The Rationale for Banning Human Chorionic Gonadotropin and Estrogen Blockers in Sport

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CLINICAL REVIEW: The Rationale for Banning Human Chorionic Gonadotropin and Estrogen Blockers in Sport

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Context: The objective of the study was to review the rationale underlying the banning of human chorionic gonadotropin (hCG) and estrogen blockers (antiestrogens, specific estrogen receptor modulators, aromatase inhibitors) in sports for male and female athletes in the light of gender differences in regulation of reproductive physiology.

Evidence Acquisition: We reviewed well-controlled clinical studies of exogenous testosterone effects on human muscle size and strength in men and all available evidence relevant to the effects of hCG and estrogen blockers on blood testosterone in men and women.

Evidence Synthesis: Well-designed placebo-controlled clinical studies in men with suppressed pituitary-testicular axis establish a strong case that, across a wide range from sub- to supraphysiological doses, muscle growth and strength is proportional to exogenous testosterone dose and resulting blood testosterone concentrations. In men, there is unequivocal evidence that hCG and estrogen blockers cause consistent and sustained rise in blood testosterone concentrations. In women, although there has been no direct testing of ergogenic or myotropic properties of exogenous testosterone in healthy women, either hCG or estrogen blockers do not produce any consistent or biologically significant increase blood testosterone concentrations.

Conclusions: In men undergoing potential stimulation of endogenous blood testosterone concentrations, blood testosterone concentration is a reasonable surrogate measure for muscle growth and increased strength in men. Because hCG and estrogen blockers produce marked increase in blood testosterone concentration in men, this provides strong evidence to support the banning of hCG and estrogen blockers in men. In women, however, the negligible effect on blood testosterone suggests that drug-induced performance enhancement by hCG or estrogen blockers is highly unlikely. Furthermore, routine urinary hCG testing in young women risks invasion of privacy by detecting unrecognized pregnancy. These considerations suggest that prohibition of hCG and estrogen blockers should be restricted to men in which they are well justified. (J Clin Endocrinol Metab 91: 1646–1653, 2006)

HORMONE ABUSE IS an important but often overlooked aspect of endocrinology. Among the most prevalent and serious form of hormone abuse is sports doping in which hormones remain the most popular and effective drugs for performance enhancement. If athletes succeed in violating fair competition and endangering their health by using ergogenic drugs, such hormone abuse would become effectively mandatory in elite sports with drastic implications not confined to sports but extending to the community at large for whom champions in sport are feted and emulated. Although there is increasing concern about the possible abuse of erythropoietin, GH, and glucocorticoids, the major form of sports doping remains androgen abuse. Although androgen physiology differs fundamentally in men and women, at suitable doses exogenous androgens enhance muscle mass and strength in all athletes. As a result, since the early 1970s exogenous androgens have been banned for men and women in sports. This ban has been enforced by urine testing using mass spectrometry-based methods to detect illicit administration of natural and synthetic androgens.

The regulation of sports doping is now the responsibility of the World Anti-Doping Agency (WADA), a Montréal-based subsidiary of the International Olympic Committee established in 1999, which coordinates the international fight against drug and related cheating in elite sports. Because fame and money are the drivers for drug cheating in sports, WADA’s policing at the top international level dictates an effective downward hierarchy of surveillance to national and regional levels of international sports. However, sports not participating at an international level can evade conforming with WADA scrutiny. The notorious toleration of androgen abuse in U.S. baseball and football, undermining both the integrity of sport and its respectability as the pinnacle of healthfulness, exemplifies the likely fate of other sports if they failed to go beyond outdated and laissez faire self-regulatory policing of drug cheating. Among WADA’s activities is the annual publication of the WADA Prohibited List in which proscribed drugs and methods of cheating are defined. Where there is a valid medical reason requiring therapeutic use of a banned substance, a therapeutic use exemption (TUE) can be approved.

