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Clinical Concerns on Sex Steroids Variability in Cisgender and Transgender Women Athletes

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ABSTRACT

In the female athletic community, there are several endogenous and exogenous variables that influence the status of the hypothalamus-pituitary-ovarian axis and serum sex steroid hormones concentrations (e. g., 17β-estradiol, progesterone, androgens) and their effects. Moreover, female athletes with different sex chromosome abnormalities exist (e. g., 46XX, 46XY, and mosaicism). Due to the high variability of sex steroid hormones serum concentrations and responsiveness, female athletes may have different intra- and inter-individual biological and functional characteristics, health conditions, and sports-related health risks that can influence sports performance and eligibility. Consequently, biological, functional, and/or sex steroid differences may exist in the same and in between 46XX female athletes (e. g., ovarian rhythms, treated or untreated hypogonadism and hyperandrogenism), between 46XX and 46XY female athletes (e. g., treated or untreated hyperandrogenism/disorders of sexual differentiation), and between transgender women and eugonadal cisgender athletes. From a healthcare perspective, dedicated physicians need awareness, knowledge, and an understanding of sex steroid hormones' variability and related health concerns in female athletes to support physiologically healthy, safe, fair, and inclusive sports participation. In this narrative overview, we focus on the main clinical relationships between hypothalamus-pituitary-ovarian axis function, endogenous sex steroids and health status, health risks, and sports performance in the heterogeneous female athletic community.

Introduction

From a clinical perspective, female athletes represent a highly heterogeneous community (▶ **Table 1**). Due to both physiological and non-physiological factors, there exists different hypothalamus-pituitary-ovarian (HPO) axis and sex steroid hormone statuses. In addition, there are female athletes with different sex chromosomes (e. g., 46XX, 46XY, and mosaicism) and endocrine profiles due to endocrine diseases with altered genetic expression such as hyperandrogenism, with or without disorders of sexual differentiation (DSD), and due to gender dysphoria (▶ **Table 2**). Consequently, the genetic sex and general features of female athletes should not be taken for granted. Furthermore, due to genetic traits, HPO-axis status, and sex steroid hormone variability, these athletes will have different intra- and inter-individual biological and functional characteristics, and thus different gonadal statuses, health risks, and exercise capacities.

Given this context, there are many unresolved clinical and ethical concerns that have been reported in the female athletic community. For instance, in sports-related hypogonadism, there are concerns regarding responsibility, health prevention, and early differential diagnosis. Moreover, concerns regarding health protection, sports eligibility, and fairness have been remarked upon for female athletes affected by untreated hyperandrogenism and those treated for gender dysphoria, particularly when they compete against eugonadal cisgender athletes.

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Due to the relative novelty of these issues and difficulties in experimental standardization, few reproducible and comparable scientific investigations that are useful for a systematic analysis are available. Furthermore, for ethical and technical reasons, not all clinical conditions can be investigated in all sports. In existing observational studies, the data are often controversial, and some conditions, such as the effects of hyperandrogenism, are likely to be underestimated due to collider bias [1]. Unfortunately, in this area of investigation, demagogic, economic, legal, opportunistic, political, social, and/or speculative issues often dominate over health-related issues and sports medicine competences and responsibilities.

To sensitize sport physicians in supporting safe and physiologically healthy sports participation, this narrative overview focuses on several clinical issues concerning sex steroid hormones, gonadal status, and exercise performance in three groups of adult female athletes: a) 46XX normo-androgenic, b) 46XX and 46XY individuals affected by hyperandrogenism/DSD, and c) 46XY male-to-female transgender women (TW). The links between sex steroid hormones and exercise performance are considered of clinical relevance even because, in some clinical situations, the normalization of hormonal imbalance could worsen individual sport performance, thus representing a possible negative factor for some female athletes, even if necessary for health and wellness.

As this is a controversial topic, we attempted to restrict our focus to the clinical context of sports endocrinology, without discussing ethical, legal, political, or sports regulations that have been adequately discussed elsewhere [2–10].

46XX normo-androgenic adult female athletes

The pleiotropic effects of sex steroid hormones

Following puberty, female sex steroid hormones are secreted by the ovaries in a cyclical, monthly rhythm (17β-estradiol mainly during the follicular phase and progesterone during the luteal phase) under the pulsatile control of the hypothalamic gonadotropin-releasing hormone (GnRH) and the pituitary gonadotropins, such as luteinizing hormone (LH) and follicle-stimulating hormone (FSH) [11]. Depending on exercise intensity and HPO-axis status, serum 17β-estradiol and progesterone may rapidly increase after exercise [12]. Moreover, exercise directly activates estrogen receptor alpha (ERα) in muscles, up-regulating myogenic-related gene expression independently of the serum 17β-estradiol levels [13].

In normo-androgenic, eugonadal female athletes, androgens are physiologically produced, with serum concentrations like adult males for androstenedione, dehydroepiandrosterone (DHEA), and dehydroepiandrosterone sulphate (DHEAS), and at substantially lower concentrations for dihydrotestosterone (DHT) and testosterone. Half of circulating testosterone is secreted in equal amounts by the ovaries and adrenal glands, and the other 50 % is produced by the peripheral conversion of ovarian and adrenal androstenedione [14]. Testosterone is transformed into DHT by the enzyme 5α-reductase in different organs and tissues. Under physiological conditions, DHEA and DHEAS, which are produced by the adrenal glands (90 %) and ovaries (10 %), are converted to 17β-estradiol, testosterone, and DHT [14].

