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Indirect androgen doping by oestrogen blockade in sports

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Abstract

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Androgens can increase muscular mass and strength and remain the most frequently abused and widely available drugs used in sports doping. Banning the administration of natural or synthetic androgens has led to a variety of strategies to circumvent the ban of the most effective ergogenic agents for power sports. Among these, a variety of indirect androgen doping strategies aiming to produce a sustained rise in endogenous testosterone have been utilized. These include oestrogen blockade by drugs that act as oestrogen receptor antagonists (antioestrogen) or aromatase inhibitors. The physiological and pharmacological basis for the effects of oestrogen blockade in men, but not women, are reviewed.

Keywords: oestrogen, androgen, sports doping, antioestrogen, aromatase inhibitor, performance enhancement, elite sport, power sport

Androgen doping

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At suitable doses, exogenous androgens enhance muscle mass and strength in athletes regardless of gender or age. As a result, in the early 1970s, International Olympic Committee banned exogenous androgens for male and female athletes, a ban now enforced by its World Anti-Doping Agency that specifies urine testing using mass spectrometric detection of any synthetic androgens or illicit administration of natural androgens. Nevertheless, androgens remain the most-widely abused class of ergogenic drugs in sports. In 2006, the 34 international World Anti-Doping Agency-accredited doping-control laboratories registered 4332 positive findings, of which 45% were due to androgens, three times the next most-frequent category of banned agents. The exquisitely sensitive detection of even trace amounts of synthetic androgens for months after last administration has created a strong disincentive to use this most effective and available class of doping agents. Subsequently, strategies have been developed to circumvent the ban on androgen doping by various indirect androgen doping approaches. These aim to increase endogenous testosterone, hoping it would exploit the myotrophic effects of androgens but bypassing the sanctions on direct androgen doping.

Indirect androgen doping

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Indirect androgen doping methods aim to stimulate luteinizing hormone (LH)-dependent Leydig cell testosterone biosynthesis and secretion. The two main indirect androgen doping approaches have been either (a) direct stimulation by administration of exogenous LH or human chorionic gonadotrophin, a placental glycoprotein and long-acting natural analogue of LH or (b) indirect stimulation by increasing endogenous LH (Handelsman, 2006).

Endogenous LH secretion is tightly regulated by hypothalamic gonadotrophin-releasing hormone (GnRH) secretion (Keenan *et al*., 2006). The distinctive feature of GnRH physiology is that its intermittent secretion in brief bursts from hypothalamic neurons into the pituitary portal system is both

necessary and sufficient to entrain the physiological pattern of blood LH levels, characteristically highly pulsatile with peaks at 60- to 90-min intervals (Belchetz *et al*., 1978; Nakai *et al*., 1978). Administration of exogenous GnRH in any non-pulsatile fashion rapidly desensitizes pituitary gonadotrophs and suppresses their secretion of LH, which only recovers when intermittent GnRH administration is restored (Belchetz *et al*., 1978; Nakai *et al*., 1978). Consequently, replicating physiological pulsatility by intermittent delivery of brief bursts of GnRH is a *sine qua non* to maintain physiological circulating LH and testosterone levels. For example, in men who are gonadotrophin-deficient due to GnRH deficiency, restoration of physiological circulating LH and testosterone levels is only achieved by intermittent GnRH administration, typically administered by mechanical pumps worn around the clock and delivering timed, small GnRH doses at 60- to 90-min intervals (Hoffman and Crowley, 1982; Pitteloud *et al*., 2002). Although not directly tested, this cumbersome treatment if it was superimposed on normal GnRH physiology in eugonadal men is likely to suppress, rather than enhance, endogenous LH and testosterone secretion. Similarly, sustained non-physiological stimulation of pituitary gonadotrophs by superactive GnRH agonists in older men with prostate cancer causes a transient ‘flare' lasting 5–10 days during which LH and testosterone are moderately elevated (Labrie *et al*., 1987; Thompson *et al*., 1990; Bubley, 2001; Noguchi *et al*., 2001; Tsushima *et al*., 2001; Debruyne *et al*., 2006) before the onset of the profound and sustained inhibition of LH and testosterone secretion, now used clinically to maintain medical castration for hormone-dependent cancers (Engel and Schally, 2007). Hence, although exogenous GnRH and its superactive analogues can transiently increase endogenous LH levels by direct stimulation of pituitary gonadotrophs, such pharmacological (non-pulsatile) GnRH exposure cannot sustain supraphysiological LH and testosterone levels in men. GnRH and its analogues are not banned by World Anti-Doping Agency as sports doping agents.

