Commentary

Hyperandrogenism and Intersex Controversies in Women's Olympics

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International sports governing bodies such as the International Association for Athletics Federation and the International Olympic Committee have recently revised their policies for inclusion of athletes competing in women's international sports competitions. Previously, the focus was on verification of gender or femininity. The mishandling of Caster Semanya's case brought the complex issues of fairness with regard to athletes with disorders of sexual development or hyperandrogenism into both public and private debates. The new International Association for Athletics Federation and International Olympic Committee policies for inclusion in women's sporting events rest largely on the serum testosterone level, mandating that it be less than the lower limit of normal for men as the defining criteria. This report provides an overview of past problems and an update of the newly adopted policies for eligibility for competition in women's events. Endocrinologists will play a key role in the evaluation and treatment of women athletes who have elevated androgen levels, regardless of the underlying cause. (*J Clin Endocrinol Metab* 97: 3902–3907, 2012)

Caster Semenya, an 18-yr-old woman from South Africa, caused an international stir in 2009 when she won the 800-m race at the Track and Field World Championship in Berlin by 2.45 sec (1). She did not set a new world record, but her definitive victory and physical appearance raised questions about the participation of women with masculine build or intersex characteristics in international competitions. At the time of the Berlin competition, neither genetic testing nor medical evaluations were conducted on a routine basis, but suspicious cases could be referred for evaluation. In the midst of intense press coverage, Ms. Semenya was subjected to such an evaluation (1). The results have not been made public; however, speculation ensued regarding a possible intersex condition including undescended testes and high androgen levels. Her evaluation was described as bungled from the beginning but reflected the policies of both the International Association of Athletics Federations (IAAF) and the International Olympic Committee (IOC) for investigation of possible gender discrepancies.

This case, coupled with an equally problematic investigation of Santhi Soundarajan in 2006, prompted the IAAF and IOC to revisit the issue of fairness in women's sports, in particular the conundrum of fitting persons with complex genetic and phenotypic sex characteristics into dimorphic gender-based competition while ensuring fairness to other competitors. Thus, in 2010, the IAAF and IOC established expert committees to review and make recommendations regarding the inclusion of women with disorders of sexual development (DSD) or hyperandrogenism in international competitions without undermining fairness and while respecting individual rights and privacy (2). The new IAAF policy was released in May 2011, and the IOC policy now in place informed the procedures followed in the London Olympics (3, 4). The policies are not without controversy. Most importantly, rather than mandating tests for genetic or phenotypic sex, the newly adopted policies specify that hormonal testing, specifically the level of serum testosterone, will determine eligibility for competition in women's events. These new policies will involve endocrinologists in the evaluation and treatment of elite female athletes.

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Abbreviations: AIS, Androgen insensitivity syndrome; DSD, disorder of sexual development; IAAF, International Association of Athletics Federations; IOC, International Olympic Committee.

Background

Women first competed in the Olympics in 1900, but only in golf and lawn tennis. A few competed with mixed teams in sailing and equestrian events. Women's track and field events were added in 1928, and the first example of a female competitor with masculine features was Stalislawa Walasiewicz (later known as Stella Walsh), who won the 100-m race in 1932 (5, 6). When Helen Stephens from Fulton, MO, took the gold at the famed 1936 Berlin Olympics, headlines read: "Fulton Flash Beats Stella the Fella." Stephens was subjected to a gender verification examination, whereas Walsh continued to compete as a woman and was later determined to have ambiguous genitalia at autopsy in 1980 (5). Also at the 1936 Olympic Games, a high jumper competing as Dora Ratjen came in fourth. Heinrich Ratjen later admitted to being a male and related that he was instructed to bind his genitals by the Nazi regime to compete as a female but may in fact have had a DSD (6, 7).

More problems ensued in elite athletic competition after 1936 as world politics and advancing social change played out in the Olympics and other international competitions. In attempts to establish the perception of dominance, a number of countries and athletes themselves resorted to creative methods of cheating to reach these goals. Gender fraud was one such method, and doping with performance-enhancing substances became prevalent and highly problematic. Sex verification of female athletes began as a means to deter gender fraud, with a secondary but unclear mission of ensuring fair competition by excluding persons with intersex medical conditions that might confer physical advantages.

