4. Linares M, *et al.* Hepatocellular carcinoma and squamous cell carcinoma in a patent with Fanconi's anemia. *Ann Hematol* 1991; **63:** 54–5.
5. Lesna M, *et al.* Liver nodules and androgens. *Lancet* 1976; **i:** 1124.
6. Mokrohisky ST, *et al.* Fulminant hepatic neoplasia after androgen therapy. *N Engl J Med* 1977; **296:** 1411–12.
7. Kosaka A, *et al.* Hepatocellular carcinoma associated with anabolic steroid therapy: report of a case and review of the Japanese literature. *J Gastroenterol* 1996; **31:** 450–4.
8. Nakao A, *et al.* Multiple hepatic adenomas caused by long-term administration of androgenic steroids for aplastic anemia in association with familial adenomatous polyposis. *J Gastroenterol* 2000; **35:** 557–62.
9. Velazquez I, Alter BP. Androgens and liver tumors: Fanconi's anemia and non-Fanconi's conditions. *Am J Hematol* 2004; **77:** 257–67.

Effects on the nervous system. Toxic confusional state and choreiform movements developed in an elderly man given oxymetholone 200 to 300 mg daily.[1]

1. Tilzey A, *et al.* Toxic confusional state and choreiform movements after treatment with anabolic steroids. *BMJ* 1981; **283:** 349–50.

Uses and Administration

Oxymetholone has anabolic and androgenic properties (see Testosterone, p.2131). It has been used mainly in the treatment of anaemias such as aplastic anaemia at a usual oral dose of 1 to 5 mg/kg daily. Treatment for 3 to 6 months has been suggested, with the drug either withdrawn gradually on remission or reduced to an appropriate maintenance dose.

◊ Reviews.

1. Pavlatos AM, *et al.* Review of oxymetholone: a 17α-alkylated anabolic-androgenic steroid. *Clin Ther* 2001; **23:** 789–801.

Aplastic anaemia. There have been mixed results[1-5] with oxymetholone in the treatment of aplastic anaemia (p.1042); generally, the response and survival rates have been disappointing. Although it was used extensively in the past, oxymetholone is now generally reserved for patients who have failed, or cannot tolerate, immunosuppressant therapy.

1. Davis S, Rubin AD. Treatment and prognosis in aplastic anaemia. *Lancet* 1972; **i:** 871–3.
2. Mir MA, Delamore IW. Oxymetholone in aplastic anaemia. *Postgrad Med J* 1974; **50:** 166–71.
3. Camitta BM, *et al.* A prospective study of androgens and bone marrow transplantation for treatment of severe aplastic anemia. *Blood* 1979; **53:** 504–14.
4. Mir MA, Geary CG. Aplastic anaemia: an analysis of 174 patients. *Postgrad Med J* 1980; **56:** 322–9.
5. Webb DKH, *et al.* Acquired aplastic anaemia: still a serious disease. *Arch Dis Child* 1991; **66:** 858–61.

Preparations

BP 2008: Oxymetholone Tablets;
USP 31: Oxymetholone Tablets.

Proprietary Preparations (details are given in Part 3)
Braz.: Hemogenin; ***India:*** Adroyd; ***Thai.:*** Androlic; ***Turk.:*** Anapolon; ***USA:*** Anadrol.

Polyestradiol Phosphate *(BAN, rINN)*

Fosfato de poliestradiol; Leo-114; Polyestradiol, Phosphate de; Polyestradiolfosfat; Polyestradioli Phosphas; Polyestradiolifosfaatti; Polyoestradiol Phosphate. A water-soluble polymeric ester of estradiol and phosphoric acid with a molecular weight of about 26 000.

Полиэстрадиола Фосфат

CAS — 28014-46-2.
ATC — L02AA02.
ATC Vet — QL02AA02.

Adverse Effects and Precautions

As for oestrogens in general (see Estradiol, p.2097). Pain may occur at the site of injection, and mepivacaine is included in some preparations to minimise this.

Pharmacokinetics

After intramuscular injection polyestradiol phosphate is released slowly into the bloodstream where it is slowly metabolised to estradiol.