Indirect androgen doping requires a sustained increased in endogenous LH secretion. In turn, this can only be achieved by manipulating physiological regulatory systems governing pulsatile hypothalamic GnRH secretion. Factors known to enhance endogenous hypothalamic GnRH secretion include (a) neurotransmitters acting on excitatory glutamate, α-aminobutyric acid, noradrenergic, galanin and/or NPY receptor systems, (b) neuropeptides such as kisspeptin and its analogues acting as GPR54 agonists (Plant, 2006) and opioid peptides or analogues acting as μ-opioid antagonists (Cicero *et al*., 1979; Delitala *et al*., 1983) and (c) blockers of sex-steroid negative feedback such as antiandrogens and oestrogen blockers like antioestrogens or aromatase inhibitors.

Furthermore, although drugs that acutely stimulate endogenous GnRH secretion via specific neurotransmitter or neuropeptide mechanisms can produce short-term or transient elevation of LH (Mendelson *et al*., 1980; Delitala *et al*., 1983; Veldhuis *et al*., 1983; Mauras *et al*., 1987; Graves *et al*., 1993), these effects attenuate over time, so they do not maintain a sustained increase in endogenous testosterone production. Drugs in these categories such as μ-opioid antagonists (naloxone, naltrexone, nalmephene) are not banned by World Anti-Doping Agency.

Blockade of oestrogen action is, however, one form of indirect androgen doping that can stimulate sustained, albeit modest, increases in endogenous LH secretion in physiological pulsatile patterns sufficient to maintain a modest increase in blood testosterone concentrations (Handelsman, 2006). This review will focus on the mechanism of action and scope of the need for detection and deterrence of oestrogen blockers as sports doping agents.

Endocrine physiology of oestrogen blockade

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The natural androgens, testosterone (T) and androstenedione, are obligate precursors of estradiol, the major natural oestrogen. The last step in the conversion of androgens to oestrogens is achieved by the steroidogenic enzyme aromatase (CYP19) in excising the C19 methyl group to convert the C19 androgen structure to a C18 structure with an aromatic A ring. Not all natural androgens are aromatizable, however, as dihydrotestosterone (DHT), the most-potent natural androgen, cannot be converted to an oestrogen. Aromatase is strongly expressed in reproductive tissues (placenta, ovary, testis, breast, uterus, prostate) as well as in non-classical oestrogen target tissues such as the brain, bone and fat (Simpson, 2004), with only low levels expressed in skeletal muscle so that tissue estradiol concentrations remain low compared with oestrogen target tissues (Aizawa *et al*., 2007). As aromatization is an irreversible reaction with no alternative pathway, complete blockade of aromatase

would effectively abolish estradiol synthesis and eliminate oestrogenic oestrogen receptor (ER)-mediated effects.

Oestrogen action is mediated by the nuclear ER-α and -β, homologous but distinct members of the superfamily of steroid nuclear receptors that act as ligand-activated transcription factors (Mangelsdorf *et al*., 1995). ER-α and -β are expressed strongly in the brain but much less in smooth, cardiac and skeletal muscle (Katzenellenbogen *et al*., 2000; Dahlman-Wright *et al*., 2006; Heldring *et al*., 2007). In skeletal muscle, ER expression is low (Lemoine *et al*., 2003) and responds to muscular training without any difference between genders (Wiik *et al*., 2005a, 2005b). Skeletal muscle also expresses the distinct, metabolically active (but not oestrogen-activated) oestrogen-related receptors α, β and γ (Smith and Muscat, 2005). There is no evidence that ER-mediated estradiol action produces any direct myotrophic or ergogenic effects in humans (Armstrong *et al*., 1996; Ribom *et al*., 2002) or animals (McCormick *et al*., 2004). A report that oestrogen replacement in menopausal women improves muscle strength also observed effects of similar magnitude from exercise that were non-additive with the effects of oestrogen replacement. This is most consistent, with the improved muscular strength on oestrogen replacement being a consequence of motivational effects of oestrogen in alleviating menopausal symptoms and encouraging more exercising rather than direct effects of oestrogens on muscle (Taaffe *et al*., 2005).

