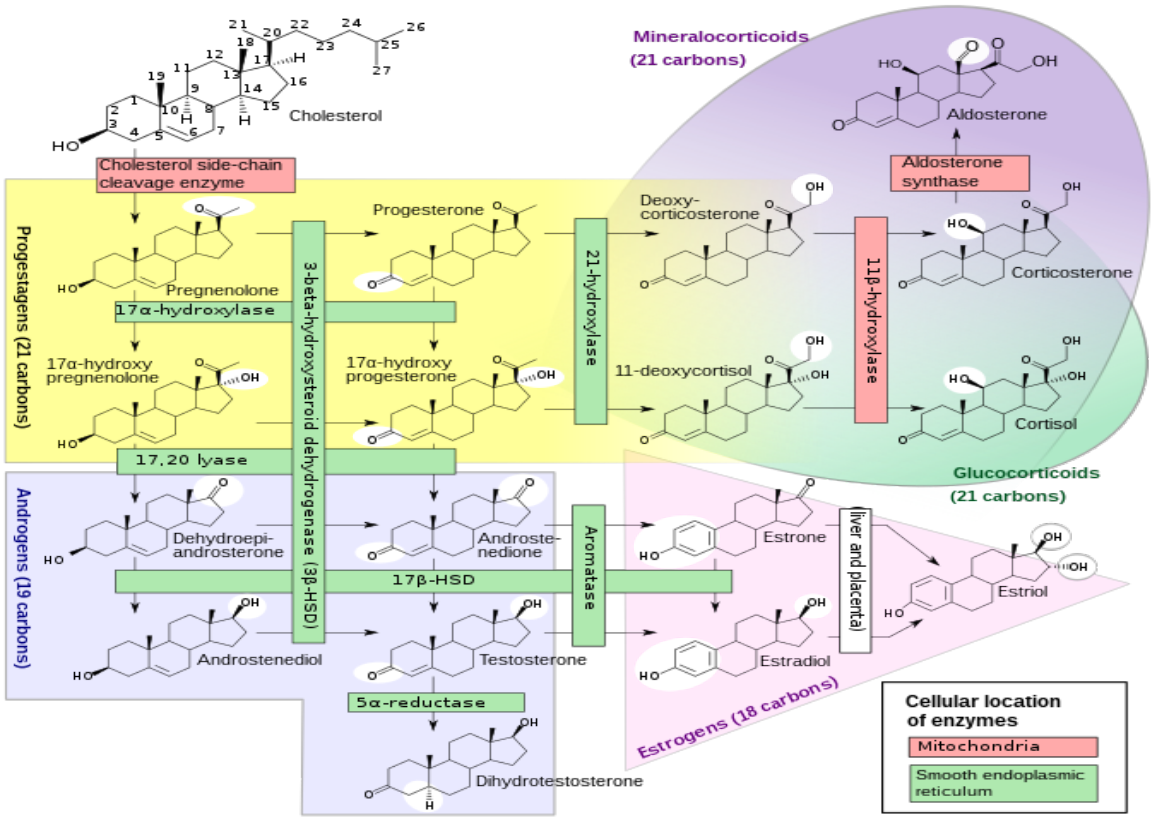
Annex 1

Major Steroidogenic Pathways



Mikael Häggström; David Richfield (12 April 2014). "Diagram of the pathways of human steroidogenesis". WikiJournal of Medicine 1 (1). doi:10.15347/WJM/2014.005. Wikidata Q28109711.