The history illustrated in Table 1 and innuendos of cheating prompted the IAAF and, subsequently, the IOC to establish rules of eligibility for competition in women's athletic events. In 1966, at the European Athletics Championships in Budapest, women athletes were required to undergo an inspection before a panel of three women doctors. The Commonwealth Games in Kingston, Jamaica, in 1966 also required a physical examination by a gynecologist of external genitalia (6, 8). Widespread resentment of these indiscreet testing methods, the so-called nude parades, prompted the IOC to consider other methods of testing.

At the 1968 Mexico City Olympics, the IOC introduced the sex chromatin (Barr body) test on a buccal smear as a method for gender verification (6, 9). The Barr body is a remnant clump of DNA that represents inactivation of one of two X-chromosomes, and thus male cells typically are negative and females are typically positive. A number of intersex conditions, however, make this test imperfect. For instance, Turner syndrome with a 45,XO chromosome pattern would render the female ineligible to compete but confers no physical advantage for the athlete. In contrast, a male with Klinefelter's syndrome, which carries a 47,XXY karyotype, would have passed the test. Several cases of mosaicism and androgen insensitivity syndrome (AIS) were identified during this process, disqualifying unsuspecting athletes (9).

The IOC continued to screen female participants even after the IAAF stopped mandatory screening in 1999 (6, 7) but replaced the Barr body test with a PCR analysis to detect the *SRY* gene, found on the Y-chromosome. This gene's product participates in the differentiation of internal gonads to testes, but later discoveries showed that other gene products also direct testes development, because rare individuals with XX chromosomes and no *SRY* genes have testicular tissue. Furthermore, it is also possible for the *SRY* gene to exist on the X-chromosome as a result of translocation during meiosis (10). The PCR test was abandoned after both technical and biological problems disqualified athletes later determined to be acceptable competitors. The IOC finally stopped mandatory testing of female athletes in 1999 (6, 7). The gender verification process, whether by physical examination or chromosomal inquiry, was a deterrent to gender fraud but presented logistic and biological issues that undermined the intended outcomes of fairness to all athletes. Using these tests, population-based estimates suggest that approximately one in 500–600 athletes would have been deemed ineligible for competition (10, 11).

IAAF and IOC: Current Guidelines

The IAAF was severely criticized for the clumsy handling of the Semenya case, both for the lack of a clear policy for inclusion in women's sports and for the public humiliation that the suspicion-based investigation caused Ms. Semenya. After a series of meetings with experts in the field, the IAAF released its updated policy that is based on the notion that hyperandrogenism, not chromosomes or the appearance of the genitalia, confer advantage in competition. This policy has been in effect since May 1, 2011 (3). The IOC released a similar policy in June 2012 (4). The IAAF policy defines the normal male range of total testosterone in serum as at least 10 nmol/liter (3). Only those athletes with testosterone levels below this range or an androgen resistance condition are permitted to participate in women's competitions. Under these new guidelines, an athlete can be identified for examination in two ways: 1) if she has already been diagnosed with hyperandrogenism or is "still in the course of diagnosis," she is required to

TABLE 1. History of gender policies in national and international athletics

Dates and sporting events	Policies and actions	Notable events	Refs.
1932	No policy	Stalislawa Walasiewicz wins the 100-m race	5, 6
1936	No policy	Helen Stephens beats Stella Walsh in the 100-m race and is subjected to gender verification examination; Heinrich Ratjen (a male, possibly with DSD) competed as Dora under Nazi orders and came in fourth	5, 6
1946	IAAF requires medical certificates to prove female	Nonstandardized certificates were issued by family or team doctors; first type of Fem card	2, 5, 6
1948 London Olympics	IOC follows IAAF, requires women to produce medical certificates	Controversy continues, cases of gender fraud and probable DSD generate news	2, 5, 6
1966–1967 numerous track and field events	Femininity testing by examination at the event	Described as naked parades	5, 6
1968 Winter Games, 1968 Summer Olympics	Barr body testing on a buccal smear	Every female Olympian was tested and given a gender certificate, known as a Fem card	2
1977	New York State Supreme Court rules that Renee Richards should be allowed to compete on the Women's Tennis Tour	Renee Richards, who underwent sex reassignment surgery at age 40, reached a rank of 20th in women's singles in 1979	24, 25
1985	Fem cards required	Maria Jose Martinez Patino failed the Barr body test, was disqualified, and lost a scholarship; later found to have complete AIS and after prolonged appeal was reinstated in 1988	1, 2, 5, 6
1990	IAAF recommends that gender verification be discontinued	Reliance on observation through athletic clothing and urine voiding, observed voiding if gender was challenged	1, 2, 5–7
1992 Winter Olympics	IOC institutes PCR for *SRY* analysis of all women	Female competitors have to prove that they are not male; technical problems occur	7, 13
1994 New York Gay Games	Federation of Gay Games (FGG) enacts transgender policy; female competitors have to prove completed transition (surgery plus hormonal support) for 2 yr	Protests from the international community prompt changes to the policy	24, 25
1996 Summer Olympics	PCR testing for *SRY* continues	8 of 3387 female athletes fail the test, 7 of which had partial or complete AIS, the 8th presumably had 5α-reductase deficiency; all 8 women were allowed to compete	5, 6, 13
1998 Amsterdam Gay Games	FGG requires medical proof of completed gender transition, including change to local documents and passports	Other stipulations: mixed-sex couples, including transgendered persons who could not document their transition, could not participate in ballroom dancing	24
2000	IOC discontinues gender testing but reserves the right to test if gender is challenged by officials or competitors	Suspicion-based medical examination	1, 2, 6, 7
2002 Sydney Gay Games	FGG loosens criteria; competitors present legal documentation, personal testimonial, or letter from medical practitioner regarding hormone treatment for 2 yr or proof of the participant living as the chosen or self-identified gender for 2 yr	FGG provides accreditation pass to registered participants, reminiscent of Fem cards	13, 24