In recent years, human chorionic gonadotropin (hCG) and estrogen blockers were added to the WADA Prohibited List for women as well as men. Whereas banning these agents appears well justified for men, there are doubts about the validity as well as adverse privacy implications for hCG testing when applied to female athletes. Similarly, the justification for prohibiting estrogen blockers in women is also dubious based on the absence of any plausible mechanism for potential estrogen-mediated ergogenic effects. This re-
view will focus on the reproductive endocrinology of these agents in men and women and the validity of their prohibition.

**Blood Testosterone as a Surrogate Variable for Sports Performance Enhancement**

For many years it was widely held that androgens would not enhance muscle mass or strength in eugonadal men and that contrary claims of performance enhancement by androgen abusers were mistaken attribution of placebo effects of diet, training, and expectation. This belief was epitomized by a technically excellent metaanalysis that concluded wrongly that androgens were no more effective than placebo (1). The fatal flaw in this analysis was that all component studies had been confined for ethical reasons to low doses of androgens that failed to emulate the massively supraphysiological doses conventionally used by androgen abusers. More recent studies from Bhasin and co-workers over the last decade (2–8) have shown incontrovertibly that testosterone has a steeply dose-dependent effect on muscle mass and strength regardless of gonadal status.

Nowadays the strongest and most coherent justification for banning androgens as performance-enhancing agents is derived from these studies that showed unequivocally for the first time that: 1) testosterone at supraphysiological doses and blood concentrations increases muscle mass and strength in healthy eugonadal men (2); 2) testosterone-induced increases in muscle mass and strength occur in men of all ages (8); and 3) testosterone effects on muscle mass and strength depend linearly on testosterone across a wide range from below to well above the physiological dose range and blood testosterone concentrations in men (5–7).

The latter findings validate the concept of blood testosterone concentrations as a surrogate marker for muscle effects of testosterone including both direct effects on muscle as well as indirect mechanisms such as via psychological effects on motivation. Thus, increases in blood testosterone concentrations within and above the normal male range, however produced, can be confidently predicted to have significant ergogenic effects. A key consequence of these findings is that testosterone effects on muscle mass and strength are proportional to dose and to blood testosterone levels attained. Similar conclusions probably apply equally to synthetic androgens, although the available evidence is far less, and to women in whom there is even less experimental evidence. Furthermore, proving an analogous case for a synthetic androgen is more difficult because of the difficulties in analytical measurement of blood levels, the variability in metabolite patterns including agonist and antagonist metabolites, and the variability of androgen activation patterns involving either 5α-reductase or aromatization.

Testosterone production rate is 20- to 30-fold higher (~7 vs. ~0.1–0.25 mg/d) in men (9–12) than women (13, 14). As a result, blood testosterone concentrations are typically approximately 10-fold higher in men (typical eugonadal range 10–30 nmol/liter), compared with normal young women (1–2.5 nmol/liter) (15). The upper limit in unselected women from the community may be a higher (3–4 nmol/liter) if women with polycystic ovary syndrome (PCOS) syndrome and its variants are included. Given the 10- to 20-fold lower testosterone production rates and blood testosterone concentrations in women, the studies of Bhasin et al. (2, 5–8) indicate it is very unlikely that changes within the physiologica range of blood testosterone concentrations in women can be considered muscle stimulating or ergogenic, although empirical proof is lacking. Nevertheless, increased blood testosterone concentrations in women that significantly exceed the normal female range are likely to be performance enhancing.

The testosterone production rate and blood testosterone concentrations in women are roughly equivalent to those in children and castrate men. As such, androgen-mediated effects such as muscle growth are implausible within that range of testosterone production and blood levels. Equivalent testosterone exposure does not cause muscle growth in boys until blood testosterone concentrations consistently exceed the prepubertal levels. This is readily explained by the binding affinity and dissociation constant of testosterone for the androgen receptor. Furthermore, the proposition that blood testosterone within the female range might exert androgenic effects has, in effect, been rendered implausible by the refutation of a synonymous hypothesis in the clinical context of castrated men. The complete androgen blockade hypothesis claimed that residual blood testosterone in men castrated for palliative treatment of advanced prostate cancer had persistent androgenic effects on androgen-sensitive prostate cancer cells that could be blocked by an antiandrogen (16). However, extensive clinical trials effectively refuted this hypothesis (17), notably in the context of this review for orchidectomized men eliminating the confounding influence of the flare phenomenon related to GnRH agonists used in medical castration. By analogy, equivalent blood testosterone concentrations in females or children are unlikely to exert significant androgenic effects. Whereas females are undoubtedly androgen responsive when they are administered exogenous testosterone or synthetic androgens, it is highly unlikely that variations in blood testosterone concentrations within the physiological range for young women have significant biological effects on muscle or other androgen sensitive variables in women. Direct clinical testing of this hypothesis involving a small effect size relative to the sensitivity of the detection methods would be difficult.