The 17β-estradiol and progesterone, by acting on respective receptors (e. g., ERα, ERβ, PR) – and the variations of 17β-estradiol/progesterone ratio – exert different pleiotropic effects influencing exercise physiology and sporting performance (▶ **Table 3**) [15–20]. In terms of exercise physiology, 17β-estradiol: a) increases 5' AMP-activated protein kinase, glucose transporter type 4, and insulin receptor substrate activation, increasing insulin sensitivity; b) increases glucose uptake and glycogen storage in muscles by reducing glycogen utilization/kinetics and liver gluconeogenesis; c) controls mitochondrial biogenesis, oxygen consumption, and mitochondrial DNA transcription; d) increases the contraction-stimulated glucose uptake in type I muscle fibers, which is beneficial during high-intensity aerobic exercise; e) favorably affects motor behavior and muscle-force generation by acting directly on tendon and muscle proteins, independent of physical activity; f) blunts muscle response to intense exercise and preserves muscle function after exercise-induced muscle damage; g) induces the normal growth hormone response to resistance exercise; and h) increases epinephrine response to exercise, whereas cortico-adrenal response to exercise seems to be uninfluenced by circulating estrogen serum concentrations [15, 17, 21–25]. Taken together, the metabolic and bio-energetic effects of 17β-estradiol appear to primarily support sports endurance. In addition, progesterone decreases insulin sensitivity, the glycogen-sparing effect of 17β-estradiol and liver gluconeogenesis by decreasing contraction-stimulated glucose uptake in type I muscle fibers [16, 17]. Female sex steroid hormones decrease the osmotic threshold for arginine vasopressin and thirst stimulation and led to greater fluid retention during hypertonic saline infusion. Moreover, female sexual hormones concentrations positively correlate with ventilatory parameters (e. g., tidal volume, inspiratory and expiratory times) and peak expiratory flow, playing a positive role in respiratory control and thoracic pump muscles in the luteal phase [26, 27].

In female athletes, endogenous androgens also exert pleiotropic effects that may influence exercise physiology and performance depending on their serum concentrations and androgen-receptor (AR) distribution and sensitivity [28] (▶ **Table 4**).

Due to physiological variability and the balance of 17β-estradiol and progesterone, fine-tuning exercise performance may change according to HPO-cycle phases, with monthly variations in different sport performance measures such as maximal aerobic capacity (VO_2max), endurance capacity, time to exhaustion, time trial performance, training strain and monotony [17, 29–31]. Furthermore, menstrual bleeding, body weight increases in the mid-late luteal phase, mood fluctuations, and/or premenstrual-syndrome (e. g., anxiety, breast tenderness, headache, inflammatory state, irritability, mood disorders, and weight increase) can negatively affect sports performance in athletes [30–33]. These data suggest that monitoring HPO-cycle phases and symptoms might provide useful feedback for supporting the health status in female athletes in devising training and predicting results in competitions [30, 32].

Sports-related hypothalamus-pituitary-ovarian axis alterations

The HPO axis in adult 46XX female athletes can be altered by common diseases such as primary or secondary hypogonadism and/or by sports-related factors, such as energy deficiency due to the combination of high energy expenditure (during exercise training) and

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▶ **Table 1** The female athletic community: a very heterogeneous genetic and biological environment.

Eugonadal Female Athletes (46 XX)	Non-eugonadal Female Athletes (46 XX)	Non-eugonadal Female Athletes (46 XY)	Transgender Women Athletes (46 XY)
Childhood (< 8 years) **Adolescence** (9–18 years) ▪ Pre-puberty ▪ Puberty ▪ Post-puberty **Early Middle adulthood** ▪ Reproductive phase ± OC ▪ Pregnancy ▪ Post-menopause ± HRT **Later adulthood** (> 65 years)	**Primary hypogonadisms** **Secondary hypogonadisms** **Sportrelated hypogonadisms-Hyperandrogenisms/DSD**: ▪ PCOS ▪ CAH ▪ Ovarian/Adrenal tumors ▪ Idiopathic ▪ AAS abuse **Ovotestis DSD** **Genetic mosaicisms**	**Hyperandrogenisms/DSD:** ▪ 5α-reductase deficiency ▪ 17β-HSD3 deficiency ▪ CAIS, PAIS **Gonadal dysgenesis** **Ovotestis DSD** **Genetic mosaicisms**	**Treated before puberty** ▪ GnRH analogues ▪ GAHT ▪ ± Anti-androgens ▪ ± Surgery **Treated after puberty** ▪ GAHT ▪ ± Anti-androgens ▪ ± Surgery **Untreated** (Not GAHT ± anti-androgens)

AAS, androgenic anabolic steroids; CAH, classic and late onset congenital adrenal hyperplasia; CAIS, complete androgen insensitivity; DSD, disorder of sexual differentiation; GnRH, gonadotropin-releasing hormone; GAHT, gender-affirming hormone therapy (i. e., exogenous 17β-estradiol or other estrogens); HRT, hormone replacement therapy; OC, oral contraceptive; PAIS, partial androgen insensitivity; PCOS, polycystic ovary syndrome, 17β-HSD3, 17β-hydroxysteroid dehydrogenase type 3. Please note all reported female athletes could abuse with AAS and other substances influencing the hypothalamus-pituitary-gonadal axis.

▶ **Table 2** Examples of treatment-related variability in serum steroid hormone concentrations in female athletes affected by sport-related hypogonadism, in some diseases causing hyperandrogenism, and in transgender women athletes treated with gender-affirming hormonal therapy (e. g., exogenous 17β-estradiol or other estrogens, ± anti-androgens) or untreated.

HORMONES	Sport-Related Hypogonadism	CAH/PCOS	Transgender Women Athletes (Treated/Untreated)
Estrogens	decreased/normal*	decreased/normal*	increased/normal#
Progestogens	decreased/normal*	decreased/normal*	normal
17OH Progesterone	normal	increased/normal*	normal
Testosterone	decreased/normal	increased/normal*	decreased/normal#
DHT	decreased/normal	increased/normal*	decreased/normal#
Androstenedione	decreased/normal	increased/normal*	decreased/normal#
DHEA, DHEAS	decreased/normal	increased/normal*	decreased/normal#
Cortisol	normal	decreased/normal*	normal
Aldosterone	normal	decreased/normal*	normal

CAH, classic and late-onset congenital adrenal hyperplasia; DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone sulphate; DHT, dihydrotestosterone; Estrogens, endogenous or exogenous 17β-estradiol or other estrogens; PCOS, polycystic ovary syndrome. Please note all reported female athletes may assume, for therapy and/or doping purposes, prohibited and non-prohibited substances further influencing their steroid hormone status. *Depending on diseases and performed therapy. #With respect to the physiological levels in untreated 46XY males.

