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5. Ehrmann DA. Polycystic ovary syndrome. *N Engl J Med* 2005; **352:** 1223–36.
6. ACOG Committee on Practice Bulletins—Gynecology. Polycystic ovary syndrome. *Obstet Gynecol* 2002; **100:** 1389–1402.
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8. Harborne L, *et al.* Descriptive review of the evidence for the use of metformin in polycystic ovary syndrome. *Lancet* 2003; **361:** 1894–1901.
9. Lord JM, *et al.* Insulin-sensitising drugs (metformin, troglitazone, rosiglitazone, pioglitazone, D-chiro-inositol) for polycystic ovary syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2003 (accessed 15/09/05).
10. Royal College of Obstetricians and Gynaecologists. Long-term consequences of polycystic ovary syndrome (Guideline no. 33 issued December 2007). Available at: http://www.rcog.org.uk/resources/Public/pdf/green_top33_pcos_a.pdf (accessed 31/03/08)

Precocious puberty

Precocious puberty is commonly understood to mean the development of secondary sexual characteristics before the age of 8 years in girls or 9 years in boys; it is four to five times more common in girls. However, the age limit used to define precocious puberty in girls has been questioned.[1] Recent data from the United States suggests that puberty is occurring earlier in girls, at age 7 years for white girls, and 6 years for African-American girls. Precocious puberty is either central, due to premature activation of the hypothalamic-pituitary-gonadal axis, or peripheral, due to secretion of extrapituitary gonadotrophins or gonadal steroids independent of gonadorelin secretion from the hypothalamus or pituitary gonadotrophins. In many cases the cause is not apparent, and they are classified as idiopathic. A small proportion of cases are due to tumours. Central precocious puberty may be caused by CNS lesions secondary to diseases such as encephalitis, meningitis, or granuloma, or due to head trauma. Peripheral precocious puberty can be associated with congenital or familial syndromes such as McCune-Albright syndrome or familial testotoxicosis (familial male precocious puberty). Congenital adrenal hyperplasia (see p.1502) can also produce premature sexual development in boys and virilisation in girls.

Apart from early sexual maturation and the associated emotional distress, the chief clinical consequence of precocious puberty is short stature as an adult, due to premature closure of the epiphyses under the influence of sex steroids.[2,3] Age, emotional impact and final height potential should be considered in deciding when to begin and end treatment.[2]

Gonadorelin analogues are the treatment of choice in central precocious puberty.[2,3] The use of continuous rather than pulsatile gonadorelin can paradoxically suppress gonadotrophin secretion by desensitisation and down regulation of pituitary receptors. Cyproterone acetate has been given at the beginning of treatment to prevent the initial stimulatory effect of the gonadorelin analogue.[2] Although originally given daily, by subcutaneous injection or nasal insufflation, intramuscular and subcutaneous depot preparations of gonadorelin analogues are more convenient, and are now more widely used.[2,3] Treatment suppresses sexual development and skeletal maturation, and most studies have reported an improvement in final height.[3,4] However, the treatment of girls with borderline early puberty (between 6 and 8 years of age) has been questioned, as studies suggest that most will reach adult height within the normal range without treatment.[1] Such girls with idiopathic slowly progressing puberty, and no evidence of advanced bone age, may not require gonadorelin therapy, but should be monitored for an onset of rapid pubertal development.[1,5] Children with concomitant growth hormone deficiency (for example after cranial irradiation) may need additional therapy with somatropin or its analogues for maximum benefit.[6] Somatropin has also been used in children who do not have growth hormone deficiency but who have a poor response to gonadorelin analogue therapy; evidence for a beneficial effect is limited.[7]

In the peripheral forms of precocious puberty the gonadorelin analogues are ineffective. Any underlying condition such as a gonadal or adrenal neoplasm should be sought and treated appropriately. Otherwise, therapy is aimed at suppressing premature sexual maturation, and drugs such as cyproterone and medroxyprogesterone have been used.[8] In girls with precocious puberty associated with the McCune-Albright syndrome, the aromatase inhibitor testolactone has been used with some success to block oestrogen biosynthesis,[9,10] ketoconazole has been used in 2 cases,[11] and tamoxifen has been reported to be beneficial.[12] Although ineffective when given alone, testolactone was reported to be of benefit when used with the anti-androgen, spironolactone, in boys with testotoxicosis;[13] a reduction in the rate of bone maturation was reported. Response diminished with long-term treatment, but could be restored by the addition of a gonadorelin analogue, deslorelin, to therapy.[14] This regimen has also been reported[15] to improve predicted adult height. Ketoconazole, which has anti-androgenic properties, has also been tried in boys with familial male precocious puberty; it had beneficial effects on testosterone concentrations and adult height reported in a series of 5 patients.[16]