Uses and Administration

Polyestradiol phosphate is a polymer of estradiol (see p.2097) that has a prolonged duration of action, and is used in the treatment of metastatic prostatic carcinoma (p.671). It has been given by deep intramuscular injection in initial doses of 80 to 160 mg every 4 weeks for 2 to 3 months, reduced to 40 to 80 mg every 4 weeks for maintenance. Higher initial doses of 320 mg and maintenance doses of 160 mg have also been used.

Preparations

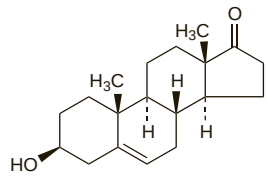
Proprietary Preparations (details are given in Part 3)
Austria: Estradurin; ***Belg.:*** Estradurine; ***Denm.:*** Estradurin; ***Fin.:*** Estradurin; ***Ger.:*** Estradurin†; ***Neth.:*** Estradurin; ***Norw.:*** Estradurin; ***Rus.:*** Estradurin (Эстрадурин)†; ***Swed.:*** Estradurin; ***Switz.:*** Estradurin.

Prasterone *(rINN)* ⊗

Dehydroandrosterone; Dehydroepiandrosteron; Dehydroepiandrosterone; Dehydroepiandrosteroni; Dehydroepiandrosteronum; Dehydroisoandrosterone; DHEA; GL-701; Prasterona; Prastérone; Prasteronum. 3β-Hydroxyandrost-5-en-17-one.

Прастерон

$C_{19}H_{28}O_2$ = 288.4.
CAS — 53-43-0.
ATC — A14AA07.
ATC Vet — QA14AA07.



Pharmacopoeias. In *Fr.*

Prasterone Enantate *(rINNM)* ⊗

Dehydroepiandrosterone Enanthate; EDHEA; Enantato de prasterona; Prastérone, Enantate de; Prasterone Enanthate; Prasteroni Enantas. 3β-Hydroxyandrost-5-en-17-one heptanoate.

Прастерона Энантат

$C_{26}H_{40}O_3$ = 400.6.
CAS — 23983-43-9.
ATC — A14AA07.
ATC Vet — QA14AA07.

Prasterone Sodium Sulfate *(rINNM)* ⊗

Dehydroepiandrosterone Sulphate Sodium; DHA-S (prasterone sulfate); DHEAS (prasterone sulfate); PB-005; Prasterone Sodium Sulphate; Prastérone, Sulfate Sodique de; Prasteroni Natrii Sulfas; Sulfato sódico de prasterona. 3β-Hydroxyandrost-5-en-17-one hydrogen sulphate sodium.

Прастерона Натрия Сульфат

$C_{19}H_{27}NaO_5S$ = 390.5.
CAS — 651-48-9 (prasterone sulfate); 1099-87-2 (prasterone sodium sulfate).
ATC — A14AA07.
ATC Vet — QA14AA07.

Pharmacopoeias. *Chin.* and *Jpn* include the dihydrate.

Profile

Prasterone is a naturally occurring adrenal androgen that is a precursor of androgens and oestrogens. Prasterone enantate, in a dose of 200 mg every 4 weeks, is given by intramuscular depot injection with estradiol valerate as menopausal HRT (p.2076). Prasterone is also being investigated in adrenal insufficiency and in SLE, and the sodium sulfate has been investigated for the treatment of burns and acute asthma.

◊ General reviews.

1. Kroboth PD, *et al.* DHEA and DHEA-S: a review. *J Clin Pharmacol* 1999; **39:** 327–48.
2. Pepping J. DHEA: dehydroepiandrosterone. *Am J Health-Syst Pharm* 2000; **57:** 2048–56.
3. Cameron DR, Braunstein GD. The use of dehydroepiandrosterone therapy in clinical practice. *Treat Endocrinol* 2005; **4:** 95–114.