Oestrogen blockade decreases oestrogen action in target tissues, including the hypothalamus and pituitary. Oestrogen negative steroidal feedback is a critical component of the hormonal regulation of gonadal function not only in women but also in men, where it depends on local aromatization within the hypothalamus (Winters *et al*., 1979; Winters and Troen, 1985; Hayes *et al*., 2000, 2001; Schnorr *et al*., 2001). Blocking oestrogenic negative feedback therefore replicates the effects of castration and unleashes a reflex increase in episodic hypothalamic GnRH secretion into the pituitary portal system. This then entrains enhanced pulsatile LH and follicle-stimulating hormone secretion from pituitary gonadotrophs into the bloodstream. The gonadotrophin-hypersecretion response to oestrogen blockade is qualitatively similar in all adults; however, downstream consequences depend on gender, gonadal function and age. In pre-menopausal women with responsive ovaries, the surge in gonadotrophin secretion increases follicular growth and development leading to increased estradiol biosynthesis and secretion and ovulation, often multiple, of dominant follicle(s). This resembles the effects of exogenous gonadotrophins except that ceiling effects of pituitary gonadotrophin secretion limit the degree of ovarian stimulation so that antioestrogens have much lower risks of ovarian hyperstimulation. Stimulating ovulation created the first clinical use of antioestrogens, and clomiphene has been used therapeutically to induce ovulation since the early 1960s (Dickey and Holtkamp, 1996), remaining after 4 decades the standard first-line treatment for anovulatory infertile women with hypothalamic amenorrhoea (Beck *et al*., 2005). The consequences of oestrogen blockade in pre-menopausal women may differ according to the class of oestrogen blocker drug used. All antioestrogens (that is, competitive antagonists of estradiol at hypothalamic and pituitary ERs) create a reflex rise in blood gonadotrophins and estradiol. In contrast, aromatase inhibitors, by abolishing estradiol synthesis, additionally reduce or eliminate the reflex rise in blood estradiol with the net effects depending on the balance between gonadotrophin hyperstimulation and blockade of estradiol synthesis. For these reasons, aromatase inhibitors are generally not recommended for treatment of breast cancer in pre-menopausal women (Smith and Dowsett, 2003).

In women lacking functional ovaries (for example, post-menopausal, post-ovariectomy), however, the oestrogen blockade-induced gonadotrophin surge is unable to stimulate primordial follicles to produce either mature follicles or ovarian oestrogen secretion. In this setting with inactivation of the closed-loop negative feedback, oestrogen blockade by either drug class is more effective at enhancing complete oestrogen withdrawal and facilitating their efficacy in treatment of oestrogen-dependent cancer, not only in the breast but also in uterine, ovarian and hepatic tumours (Brueggemeier *et al*., 2005). Similarly, the low-oestrogen background in post-menopausal women is also a suitable setting for the tissue-selective partial oestrogen agonists (‘specific oestrogen receptor modulators') for treatment of osteoporosis (Riggs and Hartmann, 2003).