1. Kaplowitz PB, *et al.* Reexamination of the age limit for defining when puberty is precocious in girls in the United States: implications for evaluation and treatment. *Pediatrics* 1999; **104:** 936–41.
2. Merke DP, Cutler GB. Evaluation and management of precocious puberty. *Arch Dis Child* 1996; **75:** 269–71.
3. Partsch C-J, *et al.* Management and outcome of central precocious puberty. *Clin Endocrinol (Oxf)* 2002; **56:** 129–48.
4. Klein KO, *et al.* Increased final height in precocious puberty after long-term treatment with LHRH agonists: the National Institutes of Health experience. *J Clin Endocrinol Metab* 2001; **86:** 4711–16.
5. Léger J, *et al.* Do all girls with apparent idiopathic precocious puberty require gonadotropin-releasing hormone agonist treatment? *J Pediatr* 2000; **137:** 819–25.
6. Adan L, *et al.* Adult height in 24 patients treated for growth hormone deficiency and early puberty. *J Clin Endocrinol Metab* 1997; **82:** 229–33.
7. Walvoord EC, Pescovitz OH. Combined use of growth hormone and gonadotropin-releasing hormone analogues in precocious puberty: theoretic and practical considerations. *Pediatrics* 1999; **104** (suppl): 1010–14.
8. Stanhope R, Traggiai C. Precocious puberty (complete, partial). *Endocr Dev* 2004; **7:** 57–65.
9. Feuillan PP, *et al.* Long term testolactone therapy for precocious puberty in girls with the McCune-Albright syndrome. *J Clin Endocrinol Metab* 1993; **77:** 647–51.
10. Albers N, *et al.* McCune-Albright syndrome - the German experience. *J Pediatr Endocrinol Metab* 2002; **15** (suppl): 897–901.
11. Syed FA, Chalew SA. Ketoconazole treatment of gonadotropin independent precocious puberty in girls with McCune-Albright syndrome: a preliminary report. *J Pediatr Endocrinol Metab* 1999; **12:** 81–3.
12. Eugster EA, *et al.* Tamoxifen treatment for precocious puberty in McCune-Albright syndrome: a multicenter trial. *J Pediatr* 2003; **143:** 60–6.
13. Laue L, *et al.* Treatment of familial male precocious puberty with spironolactone and testolactone. *N Engl J Med* 1989; **320:** 496–502.
14. Laue L, *et al.* Treatment of familial male precocious puberty with spironolactone, testolactone, and deslorelin. *J Clin Endocrinol Metab* 1993; **76:** 151–5.
15. Leschek EW, *et al.* Six-year results of spironolactone and testolactone treatment of familial male-limited precocious puberty with addition of deslorelin after central puberty onset. *J Clin Endocrinol Metab* 1999; **84:** 175–8.
16. Soriano-Guillén L, *et al.* Adult height after ketoconazole treatment in patients with familial male-limited precocious puberty. *J Clin Endocrinol Metab* 2005; **90:** 147–51.

Premenstrual syndrome

Gonadorelin analogues have been used to treat patients with severe symptoms attributable to the premenstrual syndrome (p.2099), with 'add-back' therapy with oestrogen plus progestogen to prevent the symptoms of oestrogen deficiency.

Turner's syndrome

Turner's syndrome is a congenital disorder associated with the absence of an X or Y chromosome, resulting in an individual with only a single X chromosome who is female in phenotype but in whom the ovaries do not develop. In addition to this gonadal dysgenesis, which results in infertility and primary amenorrhoea, various physical abnormalities may be present including short stature, a short webbed neck and characteristic facial appearance, shield-like chest, multiple naevi, and certain renal and cardiovascular abnormalities. Hypothyroidism and glucose intolerance may occur.