(*Continued*)

TABLE 1. Continued

Dates and sporting events	Policies and actions	Notable events	Refs.
2003	IOC Medical Commission rules on sex reassignment issues, Stockholm Consensus	Mandates sex reassignment surgery and hormonal therapy for 2 yr if the transition occurs after puberty; no comment about testosterone injections for female to male transitions; however, transsexuality has to be recognized by the World Anti-Doping Agency, and a Therapeutic Use Exemption authorized	1, 13, 25, 26
2004 Summer Olympics	IOC adopts Stockholm Consensus		25, 26
2006 Asian Games in Doha, Qatar		Santhi Soundarajan was stripped of a silver medal in women's 800-m race; testing was performed after a challenge and observed voiding abnormality	1, 13
2009 World Championship Track and Field, Berlin		Caster Semenya is ordered by IAAF to undergo gender testing after winning a gold medal	1, 2
2011, 2012	IOC Medical Commission and IAAF adopt new policies: to compete in women's competition, the athlete must be recognized by law as a woman and have androgen levels below the male minimum or <10 nmol/liter	Persons with AIS are permitted as exceptions; the policy requires persons who fail the androgen testing limits to undergo treatment to normalize androgen levels	3, 4

notify the IAAF for evaluation, and 2) the "IAAF Medical Manager may initiate a confidential investigation of any female athlete if he or she has reasonable grounds for believing that a case of hyperandrogenism may exist" (3). The "reasonable grounds" for a case "may be derived from any reliable source," including information given to any IAAF medical delegate or other responsible medical official. If an athlete is identified for further evaluation, she must undergo any or all of three levels of testing: 1) an initial clinical exam, 2) an endocrine assessment, and/or 3) a "full exam" with possible genetic testing, psychological assessment, and imaging (3). If she does not meet the criteria, including a testosterone level below 10 nmol/liter, she will be given a therapeutic proposal and will be further banned from competition until she receives medical intervention, presumably with hormonal therapy or gonadectomy (3, 12). The new policies also recognize the right to privacy and the need for a comprehensive evaluation of suspected hyperandrogenism in women by specialists including endocrinologists, gynecologists, psychologists, and others with expertise in conditions causing excess androgen production.

The Controversy

Differences in stature, muscle bulk, and cardiovascular capacity confer an advantage for males over females in many sports. This advantage thesis is the basis by which international sports federations continue to segregate competition by sex. Gender verification has been the prevailing criterion to create a climate of fair play (13). Interestingly, there are at least 200 autosomal performance-enhancing polymorphisms (14). Many elite athletes have biological advantages that do not disqualify them from competition. Some elite endurance runners and sprinters have mitochondrial variants that provide increased aerobic capacity and resistance to fatigue (15–17). Athletes with mutations in the *ACE* gene (affecting muscle growth and efficiency) or the *NOS* gene (affecting blood flow to skeletal muscles) have also been identified (14, 18). Finally, basketball players with unusually large hands and feet due to acromegaly are not excluded from competition nor forced to undergo medical treatment to regulate hormonal levels to even the playing field with other competitors (19, 20). Even though testosterone levels are substantially higher in men compared with women, is it an appropriate measure for the determination of eligibility for competition in women's events?