HIV infection and AIDS. Plasma concentrations of endogenous prasterone are reported to be abnormally low in patients with AIDS, and it has been suggested that use of prasterone might be of benefit; however, large controlled studies are lacking.[1] Small controlled studies have confirmed that oral use increases circulating concentrations of prasterone and its sulfated form, and have reported improvements in quality of life measures[2] and reductions in symptoms of mild depression,[3] but no beneficial antiviral or immunomodulatory effects.[4] Also, there were no significant changes in measures of serum lipids, insulin, growth hormone, or the overall function of the gonadal or hypothalamic-pituitary-adrenal axes.[5]

1. Centurelli MA, *et al.* The role of dehydroepiandrosterone in AIDS. *Ann Pharmacother* 1997; **31:** 639–42.
2. Piketty C, *et al.* Double-blind placebo-controlled trial of oral dehydroepiandrosterone in patients with advanced HIV disease. *Clin Endocrinol (Oxf)* 2001; **55:** 325–30.
3. Rabkin JG, *et al.* Placebo-controlled trial of dehydroepiandrosterone (DHEA) for treatment of nonmajor depression in patients with HIV/AIDS. *Am J Psychiatry* 2006; **163:** 59–66.
4. Abrams DI, *et al.* Dehydroepiandrosterone (DHEA) effects on HIV replication and host immunity: a randomized placebo-controlled study. *AIDS Res Hum Retroviruses* 2007; **23:** 77–85.
5. Poretsky L, *et al.* Endocrine effects of oral dehydroepiandrosterone in men with HIV infection: a prospective, randomized, double-blind, placebo-controlled trial. *Metabolism* 2006; **55:** 858–70.

Replacement therapy. There has been much speculation about the physiological role and importance of prasterone, which is the most abundant steroid hormone in the circulation. It is produced by the adrenal gland and is a precursor of androgens and oestrogens. Serum concentrations peak at about 20 years then gradually decline with age. Epidemiological and *animal* studies suggest that certain age-related diseases may be linked to this decline, including reduced immunocompetence, obesity, diabetes, and cancers.[1] It has been suggested, therefore, that replacement therapy with prasterone might alleviate some of the problems of ageing. Prasterone has been studied for its effect on cognition and memory, sexual function, insulin sensitivity, cardiovascular risk factors, muscle strength and body composition, bone loss, and immune function, but results have generally been conflicting,[1,2] and there is insufficient evidence of safety and efficacy to recommend such use. A systematic review[3] of studies in healthy adults taking prasterone supplementation found no support for an improvement in cognitive function. A review[4] of the use of prasterone as a 'food supplement' noted that although it was being taken in the belief that it could reverse some of the effects of ageing there was no good evidence of this. Various androgenic effects, including hirsutism and voice changes, have been reported in women taking prasterone and there is a theoretical possibility that it might promote growth of hormone-sensitive tumours in both sexes.[1,4]

Prasterone has also been studied as replacement therapy for patients with adrenal insufficiency, who have subnormal levels of prasterone. Such therapy, usually in oral doses of 50 mg daily, has been reported to raise serum levels of prasterone to normal, and improve measures of well-being, mood, and fatigue.[1,5-7] There have been mixed results from studies of the effects of prasterone on carbohydrate metabolism with reports of either no effect[8,9] or increased insulin sensitivity.[10]