As with other forms of ovarian failure, HRT with oestrogen and intermittent progestogen is indicated in women with Turner's syndrome, in order to produce sexual maturation and the development of secondary sexual characteristics as well as to avoid complications such as osteoporosis. Clinical opinion has generally been that therapy should begin with low doses of oestrogen in girls of prepubertal age, gradually increasing the dose to promote slow development of secondary sexual characteristics and eventual breakthrough bleeding, at which point a cyclic progestogen should be added to oestrogen maintenance to minimise the risk of endometrial hyperplasia and cancer. In general, therapy is started around 14 to 15 years of age, but may be started as early as 12 years of age in girls who have reached a satisfactory height, especially those who have been treated with growth hormone.[1-3] There is no consensus on which oestrogen is preferred for these patients; conjugated oestrogens, ethinylestradiol, and estradiol have all been used. An oral contraceptive may be used for maintenance therapy.[3]

A minority of patients with Turner's syndrome have some residual ovarian function, and there are a few reports of pregnancy in such patients. In women without ovaries it may be possible to maintain pregnancy by appropriate endocrine replacement after implantation of a fertilised donor egg.[1]

Short stature is the most common clinical manifestation of Turner's syndrome. Growth hormone therapy has been widely used and may be considered from as early as 2 years of age,[2] but there is considerable debate about the extent of the benefit in terms of final height. Results from 622 girls enrolled in the National Cooperative Growth Study[4] suggested a mean height gain of 6.4 ± 4.9 cm, and another cohort database[5] of 485 girls found that when treatment was started before puberty a mean increase in final height of 5 cm or more would be expected. A systematic review[6] of 4 controlled studies found that growth hormone increased short-term growth, but that there was limited controlled data on final height. It has been suggested[1] that a final height of 150 cm is an achievable goal for most patients. Growth hormone therapy during childhood and adolescence may also be important in maximising bone mass and reducing the risk of osteoporosis.[7] Although it is generally recommended that oestrogen replacement be delayed where growth promotion is a priority,[1,2] optimal oestrogen replacement therapy may also be important in maximising final height. In a comparison[8] of the introduction of conjugated oestrogen therapy at 12 or 15 years of age, the combination of growth hormone and oestrogen initially stimulated growth velocity and bone maturation more than growth hormone alone, but subsequently declined after about 2 years. Patients who received growth hormone for a longer period before starting oestrogen therapy attained greater adult height, a finding also noted in another study;[9] it was suggested that early use of growth hormone could allow oestrogen therapy to be begun at a more appropriate, younger age without compromising final height. However, the use of low-dose oestrogen from an even earlier age (as young as 8 years) to stimulate linear growth does not add to the effect of growth hormone therapy and may even reduce final height.[10] Combination of growth hormone with a non-aromatisable anabolic steroid such as oxandrolone is recommended as an option in girls aged 8 to 12 years if therapy is begun late,[1] or if response to growth hormone is inadequate.[2]

Adult women with Turner's syndrome require multidisciplinary management including cardiovascular monitoring, psychological support, and a programme of prevention for diabetes, osteoporosis, and hypertension.[1,2]

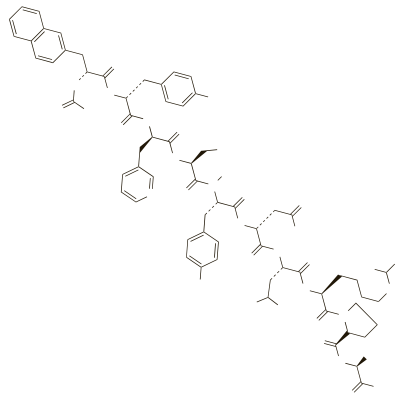
1. Saenger P, *et al.* Recommendations for the diagnosis and management of Turner syndrome. *J Clin Endocrinol Metab* 2001; **86:** 3061–9.
2. Frías JL, *et al.* Health supervision for children with Turner syndrome. *Pediatrics* 2003; **111:** 692–702.
3. Sybert VP, McCauley E. Turner's syndrome. *N Engl J Med* 2004; **351:** 1227–38.
4. Plotnick L, *et al.* Growth hormone treatment of girls with Turner syndrome: the National Cooperative Growth Study experience. *Pediatrics* 1998; **102:** 479–81.
5. Betts PR, *et al.* A decade of growth hormone treatment in girls with Turner syndrome in the UK. *Arch Dis Child* 1999; **80:** 221–5.
6. Cave CB, *et al.* Recombinant growth hormone in children and adolescents with Turner syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 15/09/05).
7. Rubin K. Turner syndrome and osteoporosis: mechanisms and prognosis. *Pediatrics* 1998; **102** (suppl): 481–5.
8. Chernausek SD, *et al.* Growth hormone therapy of Turner syndrome: the impact of age of estrogen replacement on final height. *J Clin Endocrinol Metab* 2000; **85:** 2439–45.
9. Reiter EO, *et al.* Early initiation of growth hormone treatment allows age-appropriate estrogen use in Turner's syndrome. *J Clin Endocrinol Metab* 2001; **86:** 1936–41.
10. Quigley CA, *et al.* Growth hormone and low dose estrogen in Turner syndrome: results of a United States multi-center trial to near-final height. *J Clin Endocrinol Metab* 2002; **87:** 2033–41.