Whereas most focus on ergogenic effects of androgens including testosterone concerns direct muscular effects, additional nonmyotrophic mechanisms, especially psychotrophic effects of testosterone, may in theory contribute to performance enhancement. Exogenous androgens have long been known to be mood elevating, with testosterone being among the first generation of modern antidepressants (18). In men, standard replacement doses of testosterone have weak antidepressant properties in well-controlled studies (19–21), whereas high doses of androgens are associated with hypomania (22–26), with a claimed prevalence estimated at approximately 5% (26). It is therefore plausible that supraphysiological abuse doses of testosterone may have motivational effects on mood and behavior, which can become focused on enhanced training and/or interpersonal aggression or hostility. In women, recent placebo-controlled studies (27–31) have shown marginal effects of exogenous
transdermal testosterone in elevating some aspects of mood, but these effects were seen only with blood testosterone concentrations exceeding the eugonadal female range. The latter observation is not surprising because these studies mostly aimed to deliver 0.3 mg testosterone per day, at the upper end of estimates of normal female testosterone daily production rate, but this would be superimposed on and add to the endogenous testosterone production rate, which is minimally or not suppressed by negative feedback from exogenous testosterone in women, unlike in men in whom testosterone participates in a tight negative feedback on pituitary LH drive to Leydig cell testosterone production. Given the modest effects of standard male testosterone replacement doses in men, it is therefore unlikely that variations of blood testosterone within the female range will have major psychotropic effects on women relevant to sport performance for similar quantitative reasons as for the myotropic effects.

Regardless of potential myotropic or ergogenic effects of blood testosterone concentrations in young women, some variation in blood testosterone concentrations is already considered implicitly acceptable in sports. For example, women with PCOS, its variant, and various related conditions such as hirsutism and obesity-related ovarian dysfunction typically have mildly elevated blood testosterone concentrations up to blood testosterone concentrations of 3–4 nmol/liter. Beyond those levels, a virilizing tumor may be suspected clinically. Such women are clearly overrepresented in female power sports and are not considered ineligible to compete fairly unless there is evidence of drug use. In appraising the effects (if any) of hCG or estrogen blockers on women, this variation in acceptable blood testosterone concentrations should be considered.

**hCG**

hCG is a dimeric glycoprotein consisting of an α- and β-subunit (32) normally produced by the human placenta. The α-subunit is the product of a single copy gene identical with the α-subunit of the other three pituitary glycoprotein hormones LH, FSH, and TSH (33). The β-subunit of hCG is derived from a multicopy gene arising by duplication of the homologous single copy LH β-subunit gene. Crucially, hCG β-subunit includes a read-through C-terminal extension of 29 amino acids, containing four O-linked sialic acid capped glycosylation sites that markedly prolong the circulating half-life and biopotency of hCG, making it a naturally occurring analog of LH (34, 35).

Endogenous hCG is produced by the normal placenta in pregnancy or placental trophoblastic (hydatidiform mole, choriocarcinoma), gonadal (ovarian, testicular or extragonadal teratoma), or ectopic and nontrophoblastic tumors. In clinical practice, the identification of hCG immunoreactivity in blood or urine is used for early pregnancy diagnosis as well as a tumor marker. Biologically active heterodimeric hCG is manufactured pharmaceutically as a biological product either purified from human pregnancy urine or as a recombinant glycoprotein purified from genetically engineered mammalian cells.