insufficient caloric intake. The hormonal profile in elite athletes, both males and females, is largely influenced by the type of sport [9]. In particular, it has been reported that a high percentage of female elite athletes (up to 60 % of gymnasts and dancers) have serious reproductive disorders such as oligomenorrhea, functional hypothalamic amenorrhea, anovulation, and infertility due to sports-related hypogonadism caused by energy deficiency and marked alterations in body composition, which in turn determine an increased activity of the hypothalamic-pituitary-adrenal (HPA) axis [34]. Indeed, the main sports-related factors that, either alone or in association with other complex mechanisms, inhibit the HPO axis are relative energy deficiency in sports (RED-S) and psycho-physical stress [35–39]. In addition to the reproductive consequences of HPA inhibition (▶ **Table 5**), RED-S could be associated with decreased bone mineral density, impaired bone microarchitecture, and decreased bone strength, increasing the risk of bone stress fractures in athletes. Moreover, RED-S could be responsible per se for other non-reproductive health consequences: iron deficiency anemia, growth retardation in adolescence because of a GH secretion disorder, endothelial dysfunction, gastrointestinal disorder (e. g., constipation), or increased susceptibility to gastrointestinal and respiratory tract illness due to alteration of the immunological system. The main strategy to prevent/counteract the complications of RED-S is nutritional education, and changes in food choice and intake in relation to individual energy expenditure; particularly, supplementation with vitamin D and calcium should be considered, independently of normal nutrition practices in order to prevent bone tissue alterations [37, 38]. Apart from RED-S and psycho-physical stress, the etiology of sports-related hypogonadism is multi-factorial and complex, and includes age, drugs, epigenetics and genetic factors, social issues, type of sport and training, and the abuse of prohibited substances (i. e., mainly androgenic anabolic steroids (AAS)), which all exhibit substantial inter-individual variability [40]. In most cases, the first alteration is progressively

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▶ **Table 3** Examples of non-reproductive biological effects of physiological female sex steroid hormones concentrations (17β-estradiol and progesterone) that could influence health status, exercise capacity and sporting performance in female athletes (in alphabetical order).

Sex Hormone	Glucose Metabolism	Lipid and Protein Metabolisms	Other Effects*
17β-estradiol	**Increases** AMPK/GLUT4/IRS1 activation Glycogen storage Insulin sensitivity and signaling Muscles glucose uptake Type I fibers glucose uptake (Contraction-stimulated)	**Increases** FFA availability FFA oxidation FFA uptake Lipolysis Muscles lipid stores Liver lipogenesis WAT lipogenesis	**Increases** Bone mineral density GH-IGF-I secretion GH response to exercise Mood state Motor/walking behavior Muscles mass Muscle force generation Recovery from muscle damage Sense of well-being
	Decreases Glycogen utilization Glucose kinetic Liver gluconeogenesis	**Decreases** Protein catabolism Protein oxidation	**Regulates** CNS neurotransmission (i. e., dopamine) CNS reward responses Mood state Osmotic threshold for AVP Renal fluid/sodium absorption Sodium appetite Stress hormones responses Thirst control Vascular tone
Progesterone	**Increases** Insulin resistance	**Increases** Fat utilization Protein catabolism	**Increases** CNS sensitivity to $PaCO_2$
	Decreases Glycogen-sparing effects of 17β-E_2 Glucose kinetic Hepatic gluconeogenesis Type I fibers glucose uptake (Contraction-stimulated)		**Regulates** Osmotic threshold for AVP Renal fluid/sodium absorption (i. e., anti-aldosterone effect) Sodium appetite Thirst control Ventilatory parameters (e. g., tidal volume, inspiratory and expiratory times) and peak expiratory flow
17β-estradiol/ Progesterone ratio	***Influences/Regulates*** Motor behavior, body composition, body temperature, breathing, cardiovascular system, cognitive processes, fluid intake, muscle metabolism and bioenergetics, mood state, substrate metabolism, thermoregulation, water, and salt balance		

AMPK, 5' AMP-activated protein kinase; AVP, arginine-vasopressin; CNS, central nervous system; FFA, free fatty acids; GH, growth hormone; GLUT4, glucose transporter type 4; IGF-I, insulin growth factors-I; IRS1, insulin receptor substrate 1; PaCO2, carbon dioxide partial pressure; WAT, white adipose tissue; 17β-E2, 17β-estradiol. *Related to direct effects of 17β-estradiol and/or progesterone and/or 17β-estradiol/progesterone ratio.

altered GnRH secretions, which reduce LH pulse frequency and cause a progressive and often biphasic reduction of female sex steroid hormones (i. e., firstly progesterone and successively 17β-estradiol) and a reduction of LH-dependent androgens concentration.

Where health risks are concerned, sports-related female hypogonadism, especially in cases of delayed treatment, is associated with serious reproductive symptoms and non-reproductive complications, particularly in the presence of RED-S (▶ **Table 5**) [36–38].

Furthermore, it is not well known if and how the reduction of sex steroid hormones influences the fine adjustment of sports performance. For instance, in amenorrheic athletes, neuromuscular alterations have been reported that include reduced knee muscular strength/endurance and prolonged reaction times, [41]. In cases of oligomenorrhea and in presence of an increased 17β-estradiol/progesterone ratio, due to progesterone reduction, a negative effect on sports performance may be related to water retention, increased body weight, and other unknown mechanisms. Moreover, the absence of 17β-estradiol and progesterone could lead to advantages in sports performance due to the absence of menstrual bleeding, body weight and mood fluctuations, and premenstrual syndrome [30–33].

46XX and 46XY female athletes affected by hyperandrogenism

The clinical profile of hyperandrogenism

Female athletes can be affected by a wide spectrum of genetic diseases that influence ovarian and/or adrenal steroid hormone production, and they are characterized by variable supra-physiological serum concentrations of testosterone, DHT, androstenedione, DHEA and/or DHEAS, as well as variable decreases in 17β-estradiol, progesterone, cortisol, and aldosterone serum concentrations, also depending on performed therapy (▶ **Tables 1,2**).

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▶ **Table 4** Non-reproductive biological effects of testosterone influencing health status, exercise capacity, and sporting performance in male and female athletes (in alphabetical order). (Modified from Sgrò P, Di Luigi L. Sport and male sexuality. J Endocrinol Invest 2017; 40: 911–923 [28]).