1. Dhatariya KK, Nair KS. Dehydroepiandrosterone: is there a role for replacement? *Mayo Clin Proc* 2003; **78:** 1257–73.
2. GISEG (Italian Study Group on Geriatric Endocrinology). Consensus document on substitution therapy with DHEA in the elderly. *Aging Clin Exp Res* 2006; **18:** 277–300. Also available at: http://www.kurtis.it/abs/index.cfm?id_articolo_numero=2297 (accessed 13/11/07)
3. Grimley Evans J, *et al.* Dehydroepiandrosterone (DHEA) supplementation for cognitive function in healthy elderly people. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 13/11/07).
4. Anonymous. Dehydroepiandrosterone (DHEA). *Med Lett Drugs Ther* 1996; **38:** 91–2.
5. Arlt W, *et al.* Dehydroepiandrosterone replacement in women with adrenal insufficiency. *N Engl J Med* 1999; **341:** 1013–20.
6. Hunt PJ, *et al.* Improvement in mood and fatigue after dehydroepiandrosterone replacement in Addison's disease in a randomized, double blind trial. *J Clin Endocrinol Metab* 2000; **85:** 4650–6.
7. Brooke AM, *et al.* Dehydroepiandrosterone improves psychological well-being in male and female hypopituitary patients on maintenance growth hormone replacement. *J Clin Endocrinol Metab* 2006; **91:** 3773–9.
8. Callies F, *et al.* Dehydroepiandrosterone replacement in women with adrenal insufficiency: effects on body composition, serum leptin, bone turnover, and exercise capacity. *J Clin Endocrinol Metab* 2001; **86:** 1968–72.
9. Libè R, *et al.* Effects of dehydroepiandrosterone (DHEA) supplementation on hormonal, metabolic and behavioral status in patients with hypoadrenalism. *J Endocrinol Invest* 2004; **27:** 736–41.
10. Dhatariya K, *et al.* Effect of dehydroepiandrosterone replacement on insulin sensitivity and lipids in hypoadrenal women. *Diabetes* 2005; **54:** 765–9.

Systemic lupus erythematosus. In a number of small studies carried out by one group,[1-5] there was symptomatic improvement in SLE (p.1513), and a reduction in corticosteroid dosage, in women who received oral prasterone 200 mg daily for several months. Although they considered that there was clear evidence of benefit,[6] larger studies[7-9] have produced more statistically ambiguous results. They suggested that prasterone might stabilise or improve disease, and reduce corticosteroid requirements and time to disease flare, but only in patients with active disease. Nested data from one of these studies[10] also showed that prasterone treatment for up to a year improved bone mineral density of the lumbar spine and hip. The results of a larger study designed to confirm this effect on bone were not statistically significant in favour of prasterone, but an open-label 1-year extension study does suggest that long-term treatment might maintain or improve bone mineral density; the full results of these latter studies are yet to be published.[11] In a study[12] of lumbar spine bone mineral density in women with quiescent SLE, prasterone may have had a protective effect in postmenopausal women who were not otherwise treated with oestrogens or bisphosphonates, but there was no change in premenopausal women.

1. van Vollenhoven RF, *et al.* An open study of dehydroepiandrosterone in systemic lupus erythematosus. *Arthritis Rheum* 1994; **37:** 1305–10.
2. van Vollenhoven RF, *et al.* Dehydroepiandrosterone in systemic lupus erythematosus. *Arthritis Rheum* 1995; **38:** 1826–31.
3. van Vollenhoven RF, *et al.* Treatment of systemic lupus erythematosus with dehydroepiandrosterone: 50 patients treated up to 12 months. *J Rheumatol* 1998; **25:** 285–9.
4. Barry NN, *et al.* Dehydroepiandrosterone in systemic lupus erythematosus: relationship between dosage, serum levels, and clinical response. *J Rheumatol* 1998; **25:** 2352–6.
5. van Vollenhoven RF, *et al.* A double-blind, placebo-controlled, clinical trial of dehydroepiandrosterone in severe systemic lupus erythematosus. *Lupus* 1999; **8:** 181–7.
6. van Vollenhoven RF. Dehydroepiandrosterone in systemic lupus erythematosus. *Rheum Dis Clin North Am* 2000; **26:** 349–62.
7. Petri MA, *et al.* Effects of prasterone on corticosteroid requirements of women with systemic lupus erythematosus: a double-blind, randomized, placebo-controlled trial. *Arthritis Rheum* 2002; **46:** 1820–9.

8. Chang D-M, *et al.* Dehydroepiandrosterone treatment of women with mild-to-moderate systemic lupus erythematosus. *Arthritis Rheum* 2002; **46:** 2924–7.
9. Petri MA, *et al.* Effects of prasterone on disease activity and symptoms in women with active systemic lupus erythematosus: results of a multicenter randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2004; **50:** 2858–68.
10. Mease PJ, *et al.* Effects of prasterone on bone mineral density in women with systemic lupus erythematosus receiving chronic glucocorticoid therapy. *J Rheumatol* 2005; **32:** 616–21.
11. Genelabs Technologies Inc., USA. Genelabs updates development options for its investigational lupus drug after FDA meeting (issued January 13, 2006). Available at: http://www.genelabs.com/pressReleases/011306.html (accessed 13/11/07)
12. Hartkamp A, *et al.* The effect of dehydroepiandrosterone on lumbar spine bone mineral density in patients with quiescent systemic lupus erythematosus. *Arthritis Rheum* 2004; **50:** 3591–5.