**Estrogen blockers**

Estrogen blockers include antiestrogens such as steroidal and nonsteroidal drugs that block estrogen receptor action and aromatase inhibitors that block the enzymatic synthesis of estradiol.

The original class of estrogen blockers was antiestrogens. These are drugs that bind to and block estrogen receptor-α and/or -β. The original antiestrogens were the nonsteroidal drugs clomiphene (Clomid) and tamoxifen (Nolvadex). Subsequently newer estrogen receptor blockers have been developed as a class of partial or mixed estrogen agonists, often described by the marketing term specific estrogen receptor modulator (SERM). These agents display a mixture of estrogen agonist and antagonist properties that differ between tissues and between drugs. Drugs in this growing class include the nonsteroidal drugs raloxifene (Evista), toremifene (Fariston), droloxifene (FK-435), lasoxifene (LY326315), idoxifene (CB-7432), arzoxifene, and bazedoxifene as well as the steroidal estrogen analog fulvestrant (Faslodex, ICI 182,780).

Aromatase inhibitors are also a rapidly growing class of drugs including both steroidal and nonsteroidal mechanism-based inhibitors (36). The steroidal agents are mostly androstenedione analogs like testolactone, formestane (Lentaron), exemestane (Aromasin), and atamestane. The nonsteroidal agents are fadrozole, letrozole ( Femara), anastrozole (Arimidex), vorozole (Rivizor), and finrazole (MPV-2213).

**Men**

For men, the prohibition on hCG and estrogen blockers is unequivocally justified. Both produce sustained and significant increases in endogenous testosterone production and blood testosterone concentrations. Whereas there are no direct studies of the ergogenic effects of hCG or of estrogen blockers, the case for prohibition is well established using blood testosterone concentrations as a reliable surrogate variable for increases in muscle mass and strength. One study of 40 healthy older men (>60 yr of age) showed increased lean (muscle) mass but no increase in shoulder or knee strength measured by dynamometry during 3 months treatment with recombinant hCG, compared with placebo (37). It is likely, however, that the modest, replacement dosage and older age of the participants may underestimate the ergogenic potential of hCG for elite male athlete who would seek to abuse this drug.

**hCG**

Clinically, hCG is used as a naturally occurring long-acting and potent LH analog. The only legitimate clinical indication for hCG is to restore endogenous testosterone production and normalize blood testosterone concentrations in gonadotrophin-deficient men (38) including delayed male puberty. There are virtually no proven off-label uses for hCG in routine clinical endocrinology practice. Among androgen abusers, however, hCG is apparently misused by male athletes in two settings according to the underground androgen abuse folklore. In one scenario men who have developed sustained inhibition of their hypothalamic-pituitary testicular axis from prolonged high-dose androgen abuse seek to rectify this by increasing testicular testosterone production using hCG. In reality, this continues hypothalamic-pituitary
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suppression, which causes the reduced testis size and testo-
tosterone production and defers the problem of hypo-
thalamo-pituitary recovery, which is usually slow but com-
plete (39), so that hCG treatment, although feasible (40–43),
is rarely justified clinically (44). The other setting is that of
androgen abusers seeking to avoid detection of synthetic
androgens or exogenous testosterone by stimulating endo-
genous testosterone production. Preliminary information sug-
gests that the testosterone-to-epitestosterone (T/E) ratio is
unaffected by hCG treatment (45), consistent with its stim-
ulation of endogenous testosterone production by Leydig
cells, producing a characteristic testosterone to estrogen ratio
for that individual, which is no different from natural endo-
genous testosterone production.

In normal men, hCG produces a sustained and dose-
dependent increase in blood testosterone concentrations
through stimulation of Leydig cell testosterone secretion.
This is well established for purified urinary (46, 47) and
recombinant (48) hCG. Typically, the basal blood testoster-
one concentrations (∼20 nmol/liter) are increased to con-
centrations of 30–40 nmol/liter, peaking between 2 and 4 d
after a single injection at typical clinical doses (46, 48). Both
the peak blood testosterone responses and the time of peak
are log-dose dependent for purified urinary (46) and recom-
binant (48) hCG. These markedly increased blood testoster-
one concentrations, with increments of 10–30 nmol/liter, are
within the range defined experimentally as having a log-
linear relationship with increased muscle mass and strength
in men. They are therefore highly likely to increase muscle
mass and strength. Hence, prohibition of hCG for men is well
justified.