Somatic Growth Body Composition	**Metabolisms**	**Behaviour**
Increases Bone mineral density Epiphyseal cartilage closure Erythropoiesis and hemoglobin Muscle mass and male distribution Secondary sexual characteristics Somatic masculinization	**Increases** Anaerobic glycolytic capacity Enzyme's activity in mitochondria Phosphocreatine content in muscles Protein anabolism Sarco-tubular enzymes activity	**Increases** Aggressiveness Dominance Inclination to command
Decreases Fat mass	**Decreases** Protein catabolism	**Decreases** Empathy Negative reaction to external stimuli Perception of negative emotions Sense of fatigue
Endocrine system **Psycho-Physical Stress**	**Functional Skills**	**Psycho-Functional Skills**
Growth control Inhibits CRH-ACTH- Cortisol responses to stress Insulin-like effects Peripheral anti-glucocorticoids effects (for competition at receptor level) Pro-insulin effects Synergistic effects with growth hormone	**Increases** Aerobic and anaerobic capacity Cardiovascular efficiency Explosive strength Muscle strength Muscle adaptation to training Neuromuscular excitability Neuromuscular conduction	**Increases** Aggressiveness in competition Motivation to compete Resistance to fatigue Visual-spatial orientation **Decreases** Negative reaction to alarms
ACTH, adrenocorticotropin hormone; CRH, corticotropin-releasing hormone		

Health complications may be observed, which depend on the features of the primary disease, the time of onset of hyperandrogenism (e. g., in the fetus, at birth, at puberty, in adulthood), AR distribution and sensitivity, time of diagnosis, therapy (treated or untreated), specific symptoms and different endocrinological situations. Generally, female athletes may have symptoms of abnormal gonadal and DSD with ambiguous genitalia, which may range from a nearly male appearance to minimal clitoromegaly, and/or symptoms of virilization, differently associated symptoms of female hypogonadism, altered adrenal steroid secretion (e. g., aldosterone, cortisol), and increased risk of general short- and long-term health complications, particularly if they are not adequately diagnosed and treated (▶ **Table 5**).

When hyperandrogenism is associated with DSD, a different phenotype at birth may be observed and when ambiguous genitalia lead to difficulties in diagnosis and final sex assignment, a female gender is assigned at birth in most cases. The conditions of hyperandrogenism associated with DSD are genetic disorders such as classic congenital adrenal hyperplasia (CAH), 5α-reductase deficiency, 17β-hydroxysteroid dehydrogenase type 3 (17β-HSD3) deficiency, partial or complete androgen insensitivity syndrome (AIS), and ovotestis DSD. The symptoms of virilization may be observed at birth or puberty and are often associated with primary amenorrhea. In some cases of DSD associated with a completely normal female phenotype, a diagnosis is not made until they are investigated for primary amenorrhea or found to have a high serum testosterone concentration when blood is analyzed for clinical or anti-doping purposes.

Congenital adrenal hyperplasia

Classic CAH comprises a group of autosomal recessive disorders that cause the deficiency of specific enzymes involved in the adrenal steroidogenesis. The common form is 21-hydroxylase deficiency (21-OHD) due to mutations in the 21-hydroxylase (CYP21A2) gene; other virilizing forms include 3β-hydroxysteroid dehydrogenase and 11β-hydroxylase deficiencies, associated with mutations in the 3β-hydroxysteroid dehydrogenase (HSD3B2) and 11β-hydroxylase (CYP11B1) genes, respectively [42]. The features associated with classic CAH encompass a wide clinical spectrum reflecting the specific mutation, and the clinical manifestations of 21-OHD deficiency range from salt-losing syndrome and severe virilizing forms to the mild forms. Classic CAH generally appears in the neonatal period and the presentations of clinical features differ depending on the chromosomal sex of the affected infant. Salt-losing CAH is a medical emergency because of the risk of hyponatremia, hyperkalemia, hypotension, and fatal outcome within the first 2–3 weeks of life if not recognized. In addition, the extent of prenatal virilization can lead to mis-assignment of sex at birth. Infant females with classic CAH generally present ambiguous genitalia in the neonatal period, from a nearly male appearance with penile urethra and bilateral undescended testes to minimal clitoromegaly, with normal female internal genitalia. The most common physical findings in affected girls include clitoromegaly, fused labia majora, and a single perineal orifice; occasionally, the minimally virilized girl may not be identified until progressive clitoromegaly prompts a medical evaluation. Both male and female children with CAH can present with premature pubarche, tall stature, accelerated linear growth velocity, and advanced skeletal maturation. Symptoms

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▶ **Table 5** Symptoms and health complications in female athletes affected by sport-related hypogonadism and by diseases causing hyperandrogenism/disorders of sexual differentiation, and in transgender women athletes treated with gender-affirming hormone therapy (e. g., exogenous 17β-estradiol or other estrogens, ± anti-androgens) or untreated (in alphabetical order).

SYMPTOMS AND HEALTH COMPLICATIONS		
Sport-Related Female Hypogonadism (+/− RED-S)	**Female Athletes with Hyperandrogenism/DSD**	**Transgender Women Athletes* (Treated with GAHT/Untreated)**
Reproduction Amenorrhea Anovulation Infertility Oligomenorrhea		**Reproduction/Sexuality** Erectile Dysfunction# Genital Pain Infertility
Reproduction/Sexuality Breast Atrophy Delayed Puberty	**Reproduction/Sexuality** Acne Androgenic Alopecia Breast Atrophy Clitoromegaly Common Urogenital Sinus Delayed Puberty Fused Labia Majora Hirsutism Male Muscle Distribution Pseudo-Puberty Reduced Feminization Voice Deepening Delayed Puberty	**General Health** Anxiety Cardiovascular Diseases Depression Eating Disorders Fat Mass Increase Hypertension Hypertriglyceridemia Iatrogenic Risk Impaired Fasting Glycemia Inguinal Hernia (?) Insulin Resistance Muscle Hypotrophy Prolactinomas Substance Abuse Suicidality Thromboembolism
General Health Arrhythmias Cardiovascular Diseases Cognitive Impairment Depression Early Atherosclerosis Eating Disorders Endothelial Dysfunction Gastrointestinal Illness Iatrogenic Risks Increased Inflammation Insulin Resistance Iron Deficiency, Anemia Low IgA Low BMI Reduced Feminization Reduced Linear Growth Reduced Peak BMD, Osteopenia, Osteoporosis, and Fractures Reduced RMR Respiratory Illness	**General Health** Adrenal Insufficiency Cardiovascular Diseases Diabetes Gonadal Cancer Hyperinsulinemia Hypertension Iatrogenic Risks Insulin Resistance Obesity Salt Wasting Short Stature	

BMI, body mass index; BMD, bone mineral density; DSD, disorders of sexual differentiation; GAHT, gender-affirming hormone therapy; iatrogenic risk: all reported female athletes may assume, as therapy or for doping purposes, prohibited and non-prohibited substances that could further influence health status for their side effects; IgA, immunoglobulin A; RED-S, relative energy deficit in sport; RMR, resting metabolic rate. *The symptoms in transgender women athletes are multifactorial because they could be related to the assumed drugs, to hypoandrogenism/hyperestrogenism and to a multitude of social reasons, independently of GAHT, see text. #in the absence of surgical sex reassignment.

of CAH in adolescent females include hirsutism, irregular menses, chronic anovulation, acne, and infertility, with hirsutism being the most common presenting feature [42–44].