Abarelix *(USAN, rINN)*

Abarélix; Abarelixum; PPI-149; R-3827. *N*-Acetyl-3-(2-naphthyl)-D-alanyl-4-chloro-D-phenylalanyl-3-(3-pyridyl)-D-alanyl-L-seryl-*N*-methyl-L-tyrosyl-D-asparaginyl-L-leucyl-*N*^{6}-isopropyl-L-lysyl-L-prolyl-D-alaninamide.

Абареликс

$C_{72}H_{95}ClN_{14}O_{14}$ = 1416.1.
CAS — 183552-38-7.
ATC — L02BX01.
ATC Vet — QL02BX01.



Adverse Effects and Precautions

Immediate hypersensitivity reactions, including urticaria, pruritus, hypotension, and syncope, can occur with abarelix, and the cumulative risk of such a reaction increases with repeated doses. Patients should be monitored for at least 30 minutes after each injection. Hot flushes, sleep disturbance, breast enlargement and tenderness may result from testosterone reduction. Prolongation of the QT interval has occurred in patients receiving abarelix.

Elevations in transaminase concentrations have occurred, and liver function should be monitored before starting treatment, and periodically during treatment. The effectiveness of abarelix in the management of prostate cancer decreases with duration of therapy, and may be further reduced in patients weighing more than about 100 kg (225 pounds). The serum concentration of testosterone should be measured on day 29 of therapy and then every 8 weeks, to monitor for treatment failure.

Pharmacokinetics
Abarelix is absorbed slowly after intramuscular injection, with a peak concentration in serum reached after about 3 days. It is metabolised by hydrolysis and has an elimination half-life of about 13 days with intramuscular use.

◊ References.

1. Wong SL, *et al.* Pharmacokinetics and pharmacodynamics of a novel depot formulation of abarelix, a gonadotropin-releasing hormone (GnRH) antagonist, in healthy men ages 50 to 75. *J Clin Pharmacol* 2004; **44:** 495–502.

Uses and Administration
Like cetrorelix (p.2084), abarelix is a gonadorelin (gonadotrophin-releasing hormone) antagonist. It is used to reduce testosterone concentrations in the palliative hormonal therapy of prostate cancer (p.671). A dose of abarelix 100 mg is given intramuscularly on days 1, 15, and 29, and then every 4 weeks thereafter.

Abarelix has been investigated for the treatment of endometriosis.

Malignant neoplasms. References.

1. Tomera K, *et al.* The gonadotropin-releasing hormone antagonist abarelix depot versus luteinizing hormone releasing hormone agonists leuprolide or goserelin: initial results of endocrinological and biochemical efficacies in patients with prostate cancer. *J Urol (Baltimore)* 2001; **165:** 1585–9.
2. McLeod D, *et al.* A phase 3, multicenter, open-label, randomized study of abarelix versus leuprolide acetate in men with prostate cancer. *Urology* 2001; **58:** 756–61.
3. Trachtenberg J, *et al.* A phase 3, multicenter, open label, randomized study of abarelix versus leuprolide plus daily antiandrogen in men with prostate cancer. *J Urol (Baltimore)* 2002; **167:** 1670–4.
4. Koch M, *et al.* An open-label study of abarelix in men with symptomatic prostate cancer at risk of treatment with LHRH agonists. *Urology* 2003; **62:** 877–82.

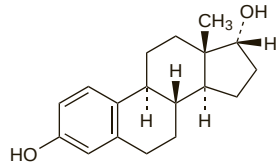
Preparations
Proprietary Preparations (details are given in Part 3)
USA: Plenaxis.