An unintended consequence of testing for male athletes
urine for hCG is the incidental diagnosis of hCG-secreting
germ cell tumors. Whereas minute amounts of hCG are de-
tectable in highly concentrated urine from healthy young
men (49), readily detectable quantities usually signify the
diagnosis of a germ cell tumor of testicular or, rarely, of
extratesticular origin or an ectopic hCG-secreting tumor.
Such incidental diagnoses are made through sports doping
tests.

An issue created by gender disparities in sports doping
rules is the definitional boundaries of gender (50). In practical
terms, the banning of hCG is required for anyone having at
least one functional testis. On that basis, it is doubtful a priori
whether a ban on hCG is justified for women or men lacking
both testes.

Estrogen blockers. There are no valid clinical indications
for estrogen blockers in men. Accepted off-label use for estrogen
blockers would be limited to men with breast cancer, an
exceptionally rare tumor. Some limited experimental uses for
estrogen blockade in men have included delayed puberty,
short stature, gynecomastia, spinal growth, and idiopathic
male infertility. Given the lack of convincing evidence es-
tablished for any of these experimental indications, it is un-
likely that TUE for estrogen blockers in men would be jus-
tified, apart from exceptional circumstances.

Because there are no proven or likely indications for es-
trogen blockers in men, there are few clinical studies on the
effects of modern estrogen blockers in men. There is, how-
ever, abundant and consistent evidence that estrogen block-
ers increase blood testosterone concentrations in men. How-
however, it is well established that in normal men antiestrogens
such as clomiphene (51, 52), tamoxifen (53–55), and ralox-
ifene (56, 57) cause a reflex rise in pituitary gonadotrophin
secretion and consequently in blood testosterone concentra-
tions. This is attributable to their inhibition of testosterone-
negative feedback on the hypothalamus, a process that in-
volves local aromatization of testosterone within the brain. A
similar increase in blood testosterone concentrations ranging
from 5 to 20 nmol/liter is reported with aromatase inhibitors
such as testolactone (58–60), exemestane (61), and anastro-
zole (62). By virtue of their common mechanism of action in
inhibiting that part of testosterone’s negative hypothalamic
feedback due to aromatization, it is highly likely that all
estrogen blockers would have similar class-wide effects, pro-
tional to their estrogen-blocking effectiveness.

It is notable that blood testosterone concentrations are
markedly increased in mice with complete inactivation of
aromatase (63) or estrogen receptors-α (64) but not -β (65),
with consequences for androgen receptor-mediated effects
on bone (65), prostate (63), and smooth muscle (66, 67), al-
though skeletal muscle effects have not yet been reported.
This predicts that more effective estrogen blockade in men
would produce significant and sustained elevations of blood
testosterone concentrations and likely myotrophic and er-
genetic effects in men treated with such drugs.

Hence, these observations make a strong case to ban es-
trogen blockers in men due to their class-wide ability to
provoke reflex increase in endogenous pituitary LH and
endogenous testosterone secretion.

Women

hCG. The prohibition of hCG in women is not clearly justified
in terms of performance enhancement or athlete safety. In
addition, routine urine hCG measurement results in signif-
icant invasion of female athlete privacy as a result of the
unintended screening for pregnancy. Each of these issues is
considered in turn.

Performance enhancement. The available evidence suggests
that hCG has negligible, if any, stimulation of blood testos-
terone concentrations in healthy young women. Together
with the prevailing low blood testosterone levels in women,
this makes it highly unlikely that any myotrophic or ergo-
genetic effects are produced by administration of hCG to
women.