5α-Reductase deficiency

The 5α-reductase deficiency is a very rare autosomal recessive condition causing an altered conversion of testosterone into DHT. Since during fetal life the development of male external genitalia is DHT-dependent, this condition leads to a male's under-virilization with identification as a female gender at birth, despite the presence of testes and normal testosterone production. During and after puberty, when circulating levels of testosterone rise in the normal adult male serum concentrations, the female individuals will undergo increasing virilization and more than half will change their gender identity, becoming males [6].

17β-Hydroxysteroid Dehydrogenase Type 3 Gene Mutation

A mutation of the 17β-HSD3 gene leads a reduced conversion of androstenedione to testosterone. These 46XY individuals develop under-virilized external genitalia, with some being identified as female at birth. As in the case of 5α-reductase deficiency, when the testes start to produce androgens at puberty, such individuals undergo marked virilization and approximately half of them will change their gender identity to male (6).

Androgen insensitivity syndrome

AIS, caused by a mutation in the androgen receptor gene, causes various features of under-virilization in 46XY individuals. In the case of complete AIS (CAIS), even though they have testes (undescended) and normal levels of serum testosterone at a different age, they respond very little or not at all to androgens and will therefore appear as fully female. In the case of partial AIS (PAIS), the phe-

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notype will vary from that of a virilized woman to an under-virilized man (6). Moreover, distinguishing the degree of androgen insensitivity is difficult and somewhat controversial. Many cases of AIS are completely normal anatomical females and not diagnosed until adulthood. Those who are diagnosed before adulthood have severe AIS, but proving someone has complete AIS is not possible. By definition, a person undiagnosed before adulthood, e. g., those identified via a blood test for an athletic biological passport, have a CAIS.

Ovotestis DSD

The ovotestis DSD (true hermaphroditism) is a very rare condition with varying karyotype, although 46XX is common. These individuals develop both ovarian and testicular tissue; they can have an ovary on one side and a testis on the other or combined tissue, so-called ovotestis. Depending on their gonadal tissue, their clinical features varied from that of a normal man to normal woman, although the external genitalia are generally ambiguous, and little is known about their final gender identity [6].

When the hyperandrogenism is not associated with DSD, the symptoms of virilization and female hypogonadism are often observed during or immediately after puberty, or even later. Conditions of female hyperandrogenism without DSD are polycystic ovary syndrome (PCOS), late-onset CAH, adrenal/ovarian androgen-secreting tumors, and idiopathic hyperandrogenism.

Polycystic ovary syndrome

PCOS is the most frequent endocrine disorder among general female population, and particularly elite female athletes [6, 45]. PCOS is characterized by high ovarian production of androgens, disorders of ovulation (anovulatory cycles), and polycystic ovarian morphology. Although the etiology of PCOS remains largely unclear, probably it is based on a genetic predisposition. Hyperandrogenism and insulin resistance are the typical endocrine features of PCOS that alter the pulsatile GnRH secretion, resulting in high LH secretion and relative FSH deficiency. The altered LH/FSH ratio causes the characteristic polycystic aspect of the ovaries, anovulation, menstrual disorders, and reduced fertility as well as hirsutism and acne [45]. In addition, women with PCOS often show insulin resistance with secondary insulin hypersecretion, which directly stimulates ovarian androgen production. Moreover, insulin inhibits hepatic synthesis of sex hormone-binding globulin (SHBG), resulting in increased levels of free (bioavailable) testosterone [44]. Insulin resistance in PCOS is associated with abdominal obesity, type 2 diabetes, dyslipidemia, and increased cardiovascular risk. However, in athletes affected by PCOS, training per se or reported sports-related factors inducing hypogonadism may reduce symptoms and androgen secretion [46–48].

Late-onset congenital adrenal hyperplasia

Late-onset CAH is also known as the non-classic form, and it is considered the mild form of CAH. However, this classification system is somewhat artificial because disease severity is better represented as a continuum based on residual enzyme activity [42]. Late-onset CAH is more common than the classic forms, with an incidence of 1:1000 vs. an incidence range of 1:5000 to 1:15,000, respectively [49]. Female children with late-onset CAH can present with premature pubarche and clitoromegaly [50]. After puberty, the clinical manifestations of late-onset CAH include hirsutism, irregular menses, chronic anovulation, acne, and infertility; whereas hirsutism is the most common clinical symptom [44, 50]. Due to similar clinical features, it may be difficult to distinguish late-onset CAH from PCOS. Generally, women with late-onset CAH present higher 17-OHP and progesterone concentrations than women with PCOS, while insulin resistance, obesity, polycystic ovary morphology, and elevated LH/FSH ratio is more common among women with PCOS. However, none of these features clearly differentiate women with late-onset CAH from those with PCOS [51] nor do Anti-Mullerian hormone serum concentrations [52].

Androgen-secreting tumors

Tumors secreting androgens are a rare cause of hyperandrogenism and can originate from ovarian or adrenal tissue; unfortunately, they are malignant in more than 50 % of cases [53]. The typical clinical presentation is a very rapid onset of female virilization, whereas small tumors can have more indolent presentations. Physical examination generally reveals abdominal or pelvic masses, and if they are adrenal in origin can be associated with increased DHEA and DHEA-S levels, and hypercortisolemia, also leading to Cushing's syndrome.

Idiopathic hyperandrogenism

Idiopathic hyperandrogenism is characterized by no secondary causes, no genetic alterations, normal menses, normal ovaries on ultrasonography, and elevated androgen levels that are generally the cause of acne and hirsutism [54].