The lack of definitive research linking hyperandrogenism in women to sporting ability is problematic, because nearly all previous research on testosterone and athletic performance has been done in males. Testosterone has been shown to act via different mechanisms in male *vs.* female animal models (21). In addition, the sensitivity to testosterone may vary between individuals of both sexes, as demonstrated by partial AIS. It is unknown, given both

the myriad complex sex traits and the number of sports involved, whether hyperandrogenism influences cardiovascular function, musculoskeletal structure, coordination and control, and the psychological aspects that relate to excellence in athleticism, either positively or negatively. Moreover, a total testosterone level at the lower level of the normal range for men is strikingly high for women, and laboratories using different techniques can report substantially different values (22, 23).

Despite this fact, the IAAF policy states (and the IOC policy infers) that a female athlete with a testosterone level in the male range (≥10 nmol/liter) must undergo treatment to lower her testosterone before competition. Given that medical treatment may be perceived as unnecessary by some individuals or in some cultures, this disregard for patient autonomy is worrisome for coercion. This policy also has no provision to pay for the medical care required for participation. Athletes from poorer nations or backgrounds who cannot afford treatment may be unjustly excluded from competition. The potential for discrimination and long-term psychological harm to these athletes is one of the considerations that prompted the new policies, but, as with any untested policy, the number of athletes disqualified, and the ultimate fairness of the policies for both individuals and women competitors is not known. It is hoped that with the focus on hyperandrogenism and not on examination or chromosomal testing, affected athletes will be identified before the competition and provided with options for treatment. Although suspicion-based identification of women athletes with hyperandrogenism is still possible, having a preemptory medical evaluation in place will provide greater confidentiality for athletes (3, 4).

Implications for Endocrinologists: Business as Usual or an Ethical Dilemma?

The new policies give endocrinologists a prominent role in the evaluation and treatment of women with the potential to become elite athletes. Whether these policies will be adopted by collegiate, state, and national athletic governing bodies is not known; however, all will be paying attention to the effectiveness of the screening guidelines in ensuring fair play. Although the upper boundary for testosterone level has been established, there are many open questions. Does the time of day of testing matter? Is it possible to predict progression of conditions causing hyperandrogenism, such that borderline cases do not become disqualified in subsequent months or years? Treatment decisions will be individualized, but to what extent is it safe and effective to reach the target in the most severe cases? Physicians may differ in their recommendations for lowering testosterone, and athletes with hyperandrogenism may elect to follow the advice or seek alternative recommendations (12). Considering anti-androgens used to treat this condition can have potentially debilitating side effects for an athlete (such as excessive thirst, electrolyte imbalances, liver toxicity, headache, fatigue, and insulin resistance), the aggressiveness of treatment is an important consideration.

In patients with some DSD, gonadectomy of undescended testes is recommended to reduce testosterone levels and to prevent malignant transformation. When should this occur? This procedure may reduce athleticism and cause side effects such as hot flashes that may further impede training of an individual with no functioning ovaries. Indeed, physicians and patients will have to weigh the short-term and long-term health consequences of androgen reduction therapy or procedures, or the converse, the addition of feminizing treatment. Although reducing excessive androgen levels in women with hyperandrogenism is considered the standard of care, treating an elite athlete who may have additional motives for needing treatment or limiting treatment will add a new dimension to decision making (12). Selected cases may present an ethical quagmire for physicians (1, 2, 12, 24, 25). Should treatment of a young woman with the potential to become an elite athlete be aimed at long-term health or short-term performance? Will physician recommendations and patient desires be aligned? When does patient autonomy trump physician recommendations?

Conclusions

The new IAAF and IOC policies for regulation of sex characteristics in women's sports now stipulate that competitors have testosterone levels lower than the lower limit of the male range, that is 10 nmol/liter or lower. This is a substantial change from previous policies that sought to assess the degree of femininity by examination of internal or external genitals, chromosomal assessment by Barr body testing, or PCR testing for the *SRY* gene, all of which posed logistical, technical, ethical, or biological problems. The controversy about the athletic advantage that hyperandrogenism confers to female athletes awaits further study, and consequently, whether these policies will ensure fairness is not known. Endocrinologists may be asked to care for elite athletes before international competition, placing them on the front lines of medical evaluation and intervention for selected cases of women with conditions that lead to elevated androgens.

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