Preparations

Proprietary Preparations (details are given in Part 3)
Mex.: Biolaif; ***Pol.:*** Biosteron; ***Port.:*** Dinistenile†.

Multi-ingredient: ***Arg.:*** Dastonil; Gynodian Depot; Supligol NF; ***Austria:*** Gynodian Depot; ***Chile:*** Gynodian Depot; ***Cz.:*** Gynodian Depot; ***Ger.:*** Gynodian Depot; ***Ital.:*** Gynodian Depot; ***Mex.:*** Binodian; Sten; ***Pol.:*** Gynodian Depot; ***Rus.:*** Gynodian Depot (Гинодиан Депо); ***Switz.:*** Gynodian Depot; ***Venez.:*** Gynodian Depot.

Progesterone *(BAN, rINN)*

Corpus Luteum Hormone; Luteal Hormone; Luteine; Luteohormone; NSC-9704; Pregnenedione; Pregnenodiona; Progesteron; Progesterona; Progesteronas; Progestérone; Progesteroni; Progesteronum; Progestina; Progeszteron. Pregn-4-ene-3,20-dione.

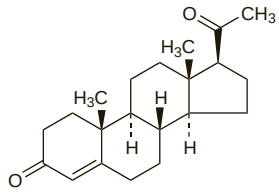
Прогестерон

$C_{21}H_{30}O_2$ = 314.5.

CAS — 57-83-0.

ATC — G03DA04.

ATC Vet — QG03DA04.



Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn, US,* and *Viet.*

Ph. Eur. 6.2 (Progesterone). A white or almost white crystalline powder or colourless crystals. It exhibits polymorphism. Practically insoluble in water; freely soluble in dehydrated alcohol; sparingly soluble in acetone and in fatty oils. Protect from light.

USP 31 (Progesterone). A white or creamy-white, odourless, crystalline powder. Practically insoluble in water; soluble in alcohol, in acetone, and in dioxan; sparingly soluble in vegetable oils. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Adverse Effects

Progesterone and the progestogens may cause gastrointestinal disturbances, changes in appetite or weight, fluid retention, oedema, acne, chloasma (melasma), allergic skin rashes, urticaria, mental depression, breast changes including discomfort or occasionally gynaecomastia, changes in libido, hair loss, hirsutism, fatigue, drowsiness or insomnia, fever, headache, premenstrual syndrome-like symptoms, and altered menstrual cycles or irregular menstrual bleeding. Anaphylaxis or anaphylactoid reactions may occur rarely. Alterations in the serum lipid profile may occur, and rarely alterations in liver-function tests and jaundice. Pain, diarrhoea, and flatulence have followed rectal use. Injection-site reactions have followed parenteral use.

Adverse effects vary depending on the dose and type of progestogen. For example, androgenic effects such as acne and hirsutism are more likely to occur with nortestosterone derivatives such as norethisterone and norgestrel. These derivatives may also be more likely to adversely affect serum lipids. Conversely, adverse effects on serum lipids appear less likely with gestodene and desogestrel, but these 2 drugs have been associated with a higher incidence of thromboembolism than norethisterone and norgestrel when used in combined oral contraceptives (see p.2063). High doses of progestogens such as those used in treating cancer have also been associated with thromboembolism. For a discussion of the effect of progestogens on the cardiovascular risk profile of menopausal HRT see p.2073. Breakthrough uterine bleeding is more common with oral progestogen-only contraceptives than when progestogens are used for menstrual irregularities or as part of menopausal HRT.

Some progestogens when given during pregnancy have been reported to cause virilisation of a female fetus. This appears to have been associated with those progestogens with more pronounced androgenic activity such as norethisterone; the natural progestogenic hormone progesterone and its derivatives such as dydrogesterone and medroxyprogesterone do not appear to have been associated with such effects.