The therapy for diseases causing hyperandrogenism, including cyproterone acetate, fludrocortisone, GnRH analogues, glucocorticoids, oral contraceptives, spironolactone, or surgery should begin immediately following a differential diagnosis, and depending on symptom severity, should be well-tailored to improve the risk/benefit ratio. Female athletes affected by severe hyperandrogenism/DSD and/or adrenal insufficiency should have been diagnosed and treated early in life. When hyperandrogenism appears at puberty or later, therapy should start only after a differential diagnosis is made and in accordance with good clinical practice criteria. In female athletes treated with prohibited drugs (i. e., fludrocortisone, glucocorticoids, and spironolactone), a therapeutic use exemption (TUE) must be requested according to World Anti-Doping Agency criteria [55, 56].

Interestingly, from our unpublished clinical experience, a dichotomic approach to medical therapy for the same type of hyperandrogenism exists. Female non-athletes more often search for the best therapy to reduce their serum androgens, while female athletes more often prefer to avoid any therapy, thereby maintaining their hyperandrogenism and consequently increasing their health complications. We do not know if the stance of female athletes is based on fear of iatrogenic risks or against a normo-androgenic status.

Female hyperandrogenism and sports performance

When female diseases inducing hyperandrogenism are undiagnosed or not adequately treated, high concentrations of serum testosterone (serum total testosterone > 1.8 nmol/L) and/or of other

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androgens could be observed given high individual variability [57]. Aside from clinical aspects, an ethical concern regarding fairness with respect to normo-androgenic female athletes also remains. This is particularly true as untreated diseases that induce hyperandrogenism may lend an unfair advantage in sports performance, and female athletes might refuse medical therapy to maintain a potential athletic advantage.

Testosterone has many dose-dependent pleiotropic effects that influence sports performance (▶ **Table 4**), and the sexual dimorphism in physical performance between eugonadal adult 46XY males and 46XX females is related to both genetics and greater testosterone levels in males [58, 59]. Weak androgens such as androstenedione, DHEA, and DHEAS are also correlated with lean mass and physical performance in normo-androgenic females. Furthermore, a positive correlation between increased DHEA, lean mass and explosive performance has been reported in female Olympic athletes [60–62]. However, no studies have evaluated the influence of weak androgens on increasing sports performance under different hyperandrogenisms, particularly when the potential role of DHEAS is considered [63].

While few would doubt the evidence indicating that administering AAS to female athletes can improve their performance, there are only a few, and controversial, studies that have evaluated exercise performance in females after testosterone administration or in female athletes affected by hyperandrogenism. A 10-week testosterone treatment at 10 mg/day in young, physically active women found that increasing total serum testosterone from 0.9 ± 0.4 to 4.3 ± 2.8 nmol/L increased aerobic running time to exhaustion (+ 8 %) and lean mass (+ 2 %) [63]. The administration of testosterone (150/300 µg/day for 12 months) in androgen-deficient women with hypopituitarism to restore physiological female total and free testosterone serum levels significantly increased fat-free mass (+ 3.4 %), cross-sectional muscle area (+ 6.6 %), and behavioral parameters (arousal, behavior/experience, and cognition) [64]. In addition, testosterone administration at different doses (3–25 mg/week) for six months in postmenopausal women (reaching a maximal serum total testosterone level of 7.3 nmol/L) resulted in dose-dependent increases in muscle mass (+ 4.4 %) and strength (+ 12–26 %) [65].

The majority of studies concerning hyperandrogenism in female athletes have evaluated PCOS, which has a high incidence in the general population (4–12 %) and even higher in elite athletes (15–31 %) [66–69]; nonetheless, few studies have evaluated CAH [66]. Interestingly, in the athletic community, the prevalence of hyperandrogenic 46XY DSD is seven per 1000, which is 140 times higher than in the general population [70]. Even if hyperandrogenism plays a role in the decision to participate in sports by influencing dominance and competitiveness, the high prevalence of DSD among elite athletes has also been attributed to factors that are associated with the Y chromosome (other than testosterone) [71].

In untreated athletes with PCOS and hyperandrogenism, increased muscle mass and strength, explosive strength, vertical jumping ability, lower limb power, muscle strength in response to resistance training, visuospatial ability, and VO_2max have been reported [46, 47, 54, 72–75]. For many scientists, female athletes with high serum testosterone concentrations have an estimated competitive advantage of at least 2–5 % over normo-androgenic athletes, except for CAIS athletes. Moreover, decreased sports performance (by about 6 % over two years) in female athletes treated for hyperandrogenism appears to support a previously testosterone-related advantage in performance [58, 59, 61, 76, 77]. A potential advantage in sports could also be related to the integrated effects of untreated hyperandrogenism plus female hypogonadism, and/or to possible TUE abuse and/or to the possible effects on the endocrine system of supplements and/or drug abuse; for example, we highlight that female athletes affected by CAH and authorized (i. e., TUE) for glucocorticoid treatment might increase the dose of glucocorticoids for doping purposes [55, 56, 78–82].

As sport endocrinologists, we cannot affirm at which exact supra-physiological testosterone concentration each female athlete might start to have specific advantages for all different psycho-physical capacities influencing all different sports performances. The pleiotropic effects of androgens, intra-individual AR distributions and sensitivity, the large intra- and inter-disease variability of weak androgens, and the fact that testosterone is not always assayed by liquid or gas chromatography-mass spectrometry all largely influence this type of evaluation. Moreover, we cannot affirm that differences in testosterone-related health risks and sports performance exist between female individuals with identical supra-physiological testosterone concentrations due to a disease or to exogenous testosterone abuse. Therefore, a generalized cut-off value for serum total testosterone concentrations that is higher than the upper normal female testosterone level (1.8 nmol/L) to grant sports eligibility in all types of female hyperandrogenism could be misleading, unfair and may facilitate short- and/or long-term health complications, particularly in female athletes that refuse therapy to maintain hyperandrogenism-related sports advantages. In theory, a case-by-case clinical assessment of health status, endocrine profile, and iatrogenic risks, and a balance between untreated disease-related risks and therapy-related risks would be necessary to provide advice regarding possible treatments, as in the general population, and evaluate sports eligibility.