In men, selective oestrogen blockade has lesser effects on peripheral tissues as circulating blood estradiol levels are low, comparable to children and post-menopausal women. Only ∼0.3% of daily

testosterone production is converted to estradiol (Longcope, 1982). Nevertheless, the higher (~100-fold) molar potency of estradiol compared with testosterone, together with the strong expression of aromatase in some specific tissues that produce estradiol locally, means that aromatization has tissue-specific biological significance in men. For example, strong aromatase expression and local estradiol production from testosterone have physiological significance in male brain, bone and fat (Murata *et al*., 2002). In contrast, other tissues such as muscle express little aromatase or ER-α or -β and are consequently little influenced by aromatization of testosterone (Simpson, 2003, 2004). Hence, oestrogen blockade in men is unlikely to exert direct myotrophic effects. Instead, the indirect effects of central oestrogen blockade producing a reflex rise in circulating blood testosterone is more relevant and possibly sufficient to exert myotrophic effects. The increase in blood testosterone concentrations is, however, modest and much less than the effects of testosterone injections, for example. This is particularly important because the magnitude of the rise in blood testosterone concentration is a valid surrogate variable for the ergogenic effects in indirect androgen doping, regardless of whether effects involve direct effects on muscle and/or indirectly via psychological effects on motivation (Handelsman, 2006).

Clinical pharmacology of oestrogen blockade

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Drugs may block oestrogen action by blocking either estradiol synthesis or action. The first class of oestrogen blockers were steroidal and non-steroidal antioestrogens that block ER action by competitively binding to ER-α and/or -β (Jordan, 2007). Subsequently, aromatase inhibitors were developed to block the enzymatic synthesis of estradiol (Brueggemeier *et al*., 2005). Although the two classes of oestrogen blockers differ in some pharmacological and clinical aspects, from the sports doping perspective, all antioestrogens are likely to have similar class- and gender-specific effects on athletes.

The original class of antioestrogens are drugs that bind competitively to oestrogen receptor α and/or β to block oestrogen action. The original antioestrogens were the non-steroidal drugs cholorotrianisene (TACE), etamoxytriphetol (MER-25), clomiphene (Clomid) and tamoxifen (Nolvadex) (Dickey and Holtkamp, 1996). Subsequently, newer oestrogen receptor blockers have been developed as a class of partial or mixed oestrogen analogues that have tissue-specific oestrogen agonist or antagonist effects (‘specific oestrogen receptor modulator'). These agents display a mixture of oestrogen agonist and antagonist properties that differ between tissues and between drugs (Jordan, 2007), and are intended for prolonged use for prevention or treatment of oestrogen-dependent cancers. For example, a favourable profile of a mixed partial oestrogen agonist is a drug that exerts oestrogen agonist effects on bone and vascular system, but is an oestrogen antagonist in the breast and uterus (Jordan and O'Malley, 2007), and the newest antioestrogen drugs have various combinations of these mixed agonist/antagonist features at each tissue. Drugs in this growing class include the non-steroidal drugs raloxifene (Evista), toremifene (Fariston), droloxifene (FK-435), lasoxifene (LY326315), idoxifene (CB-7432), arzoxifene and bazedoxefine as well as the steroidal oestrogen analogue fulvestrant (Faslodex, ICI 182780).

Aromatase inhibitors are a more recent development in pharmacological oestrogen blockade aiming to block estradiol synthesis rather than estradiol action on ERs. The astute observations that the efficacy of aminoglutethimide for treating advanced breast cancer (Santen *et al*., 1977; Smith *et al*., 1978) was largely attributable to its blocking of aromatase (Santen *et al*., 1979) provided the lead for a new class of oestrogen blocker. Aminoglutethimide was used to inhibit adrenal function as an alternative to adrenalectomy, a historical hormonal palliation for hormone-dependent cancers (Huggins and Bergenstal, 1952). Originally developed as an anticonvulsant but discarded for causing adrenal insufficiency side effects, aminoglutethimide inhibits a range of cytochrome *P*450 steroidogenic enzymes including aromatase. Subsequently, more specific and potent aromatase inhibitors were developed (Brueggemeier *et al*., 2005) including both steroidal and non-steroidal drugs. The steroidal inhibitors are androstenedione analogues such as testolactone, formestane (Lentaron), exemestane (Aromasin) and atamestane that bind irreversibly to the catalytic site of aromatase. The non-steroidal inhibitors that inhibit aromatase by binding to its haeme group include fadrozole, letrozole (Femara), anastrozole (Arimidex), vorozole (Rivizor) and finrazole (MPV-2213). The third-generation aromatase inhibitors currently used are the trizoles, letrozole and anastrozole, and examestane. Sensitive mass

spectrometric detection methods for oestrogen blockers of both classes are described (Mareck *et al.*, 2005, 2006; Mazzarino and Botre, 2006; Borges *et al.*, 2007; Crewe *et al.*, 2007; Kang *et al.*, 2007).