For the adverse effects of progestogens when administered either alone or with oestrogens as contraceptives, see p.2059. For those of menopausal HRT, see p.2071.

Carcinogenicity. In a cohort study[1] of women aged 40 to 64 years, the premenopausal use of oral progestogens alone, mainly for benign breast, uterine, and ovarian conditions, and irregular menstruation, was not associated with an increased risk of breast cancer. However, the data did suggest that there was an increased risk for current users of progestogens for longer than 4.5 years (relative risk 1.44, 95% confidence interval 1.03 to 2.00) compared with women who had never used progestogens. Limitations of this study included the lack of analysis of different progestogens or a record of the reasons for progestogen treatment.

1. Fabre A, *et al.* Oral progestagens before menopause and breast cancer risk. *Br J Cancer* 2007; **96:** 841–4.

Effects on the skin. Auto-immune progesterone dermatitis includes reactions such as eczema, urticaria, and angioedema that usually begin 3 to 10 days before the onset of menstrual flow and end 1 to 2 days into menses, which correlates with raised endogenous progesterone concentrations during the luteal phase of the menstrual cycle. The onset of the condition can be as early as menarche, and many women have never been exposed to exogenous progesterone, but it has also occurred in women with a history of oral contraceptive use. Management has been based on the suppression of endogenous progesterone secretion and oral contraceptives are usually tried first, although they appear to have limited success possibly because of the progestogen component. Other drugs that have been used include corticosteroids, conjugated oestrogens, gonadorelin analogues, androgens, and tamoxifen, but all have significant adverse effects associated with long-term use. Bilateral oophorectomy has been used in severe cases, when drug therapy has been unsuccessful.[1]

A woman with a history of auto-immune progesterone dermatitis developed pruritic, pink, oedematous plaques and macules on the upper thighs, axillae, and buttocks after the use of vaginal progestogen gel during infertility treatment.[2] The reaction was managed with topical corticosteroids. In another woman, with a history of chronic urticaria exacerbated by progesterone, the use of progesterone and various other progestogens as a component of HRT after oophorectomy caused urticaria and angioedema.[3] Desensitisation using micronised progesterone was successful in this case.

1. Baptist AP, Baldwin JL. Autoimmune progesterone dermatitis in a patient with endometriosis: case report and review of the literature. *Clin Mol Allergy* 2004; **2:** 10.
2. Jenkins J, *et al.* Autoimmune progesterone dermatitis associated with infertility treatment. *J Am Acad Dermatol* 2008; **58:** 353–5.
3. Poole JA, Rosenwasser LJ. Chronic idiopathic urticaria exacerbated with progesterone therapy treated with a novel desensitization protocol. *J Allergy Clin Immunol* 2004; **114:** 456–7.

Precautions

Progesterone and the progestogens should be used with caution in patients with hypertension, cardiac or renal impairment, asthma, epilepsy, and migraine, or other conditions which may be aggravated by fluid retention. Progestogens can decrease glucose tolerance and diabetic patients should be carefully monitored. They should also be used with care in persons with a history of depression. High doses should be used with caution in patients susceptible to thromboembolism.

Progesterone and the progestogens should not be given to patients with undiagnosed vaginal bleeding, nor to those with a history or current high risk of arterial disease and should generally be avoided in hepatic impairment, especially if severe. Unless progestogens are being used as part of the management of breast or genital-tract carcinoma they should not be given to patients with these conditions.

Although progestogens have been given as hormonal support during early pregnancy such use is not now generally advised. However, the use of a progesterone-type progestogen might still be considered for women who are progesterone-deficient. Such use may prevent spontaneous evacuation of a dead fetus, therefore careful monitoring of pregnancy is required. Progestogens should not be used diagnostically for pregnancy testing and should not be given in missed or incomplete abortion.

For precautions to be observed when progestogens are used as contraceptives, see p.2065. For those to be observed when progestogens are used in preparations for menopausal HRT, see p.2075.