Transgender women athletes

Actually, to avoid gender discrimination, male athletes affected by gender dysphoria can participate in sports as females once their medical (gender-affirming hormone therapy (GAHT) with exogenous 17β-estradiol or other estrogens ± anti-androgens, ± gender-affirming surgery) and bureaucratic transition process from male-to-female gender is completed, according to respective national laws on gender identity changes (please note in some countries GAHT and/or gender-affirming surgery are not mandatory). According to the International Olympic Committee (IOC) and other sports organization regulations, TW can participate in sports, independently of gender-affirming surgery for anatomical sexual reassignment, once their eligibility has been established by respective sports federations and, when necessary, after a TUE for prohibited drugs is obtained (i. e., for spironolactone). Given these stipulations, there should be no concerns regarding the participation of TW athletes in sports, respecting the previous IOC criteria for inclusion of TW athletes in female sports categories that required testosterone suppression below 10 nmol/L for 12 months prior to and during competition [83].

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Unfortunately, worldwide debate continues regarding possible sports advantages of being a TW athlete as opposed to a cisgender female athlete, particularly in sports such as track and field, cycling, and weight-bearing sports. Due to the social and political stance against gender discrimination, the scientific evaluation of this question is very difficult. Particularly, the new IOC framework on fairness, inclusion, and non-discrimination based on gender identity and sex variations in sports has generated a very serious debate and discussion in sport and exercise medicine and we are waiting for possible new sport federations' regulations for sport inclusion in these athletes [84–86]. In this sense, serious concerns will arise because in some countries it is possible to be a TW athlete without assuming GAHT, thus remaining, from a functional and endocrinological point of view, a male individual (in Switzerland, for example). Moreover, it will be very difficult to regulate sport participation because of the added complexity of gender non-binary people who were presumed male at birth, who may be prescribed GAHT, and who do not neatly fit into the binary categorization of most sports at the elite level.

It is not disputed that, apart from the psychological and social formation of gender and sexual orientation, an objective evaluation of the anatomical, endocrinological, and functional status of TW athletes is complex. From a mechanistic point of view, they are 46XY individuals who developed as males, often for many years, before becoming severely hypogonadal (i. e., low serum testosterone concentration and effects) (▶ **Table 2**) due to continuous estrogen administration at female replacement doses that inhibit endogenous GnRH secretion. Furthermore, GAHT with estrogen therapy induces male hyperestrogenism, and anti-androgen drugs reduce all peripheral effects of androgens [87].

Aside from possible drug-related side effects due to the association between GAHT-related severe hypoandrogenism and relative hyperestrogenism in 46XY individuals, with respect to eugonadal cisgender athletes, TW athletes are at increased risk for cardiovascular diseases, endocrine-metabolic alterations, and potential lower abdominal muscle fibrosis and hypotrophy, which could lead to inguinal hernias, as observed in an animal model (▶ **Table 5**). In addition, independently of possible side effects of GAHT on mood state, TW shows an increased rate of depression, anxiety, and suicides due to a multitude of reasons, including social and institutional discrimination, bullying, poor access to gender-affirming care, and so forth (▶ **Table 5**) [88–95].

In gender medicine, it is widely accepted that, due to genetic/cellular mechanisms (e. g., cell memory, enzymes, hormone receptor pathways) and endocrine-metabolic factors (e. g., sex steroid hormones concentrations, receptor distribution and sensitivity), a sex-chromosome-related dimorphism in exercise performance between 46XX and 46XY individuals exists [58, 96, 97]. In athletes, the 46XX/46XY dimorphism influences the psyche and behavior, stress and immune responses, disease prevalence and clinical expression, pain perception, and drug metabolism/effects. It also leads to gender-specific differences in health risks, exercise potential, and sports performance [39, 98–100]. In comparison with eugonadal adult 46XX individuals, eugonadal adult 46XY individuals have a taller stature, larger bone fulcrum, greater leverage for muscular-limb power, greater muscle area (+ 4–50 %) and strength (+ 20–40 %), greater aerobic capacity and anaerobic power, and better performance in running (+ 10–12 %) and jumping [58, 96]. However, eugonadal 46XX individuals have greater flexibility, knee and hip flexion, increased shoulder extension and external rotation, reduced knee and hip extension, better balance, and more body fat [58, 96]. Many gender divergences in physical performance begin at puberty and reach a plateau in late adolescence, with the timing and tempo closely connected to the rise in serum testosterone concentrations in boys [101].

In terms of the anatomical and functional status in TW athletes, the main issue requiring resolution is whether the genetic expression and all the factors characterizing sports performance in eugonadal 46XY individuals (e. g., behavior, bio-energetics, body composition, body temperature, bone tissue, breathing, cardiovascular system, cognitive processes, CNS, mood, muscle physiology, skeleton, substrate metabolism, stress adaptation) could be significantly modified only by a suppressed testosterone concentration plus estrogen treatment to make them as similar as possible to cisgender female athletes [102, 103].

The male-to-female transition process is associated with a reduction in lean body mass (−2.4 kg), muscle mass (−9 %), hand-grip strength (−9.5 %), total thigh muscle volume (−5 %), and quadriceps sectional area (−4 %) [104–108]. Moreover, it has been found that after 12 months of estrogen treatment for transition, the total thigh volume and lower limb strength (both absolute and height-adjusted) in TWs are higher than in cisgender individuals and in female-to-male transgender (TM) individuals [108]. Gooren et al. has reported that testosterone deprivation in TWs decreased muscle mass, thereby increasing the overlap with untreated TM individuals, but mean muscle mass remained significantly higher in TWs than in TMs. They concluded that androgen deprivation in TWs increased the overlap in muscle mass with women but does not reverse it [109]. Moreover, other longitudinal studies examining the effects of testosterone suppression on muscle mass and strength in TW athletes show very modest changes after 12 months of treatment (approximately 5 %), in terms of lean body mass and muscle size, suggesting that the muscle advantage enjoyed by TW athletes is only minimally reduced when testosterone is suppressed. In fact, given the large baseline differences in muscle mass between males and females (approximately 40 %), the reduction achieved by 12 months of testosterone suppression can reasonably be assessed as small relative to the initial superior mass [83, 110–118].