Oestrogen blockade in men

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There are no well-established clinical indications for oestrogen blockers in men. Historically, antioestrogens such as clomiphene and tamoxifen were used unsuccessfully for treatment of idiopathic male infertility (Vandekerckhove *et al.*, 2000) and are no longer recommended (Liu and Handelsman, 2003). Currently accepted off-label use of oestrogen blockers is limited to men with breast cancer (Zabolotny *et al.*, 2005). Experimental clinical uses of oestrogen blockade in men include delayed puberty, short stature, gynaecomastia and spinal growth (de Ronde, 2007). The lack of convincing efficacy evidence and necessity for these indications makes it unlikely that Therapeutic Use Exemptions for oestrogen blockers in men would be justified, apart from exceptional circumstances.

Among androgen abusers, antioestrogens are used for empirical treatment of gynaecomastia resulting from using and stopping massive doses of aromatizable androgens. The clinical efficacy of the aromatase inhibitor anastrozole for gynaecomastia, suggested by anecdotal (Rhoden and Morgentaler, 2004; Riepe *et al.*, 2004) or retrospective uncontrolled (Lawrence *et al.*, 2004) studies in adolescents with pubertal gynaecomastia, was not confirmed by a larger, randomized, placebo-controlled trial (Plourde *et al.*, 2004). There is better evidence for oestrogen blockade preventing gynaecomastia induced by androgen deprivation in older men with advanced prostate cancer. On the basis of four randomized, placebo-controlled trial involving 654 men (Boccardo *et al.*, 2005; Perdona *et al.*, 2005; Saltzstein *et al.*, 2005; Fradet *et al.*, 2007), tamoxifen is effective at preventing gynaecomastia induced by antiandrogen therapy (bicalutamide 150 mg day^{-1}) in older men with prostate cancer. These studies show not only dose-dependent effects of tamoxifen (Fradet *et al.*, 2007) but also, at the highest dose (20 mg day^{-1}), superiority over anastrozole (1 mg day^{-1}) (Boccardo *et al.*, 2005; Saltzstein *et al.*, 2005).

The lack of other well-proven indications and wide clinical usage of oestrogen blockers in men mean that there are few clinical efficacy or safety studies of these drugs in men. It is, nevertheless, well established that oestrogen blockers consistently increase blood testosterone concentrations in men by up to 50%. For example, in normal men, antioestrogens such as clomiphene (Tenover *et al.*, 1987; Guay *et al.*, 1995), tamoxifen (Parker *et al.*, 1986; Maier and Hienert, 1988; Krause *et al.*, 1992) and raloxifene (Duschek *et al.*, 2004; Uebelhart *et al.*, 2004) cause reflex increases in pituitary gonadotrophin secretion and circulating testosterone levels. Similar increases in blood testosterone concentrations ranging from 5 to 20 nmol L^{-1} are reported with aromatase inhibitors such as testolactone (Clark and Sherins, 1989; Raman and Schlegel, 2002; Zumoff *et al.*, 2003), exemestane (Mauras *et al.*, 2003) and anastrozole (Leder and Finkelstein, 2005). The mechanism is most likely to be via inhibition of androgenic negative feedback on the hypothalamus, similar to the effects of antiandrogens such as flutamide (Boccon-Gibod *et al.*, 1997; Murphy *et al.*, 2004), bicalutamide (Tyrrell *et al.*, 1998, 2006; Boccardo *et al.*, 2005) or nilutamide (Decensi *et al.*, 1994), which all cause reflex increases in blood LH and testosterone. For oestrogen blockers, the common mechanism of action—inhibiting a significant part of testosterone's hypothalamic negative feedback, which is due to aromatization—makes it highly likely that all oestrogen blockers would have similar class-wide effects, proportional to their oestrogen-blocking effectiveness.