Abuse. A case report of abuse of and dependency on progesterone.[1]

1. Keefe DL, Sarrel P. Dependency on progesterone in woman with self-diagnosed premenstrual syndrome. *Lancet* 1996; **347:** 1182.

Breast feeding. A large study[1] compared a contraceptive progesterone-releasing vaginal ring and a copper IUD for 1 year in breast-feeding women. There was little difference in infant weight gain during the study, although at 12 months the infants of mothers using the IUD were breast-fed less frequently, receiving more supplementary feeding, and were heavier. There was no adverse effect of progesterone on lactation or infant growth. Further smaller studies[2,3] have also found no adverse effect on lactation or infant growth. The American Academy of Pediatrics has found no reports of adverse effects in breast-fed infants of mothers given progesterone, and therefore considers it to be usually compatible with breast feeding.[4]

1. Sivin I, *et al.* Contraceptives for lactating women: a comparative trial of a progesterone-releasing vaginal ring and the copper T 380A IUD. *Contraception* 1997; **55:** 225–32.
2. Díaz S, *et al.* Fertility regulation in nursing women: IX contraceptive performance, duration of lactation, infant growth, and bleeding patterns during use of progesterone vaginal rings, progestin-only pills, Norplant implants, and copper T 380-A intrauterine devices. *Contraception* 1997; **56:** 223–32.
3. Massai R, *et al.* Preregistration study on the safety and contraceptive efficacy of a progesterone-releasing vaginal ring in Chilean nursing women. *Contraception* 1999; **60:** 9–14.
4. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 27/06/08)

Porphyria. Progesterone and progestogens have been associated with acute attacks of porphyria and are considered unsafe in patients with porphyria (but medroxyprogesterone has been used with buserelin to suppress premenstrual exacerbations of porphyria, see p.2084). Progestogens should generally be avoided by all women with porphyria; however, where non-hormonal contraception is inappropriate, progestogens may be used with extreme caution if the potential benefit outweighs the risk. The risk of an acute attack is greatest in women who have had a previous attack or are under 30 years of age. Long-acting progestogen preparations should never be used in those at risk.

Pregnancy. In Hungary, where 30% of all pregnant women were given hormonal support therapy with progestogens during the early 1980s, a case-control study suggested that there was a causal relationship between such treatment and hypospadias in their offspring.[1] Mixed results have been reported in other studies of the association between maternal progestogen use and the risk of hypospadias, but the indications and types of progestogens used in early pregnancy have also changed over time (for example, withdrawal bleeding induced by progestogens as a form of pregnancy testing is no longer used, and progestogen luteal support in early pregnancy is no longer recommended for routine use; see also Miscarriage, below). Nevertheless, results from a more recent case-control study[2] of deliveries between October 1997 and December 2000 suggested an increase in risk of at least twofold.

There have also been reports of nongenital malformations, including limb reduction defects, neural tube defects, and congenital heart malformations, following intra-uterine exposure to progestogens in early pregnancy. However, numerous analyses of accumulated data have found no evidence of a recognisable malformation syndrome.[3]

For details of individual case reports, see Pregnancy under Dydrogesterone (p.2096), Hydroxyprogesterone (p.2110), Norethisterone (p.2120), and Noretynodrel (p.2121). For the effects of hormonal contraceptive use during early pregnancy, see p.2067. For the risk of ectopic pregnancy with progestogen-only contraceptives, see p.2061.

1. Czeizel A. Increasing trends in congenital malformations of male external genitalia. *Lancet* 1985; **i:** 462–3.
2. Carmichael SL, *et al.* Maternal progestin intake and risk of hypospadias. *Arch Pediatr Adolesc Med* 2005; **159:** 957–62.
3. Brent RL. Nongenital malformations following exposure to progestational drugs: the last chapter of an erroneous allegation. *Birth Defects Res A Clin Mol Teratol* 2005; **73:** 906–18.

Veterinary use. An FAO/WHO expert committee examining the risks from residue of veterinary drugs in foodstuffs established an acceptable daily intake for progesterone, but concluded that there would be no need to specify a numerical maximum residue limit for progesterone in the edible tissues of cattle when products are used as growth promotors according to good prac-