It is likely that in TW athletes, and also depending on individual AR responsiveness [119], testosterone reduction cannot reset muscles to a female phenotype [102, 103, 108, 109] as testosterone suppression must not necessarily reach female serum testosterone concentrations (i. e., < 1.8 nmol/L) in all TW athletes, both prior to and during competitions, and because muscle memory for testosterone still stimulates fibers hypertrophy in response to mechanical loads [120, 121]. Furthermore, estrogen administration at relatively high doses for the 46XY gender also has a strong influence on muscle structure and physiology, attenuating the devirilization of the body's muscles [15, 25, 122, 123]. Many biological and functional differences between treated TW and eugonadal cisgender athletes exist (▶ **Table 6**), as not all gene-related gender characteristics can be partially or completely reversed by GAHT. In addition, due to gender-related drug metabolism, possible abuse with

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▶ **Table 6** Genetic-, endocrine- and treatment-related differences influencing health status, exercise physiology, and sporting performance between adult transgender women athletes treated with gender-affirming hormone therapy (e. g., exogenous 17β-estradiol or other estrogens; ± anti-androgens) and respective eugonadal cisgender adult athletes (in alphabetical order).

	Transgender Women Athletes Treated with GAHT	**Eugonadal Cisgender Athletes**
Legal, Psychological and Social Gender	**Female**	**Female**
Sex chromosomes	**46 XY**	**46 XX**
Biomechanics of movements*	Male Phenotype*	Female Phenotype
Body fat %	Lower	Higher
Bone mineral density	Normal/Reduced	Normal
E_2 and P adaptive responses to exercise	Absent	Present
Female sex hormone serum levels	Relatively High Stable EE	E_2 and P Physiological Rhythm
Hypothalamus-pituitary-gonadal axis	Inhibited	Active
Menstrual cycle	Absent	Present
Muscle cell memory for male's T levels*	Present*	Absent
Muscles distribution*	Male Phenotype*	Female Phenotype
Muscle mass and strength*	Higher vs. Female Phenotype*	Female Phenotype
Muscles response to exercise load*	Increased*	Physiological
Muscles-tendon anatomical structure*	Male Phenotype*	Female Phenotype
Peripheral responsiveness to androgens	Inhibited**/Male Phenotype	Female Phenotype
Pre-menstrual syndrome	Absent	Absent/Present
Skeletal anatomy*	Male Phenotype*	Female Phenotype
T and other androgen serum levels	± Female range	Female range
Cellular enzymes and metabolisms (e. g., heart, kidney, liver, muscles, neurons, and so forth)	Male Phenotype with Hypo-Testosteronemia*/**/***	Female Phenotype
Central nervous system physiology		
Drug metabolism/effects (i. e., gender-related pharmacology/toxicology)		
Hormone receptors (e. g., AR, ER, GR, PR)		
Hormone responses to psycho-physical stress		

AR, androgen receptors; E2, 17β-estradiol; EE, exogenous estrogens; ER, estrogen receptors; GAHT, gender-affirming hormonal treatment; GR, glucocorticoid receptors; P, progesterone; PR, progesterone receptors; T, testosterone. *These differences could be partially attenuated in the case of pre-puberty GnRH analogue therapy. ** Depending on anti-androgen assumption. *** Many cellular functions and metabolisms can be differently influenced by low serum T concentrations, as observed in male hypogonadism, and by a relatively high serum exogenous 17β-estradiol (or other estrogens) concentration.

prohibited substances may induce different effects in treated TW athletes with respect to cisgender athletes and male athletes.

We hypothesize that minimal differences between TW athletes and cisgender athletes related to behavior, mood, biomechanics of movement, functional and metabolic mechanisms, stress adaptation and fatigue perception (▶ **Table 6**), are also associated with differences in sport performance. These could be small differences, yet significant enough to separate a champion from other finishing positions.

When possible differences and advantages in sports for adult TW athletes are evaluated with respect to cisgender athletes, we highlight that transgender girls may start a treatment with GnRH analogues before puberty to suppress male pubertal development, and then later commence GAHT (± anti-androgens); if they became athletes, these TWs would not be expected to have the same differences vs. cisgender athletes and possible advantages in sports that a TW athlete may have when GAHT was commenced post-completion of male puberty (▶ **Table 6**).

Conclusions

From a healthcare perspective, sport physicians need awareness, knowledge, and understanding of sex steroid hormone variability and health concerns in the female athletic community (▶ **Tables 1,2,5**). In this context, the main issue should be to protect general and reproductive health by a) reducing all factors causing sports-related hypogonadism; b) monitoring reproductive/sexual symptoms; c) favoring specialized counseling for diagnosing and treating sport-related hypogonadism, diseases causing hyperandrogenism/DSD, and iatrogenic complications in TW athletes according to gender-based medical criteria; and d) evaluating sports eligibility when health complications appear. In addition, support staff should undertake HPO-axis-cycle profiling in athletes to support possible menstrual cycle-related sports performance issues [32].

In our opinion, it could be quite difficult to implement these roles for sports physicians as several factors (e. g., athletes' negligence, concomitant AAS abuse, ethical concerns, inefficient health care services, opportunistic behavior, personal choice, and socioeconomic aspects) can lead to the symptoms of hypogonadism

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and/or hyperandrogenism/DSD in female athletes not being declared. Moreover, due to possible health complications in TW athletes (▶ **Table 5**), difficulties in the standardization of the criteria for granting sports eligibility may exist in countries where a pre-participation medical evaluation is mandatory.

Even with individual variability and depending on performed therapy (▶ **Tables 2,6**), hyper-androgenic females and TW athletes might have small but useful advantages during sports competition. However, it is necessary to gather proportionate, evidence-based, and reproducible data to draw definitive conclusions [86, 124]. Specific case-by-case and sport-by-sport investigations are recommended and all genetic-, endocrine-, and treatment-related factors potentially influencing exercise physiology and the final result in competitions should be addressed (▶ **Tables 3,4,6**). Two serious obstacles should be taken into consideration: the final result in competitions is related to many difficult-to-measure factors, and it is challenging to detect the insignificant differences in performance (often less than 0.5–1.0 %) that separate the winner from others.

Only when we have gathered sufficient observational data on the number of female athletes with untreated hyperandrogenism and TW athletes who win first place in sports competitions will we have an idea of the true scale of this phenomenon. Moreover, observational clinical investigations on the prevalence of health complications in such populations are warranted. Even if difficult, we hope to rapidly reach a clinical and scientific consensus for health protection and sports eligibility in the female athletic community to guarantee inclusion, fairness, and safe case-by-case sports participation between cisgender and transgender female athletes and also between well-treated and untreated hyperandrogenic and transgender female athletes while simultaneously avoiding gender-related discrimination and abuse.

Conflict of Interest

The authors declare that they have no conflict of interest.

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