Experimental evidence from mouse models with more complete oestrogen blockade suggests that the observed clinical effects are not maximal, presumably reflecting the limited potency and completeness of the oestrogen blockade produced by the available drugs in men. For example, striking increases in blood testosterone concentrations are evident in mice with complete inactivation of aromatase (McPherson *et al.*, 2001) or oestrogen receptors α (Eddy *et al.*, 1996) but not β (Sims *et al.*, 2002). In the aromatase- and ER-α-knockout models, androgen receptor-mediated effects on bone (Sims *et al.*, 2002), prostate (McPherson *et al.*, 2001) and smooth muscle (Ling *et al.*, 2004; Villablanca *et al.*, 2004), but no skeletal muscle effects, are reported. Hence it is likely that more effective oestrogen blockade in men would produce significant and sustained elevations of blood testosterone concentrations possibly sufficient to produce myotrophic and performance-enhancing effects in men treated with such drugs. Hence, despite the lack of direct ergogenic studies of oestrogen blockers in

men, the available evidence provides a firm basis for the class-specific banning of oestrogen blockers in men. It is likely that their sustained and significant reflex increases in blood testosterone concentrations might be sufficient to increase muscle mass and strength if sustained. Although gender verification for female athletes is now effectively abandoned (Genel and Ljungqvist, 2005), implementing gender-specific sports doping rules requires at least an informal definition of male gender. For this purpose, a male would be defined as someone having at least one functional testis.

Oestrogen blockade in women

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The original clinical indication for oestrogen blockade was the use of antioestrogens for ovulation induction (Dickey and Holtkamp, 1996). The first widely used antioestrogen, clomiphene, was discovered accidentally during the early post-war decades, the golden age of steroid chemistry when oral contraception was developed. In a steroid analogue synthesis programme aiming to develop novel antiovulation contraceptive hormonal drugs, clomiphene was identified in a series of non-steroidal triphenylethylene compounds including chlorotrianisene and ethamoxytriphetol (MER-25) and, later, tamoxifen. Rather than inhibiting ovulation as they did in rodents, short-term treatment with these antioestrogens caused a reflex increase in pituitary gonadotrophin secretion due to inhibition of negative steroidal feedback on the hypothalamus. First reported in 1961 (Greenblatt *et al*., 1961), clomiphene-induced ovulation in anovulatory infertile women has remained standard first-line treatment for anovulatory female infertility due to polycystic ovary syndrome and hypothalamic amenorrhoea (World Health Organization grade II) for the last 4 decades (Hughes *et al*., 2000; Beck *et al*., 2005). For ovulation induction, clomiphene is administered daily for 5 days during the early follicular phase of the menstrual cycle rather than continuously, although fat depot storage prolongs the circulating half life of both its bioactive stereoisomers (Mikkelson *et al*., 1986; Fritz *et al*., 1991; Young *et al*., 1999). The stimulation of endogenous gonadotrophins produced by short courses of clomiphene treatment appears to be class-specific, as similar effects are produced by tamoxifen (Beck *et al*., 2005) and aromatase inhibitors (Casper and Mitwally, 2006) although the others are used much less often. This indication is particularly relevant for elite female athletes as intensive exercise including athletic training can cause hypothalamic amenorrhoea and its less severe but more frequent manifestations of ovulatory dysfunction (Cannavo *et al*., 2001; Nattiv *et al*., 2007). These may then require clomiphene (or other oestrogen blocker) treatment to induce ovulation for anovulatory infertility.

The more recent clinical developments of oestrogen blockade have been for hormonal chemotherapy of oestrogen-dependent tumours, primarily breast cancer (Jordan and Morrow, 1999; Smith and O'Malley, 2004). Partial or mixed oestrogen analogues having oestrogen agonist and/or antagonist properties that differ between tissues (specific oestrogen receptor modulators) have been developed for both cancer applications such as adjuvant treatment and prevention of breast and other oestrogen-dependent cancer and non-cancer applications such as post-menopausal osteoporosis and cardiovascular disease. The more recent alternative approach to inhibit oestrogen-dependent cancers was the development of oestrogen blockers based on inhibition of aromatase, the last steroidogenic step in estradiol synthesis (Brueggemeier *et al*., 2005).