Alfatradiol *(rINN)* ⊗
Alfatradiolum; Alpha-estradiol; Epiestradiol; 17α-Estradiol; NSC-20293. Estra-1,3,5(10)-triene-3,17α-diol.

Альфатрадиол

$C_{18}H_{24}O_2$ = 272.4.

CAS — 57-91-0.



Profile
Alfatradiol is the 17-α isomer of estradiol (p.2097) but has much weaker oestrogenic actions. It is a 5α-reductase inhibitor and is used topically as a 0.025% solution for alopecia androgenetica (p.1577).

Preparations
Proprietary Preparations (details are given in Part 3)
Arg.: Avixis; ***Ger.:*** Ell-Cranell alpha; Pantostin; ***Mex.:*** Avixis.

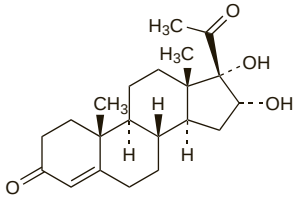
Multi-ingredient: ***Ger.:*** Ell-Cranell dexa.

Algestone Acetophenide *(USAN, rINNM)*
Acetofenido de alfasona; Acetofenido de algestona; Acetofenido de dihidroxiprogesterona; Algestone, Acétophenide d'; Algestoni Acetophenidum; Alphasone Acetophenide; Dihydroxyprogesterone Acetophenide; SQ-15101. 16α,17α-(1-Phenylethylidenedioxy)pregn-4-ene-3,20-dione; 16α,17α-Isopropylidenedioxypregn-4-ene-3,20-dione.

Альгестона Ацетофенид

$C_{29}H_{36}O_4$ = 448.6.

CAS — 595-77-7 (algestone); 24356-94-3 (algestone acetophenide).



(algestone)

Profile
Algestone acetophenide is a progestogen (see Progesterone, p.2125) that is given by intramuscular injection in monthly doses of 150 mg, with estradiol enantate, as a hormonal contraceptive (see p.2058). It has also been applied topically in the treatment of acne.

◊ References.

1. Martínez GH, *et al.* Vaginal bleeding patterns in users of Perlutal , a once-a-month injectable contraceptive consisting of 10 mg estradiol enanthate combined with 150 mg dihydroxyprogesterone acetophenide: a trial of 5462 woman-months. *Contraception* 1998; **58:** 21–7.
2. Coutinho EM, *et al.* Efficacy, acceptability, and clinical effects of a low-dose injectable contraceptive combination of dihydroxyprogesterone acetophenide and estradiol enanthate. *Contraception* 2000; **61:** 277–80.
3. Coutinho EM, *et al.* Comparison of two regimens of a monthly injectable contraceptive containing dihydroxyprogesterone acetophenide and estradiol enanthate. *Contraception* 2006; **73:** 249–52.

Preparations
Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** Atrimon; Perlutal; ***Braz.:*** Femineo†; Perlutan; Preg-Less; Unalmes†; Uno-Ciclo†; ***Chile:*** Agurin†; Unalmes; ***Mex.:*** Anafertin; Ginoplan†; Patector; Perludil; Perlutal; Yectames; ***Port.:*** Cicnor†; ***Singapore:*** Unijab; ***Spain:*** Topasel.

Allylestrenol *(BAN, rINN)*
Alilestrenol; Allylestrénol; Allylestrenolum; Allyloestrenol; Allylöstrenol; Allyyliestrenoli. 17α-Allylestr-4-en-17β-ol.

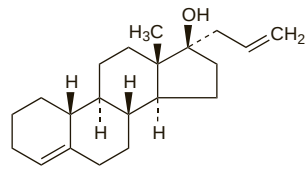
Аллилэстренол

$C_{21}H_{32}O$ = 300.5.

CAS — 432-60-0.

ATC — G03DC01.

ATC Vet — QG03DC01.



Profile
Allylestrenol is a progestogen (see Progesterone, p.2125) structurally related to progesterone that has been given in threatened and recurrent miscarriage, and to prevent premature labour. However, with the exception of proven progesterone deficiency, such use is no longer recommended. In threatened miscarriage in progesterone-deficient women a suggested oral dose is 5 mg three times daily for 5 to 7 days.