A major consideration setting the framework for consid-
ering the effects of hCG in women is the relatively high
population prevalence of women with PCOS and its variants.
These conditions span a wide spectrum of ovarian disorders
all featuring mild increased blood testosterone concentra-
tions in the female range, although still an order of magni-
tude lower than in men. Key features of PCOS are multiple
ovarian cysts associated with ovariary and menstrual dys-
function, hyperandrogenism (acne, hirsutism), and insulin
resistance (obesity, metabolic syndrome). Definitions of the
disorder vary from higher prevalence rates using a European
definition with a focus on ultrasound criteria, compared with
the American definition, which focus on clinical criteria requiring ovarian dysfunction and hyperandrogenism (68, 69). Because asymptomatic polycystic ovaries are a relatively common finding among unselected women with pooled prevalence estimates approximately 20% (68, 69), population estimates depend heavily on the criteria used. Using the narrower American definition for PCOS, the population prevalence has been estimated at 4% (70), whereas the broader European definition identifies 8–10% of unselected women as having PCOS. An even larger proportion of women have isolated features such as acne, hirsutism, and obesity insufficient to make the formal diagnosis of PCOS. Mild increase in blood testosterone concentration is a very common, near universal feature of women with PCOS and, to a lesser extent, women with incomplete forms of PCOS. Hence, blood testosterone concentrations of up to 3–4 nmol/liter in untreated women with severe PCOS are typical, compared with women with normal ovarian function (upper limit is 2–2.5 nmol/liter). It is tacitly accepted that women with even severe PCOS are not barred from sports. Indeed, it is common experience that they appear to be overrepresented in power sports (71). This indicates that mild hyperandrogenism is already an accepted feature in female sports and thereby sets an existing upper limit for what is considered acceptable. This yardstick has relevance to considering the acceptability of the minimal, if any, increases in blood testosterone produced by hCG in women.

The best available evidence indicates that administration of 250 µg recombinant hCG to young women produces a rise of approximately 0.25 nmol/liter in blood testosterone concentration (48). This increase is less than (about half) the diurnal rhythm in blood testosterone concentrations in women. Based on the findings of Bhasin et al. (2, 5–8), increases of such small magnitude are highly unlikely to have any measurable effect on muscle mass or strength. Corroborative findings are available showing minimal or no increase in blood testosterone concentrations in women treated with urinary-purified hCG at chronic low dose (72, 73) or conventional high dose (74–82). Administration of urinary hCG (5,000 to 10,000 IU, ~330–660 µg) to young women with normal ovarian function produced either no or minimal (~1 nmol/liter) increase in blood testosterone concentrations (74, 76–82). The minority of women with PCOS with higher baseline blood testosterone concentrations have slightly higher increases (2–3 nmol/liter) (74, 75, 81), but these remain of small magnitude in quantitative terms for myotrophic effects.

An important caveat on blood testosterone measurements in some of these studies is the unreliability of conventional commercial immunoassays for blood testosterone, compared with well-validated in-house immunoassays (83). In the low range of blood testosterone concentrations, such as in samples from women, children, or castrate men, the validity of commercial testosterone immunoassays has been described as comparable with random number generation (84). Because most studies of hCG effects in women have used unreliable testosterone assays, their findings remain questionable and will require further critical evaluation using mass spectrometry based methods (83, 85, 86). Beyond evaluating blood testosterone concentrations, measurements of muscle mass in women with PCOS suggest blood testosterone concentrations may be significantly correlated with their muscle mass (87–89); however, the significance of these correlations at such low blood testosterone concentrations remains speculative as far as performance capabilities go (71). As usual, the directionality of such correlations cannot be reliably determined from observational data.