As oestrogens appear to have no direct myotrophic effects, the only plausible mechanism for oestrogen blockade to have ergogenic effects would be via an indirect effect of raising endogenous blood testosterone concentrations. This uses blood testosterone concentrations as a valid surrogate measure for androgenic effects of indirect androgen doping (Handelsman, 2006), following the studies of Bhasin *et al*. (1996, 2001, 2005) showing that testosterone has wide dose-dependent effects on muscle mass and strength (Storer *et al*., 2003; Woodhouse *et al*., 2003). However, in contrast to men in whom blood testosterone concentrations are tightly defended by negative feedback regulation, women have no known homoeostatic feedback regulation of their low blood testosterone concentrations. In women, blood testosterone is derived from multiple (adrenal, ovarian, extra-glandular) sources, but oestrogen blockade is not expected to influence adrenal or extra-glandular testosterone production, and the contribution of direct ovarian testosterone secretion is small. Empirical evidence confirms that oestrogen blockade by either antioestrogens (Szamel *et al*., 1990; Jirecek *et al*., 2004; Lofgren *et al*., 2004) or aromatase inhibitors (Dowsett *et al*., 1989, 1990; Iveson *et al*., 1993; Johnston *et al*., 1994; Svenstrup *et al*., 1994; Bajetta *et al*., 1999; Tabei *et al*., 2002) does not increase blood testosterone

concentration. These findings should be interpreted cautiously as most involve older (post-menopausal) women and use blood testosterone immunoassays that are unreliable for female samples (Taieb *et al.*, 2003; Herold and Fitzgerald, 2003). It is also theoretically possible that oestrogen blocker drugs might have some intrinsic androgenic activity like many progestins (McRobb *et al.*, 2008). However, this is unlikely as modern pre-clinical drug screening would exclude androgenic activity and there are no reports of androgenic effects such as acne or hirsutism caused by antioestrogens or aromatase inhibitors such as are observed with many androgenic progestins (Dawood *et al.*, 1997).

Closely related to the effects of oestrogens are the effects of progestins as potential myotrophic or ergogenic agents. A wide range of synthetic progestins have androgenic activity either by direct interaction of the drug with the androgen receptor or through the production of androgenic metabolites *in vivo*. The possibility of progesterone receptor-mediated ergogenic effects was raised by a study finding small effects on overall muscle function in women using oral contraceptives containing norethisterone (NET), a synthetic 19-norprogestin (Redman *et al.*, 2005). However, NET and its bioactive metabolites have androgen bioactivity (Perez-Palacios *et al.*, 1992; McRobb *et al.*, 2008) so that ergogenic effects of NET (and/or its metabolites), if any, may instead represent androgen receptor-mediated increases in haemoglobin or myotrophic effects. A smaller study comparing two oral contraceptives containing two different progestins found no evidence for any androgenic effect of progestins on maximal leg strength (Peters and Burrows, 2006).

In summary, there is no convincing evidence that oestrogen blockers cause any consistent, biologically significant increase in blood testosterone concentrations in women. In the absence of direct testing of ergogenic or myotrophic properties, using blood testosterone as a surrogate marker suggests that drug-induced performance enhancement is most unlikely from oestrogen blockade. Nor is there any reason to believe that oestrogens have any other ergogenic effect whether directly on muscle, haemoglobin or indirectly via motivational effects in healthy pre-menopausal women. Finally, as oestrogen blockade for various indications is in wide, regular clinical use and poses no unusual medical risks to female athletes, there is no basis to ban oestrogen blockade in female athletes.

Abbreviations

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NET	norethisterone
TUE	therapeutic use exemption

Notes

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Conflict of interest

The author states no conflict of interest.

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