Pregnancy. A case-control study of allylestrenol use in pregnancy during 1980 to 1984 in Hungary indicated that it was not teratogenic.[1]

1. Czeizel A, Huiskes N. A case-control study to evaluate the risk of congenital anomalies as a result of allylestrenol therapy during pregnancy. *Clin Ther* 1988; **10:** 725–39.

Preparations
Proprietary Preparations (details are given in Part 3)
Cz.: Turinal†; ***Hong Kong:*** Turinal; ***India:*** Maintane; Profar; ***Indon.:*** Gravynon; Lestron; Preabor; Pregtenol; Premaston; Prenolin; Prestrenol; Progeston; ***Malaysia:*** Turinal†; ***Philipp.:*** Turinal; ***Rus.:*** Turinal (Туринал); ***Singapore:*** Turinal.

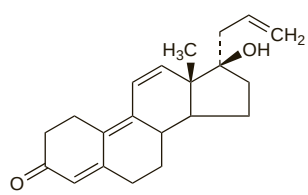
Altrenogest *(BAN, USAN, rINN)*
A-35957; A-41300; Altrénogest; Altrenogesti; Altrenogestum; RH-2267; RU-2267. 17α-Allyl-17β-hydroxy-19-norandrosta-4,9,11-trien-3-one; 17β-Hydroxy-19,21,24-trinorchola-4,9,11,22-tetraen-3-one.

Альтреногест

$C_{21}H_{26}O_2$ = 310.4.

CAS — 850-52-2.

ATC Vet — QG03DX90.



Profile
Altrenogest is a progestogen (see Progesterone, p.2125) used in veterinary medicine.

Androstanolone *(BAN, rINN)* ⊗
Androstanolo; Androstanolon; Androstanolona; Androstanoloni; Androstanolonum; Dihidrotestosterona; Dihydrotestosterone; Estanolona; Stanolon; Stanolone. 17β-Hydroxy-5α-androstan-3-one.

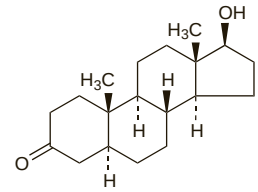
Андростанолон

$C_{19}H_{30}O_2$ = 290.4.

CAS — 521-18-6.

ATC — A14AA01; G03BB02.

ATC Vet — QA14AA01; QG03BB02.



Profile
Androstanolone is formed naturally in the body from testosterone (p.2129) by the action of 5α-reductase, and is more active than the parent compound. It has anabolic and androgenic properties and is applied topically in the form of a 2.5% gel for male hypogonadism and gynaecomastia, and for lichen sclerosus in both men and women.

◊ References.

1. Wang C, Swerdloff RS. Should the nonaromatizable androgen dihydrotestosterone be considered as an alternative to testosterone in the treatment of the andropause? *J Clin Endocrinol Metab* 2002; **87:** 1462–6.

Lichen sclerosus. For references to the use of androgens such as androstanolone in lichen sclerosus, see under Testosterone, p.2133.

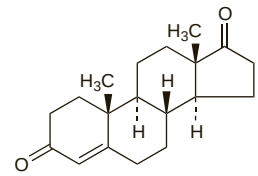
Preparations
Proprietary Preparations (details are given in Part 3)
Belg.: Andractim; ***Fr.:*** Andractim; ***Thai.:*** Andractim†.

Androstenedione ⊗
Androstenodiona. Androst-4-ene-3,17-dione.

Андростендион

$C_{19}H_{26}O_2$ = 286.4.

CAS — 63-05-8.



NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of androstenedione: Andro.

Profile
Androstenedione is a naturally occurring adrenal androgen that is a precursor of androgens and oestrogens (see p.2058). It has been used in an attempt to enhance athletic performance and as hormone replacement for men. In March 2004 the FDA banned the distribution of dietary supplements containing androstenedione, considering them to be adulterated and warning that they did not meet safety requirements.

Action. The effects of androstenedione have been studied in groups of young (under 40 years of age) and older (up to 65 years) men with normal serum testosterone concentrations.[1-4] Testosterone concentrations were reported to remain unchanged[1,4] as well as increase,[2,3] although they returned to baseline in the longer study of 12 weeks.[3] In 3 of the studies, oestrogens (oestradiol and oestrone) increased.[1-3] Changes in lipid profiles were also noted, particularly a decrease in high-density lipoprotein (HDL) cholesterol.[1,3] Androstenedione did not enhance the effects of resistance training.[1,3]