Safety. The regular exposure of women to very high levels of endogenous hCG during pregnancy as well as the extensive, reassuring safety experience of recombinant and urinary hCG during decades of use in ovulation induction and in vitro fertilization hyperstimulation provides evidence that hCG does not pose any unusual health risks for women. Known adverse effects related to hCG treatment include ovarian hyperstimulation syndrome (OHSS). OHSS is a rare but serious consequence of ovarian hyperstimulation. In effect is an FSH overdosage (and/or hypersensitivity) phenomenon, and neither is hCG primarily responsible for OHSS nor is it likely that hCG treatment alone would induce OHSS. Additional theoretical risks to women from use of exogenous hCG include disturbances of fertility either through the immediate but temporary disruption of menstrual cycling and ovulation as well as the possibility of inadvertent hCG autoimmunization so that autoantibodies might interrupt hCG action leading to recurrent abortion. Temporary disruption of ovulation and menstruation are not considered major health risks, whereas the latter hypothetical risk does not appear to have been reported as a consequence of hCG administration to women. For these reasons, there is little valid argument that hCG should be banned for female athletes for safety reasons.

Unintended health screening and privacy. Experience with urine testing of female athletes for hCG has led to detecting pregnancy or miscarriage, sometimes unknown to the athlete with potentially serious psychological consequences. For these reasons, screening women for hCG requires particular strong justification for a potential role in sports performance enhancement.

Estrogen blockers. Estrogen blockers were originally developed for use in women, mainly for prevention and adjuvant treatment for estrogen-dependent breast cancer. Subsequently estrogen blockade has developed additional applications such as for treatment of benign breast disease and anovulatory infertility due to PCOS or hypothalamic-pituitary dysfunction. More recently partial or mixed estrogen analogs having estrogen agonist and/or antagonist properties that differ between tissues have been developed as SERMs (90, 91). In addition, a new class of estrogen blockers has been developed based on inhibition of aromatase, the last steroidogenic step in estradiol synthesis (36). The abundant and increasing valid clinical indications for estrogen blockers in young women would almost certainly require granting a growing number of TUEs, creating a predictable workload.

There appear to be no specific studies of myotrophic or ergogenic effects of estrogen blockers in women. In the absence of direct studies, the blood testosterone concentrations can be used as a surrogate measure of androgenic effects from estrogen blockade. Clinical studies of antiestrogens and
aromatase inhibitors in women show no evidence of stimulation of blood testosterone concentrations.

A key difference between male and female reproductive endocrinology is that, whereas in men estradiol (derived from aromatization of testosterone) plays a significant role in negative feedback regulation of blood testosterone concentrations, in women there is no such regulation. In women the very low blood testosterone concentrations are derived from adrenal, ovarian, and extraglandular sources but are not directly involved in any homeostatic feedback regulation. Hence, estrogen blockade in women would not be expected to influence adrenal or extraglandular testosterone production and the contribution of direct ovarian testosterone secretion is small. This expectation is vindicated by empirical evidence that in antiestrogens or estrogen analogs (92–94) and aromatase inhibitors (95–101) show no effect to increase and, in some cases, reduce blood testosterone concentrations.

Caveats on interpreting these findings are that: 1) most involve postmenopausal women; 2) blood testosterone measurements are mostly made using commercial testosterone assays that are unreliable for female samples (83, 85, 86); and 3) antiestrogens might have some intrinsic androgenic activity. In regard to the first point, it is unlikely and there is no evidence that the small component of direct ovarian testosterone production is subject to feedback regulation during estrogen blockade. On the last point, all modern estrogen-blocking agents are screened for androgenic activity, and it is a reasonable assumption that they are free of major androgenic effects. There are no reports of androgenic effects such as acne or hirsutism caused by antiestrogens or aromatase inhibitors as are usually reported with many androgenic progestins such as gestrinone (102).

Conclusion

In conclusion, there is no convincing evidence that either hCG or estrogen blockers (antiestrogens, SERMs, aromatase inhibitors) cause any consistent or biologically significant increase blood testosterone concentrations in women. In the absence of direct testing of ergogenic or myotrophic properties, blood testosterone is a reasonable surrogate maker, suggesting that drug-induced performance enhancement is most unlikely.

Both classes of agent are in regular clinical use and neither poses sufficient safety risks sufficient to warrant banning in sports on the basis of protecting female athletes safety.

Finally, the adverse privacy implications of hCG testing and the unjustified workload of extra TUEs for estrogen blockers in women suggest that the prohibition of these classes of agents should be restricted to men in whom they are well justified.

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