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.

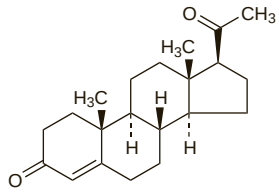
Прогестерон

$C_{21}H_{30}O_2$ = 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-

tice.[1] However, it should be noted that in the EU the use of steroidal hormones such as progestogens in veterinary practice is restricted, and their use as growth promotors is banned.

1. FAO/WHO. Evaluation of certain veterinary drug residues in food: fifty-second report of the joint FAO/WHO expert committee on food additives. *WHO Tech Rep Ser 893* 2000. Also available at: http://whqlibdoc.who.int/trs/WHO_TRS_893.pdf (accessed 27/06/08)

Interactions

Enzyme-inducing drugs such as carbamazepine, griseofulvin, phenobarbital, phenytoin, and rifampicin may enhance the clearance of progesterone and the progestogens. These interactions are likely to reduce the efficacy of progestogen-only contraceptives (see p.2067), and additional or alternative contraceptive measures are recommended.

Aminoglutethimide markedly reduces the plasma concentrations of medroxyprogesterone acetate and megestrol, possibly through a hepatic enzyme-inducing effect; an increase in progestogen dose is likely to be required.

Since progesterone and other progestogens can influence diabetic control an adjustment in antidiabetic dosage could be required. Progestogens may inhibit ciclosporin metabolism leading to increased plasma ciclosporin concentrations and a risk of toxicity (see p.1828).

Pharmacokinetics

Progesterone has a short elimination half-life and undergoes extensive first-pass hepatic metabolism when given orally; oral bioavailability is very low although it may be increased somewhat by an oily vehicle and by micronisation. Progesterone is absorbed when given buccally, rectally, or vaginally, and rapidly absorbed from the site of an oily intramuscular injection.

Various derivatives have been produced to extend the duration of action and to improve oral activity. Esters of progesterone derivatives such as hydroxyprogesterone caproate are used intramuscularly, and megestrol acetate is orally active. The ester medroxyprogesterone acetate is used orally and parenterally. 19-Nortestosterone progestogens have good oral activity because the 17-ethinyl substituent slows hepatic metabolism.

Progesterone and the progestogens are highly protein bound; progesterone is bound to albumin and corticosteroid binding globulin; esters such as medroxyprogesterone acetate are principally bound to albumin; and 19-nortestosterone analogues are bound to sex-steroid binding globulin and albumin. Progesterone is metabolised in the liver to various metabolites including pregnanediol, which are excreted in the urine as sulfate and glucuronide conjugates. Similarly, progestogens undergo hepatic metabolism to various conjugates, which are excreted in the urine. Progesterone is distributed into breast milk.

◊ Reviews.

1. Kuhl H. Comparative pharmacology of newer progestogens. *Drugs* 1996; **51:** 188–215.
2. Stanczyk FZ. Structure-function relationships, metabolism, pharmacokinetics and potency of progestins. *Drugs Today* 1996; **32** (suppl H): 1–14.
3. Schindler AE, *et al.* Classification and pharmacology of progestins. *Maturitas* 2003; **46** (suppl 1): S7–S16.

Uses and Administration

Progesterone is a natural hormone whereas progestogens are synthetic compounds, derived from progesterone or 19-nortestosterone, with actions similar to those of progesterone (for further details, see p.2058).

Progestogens derived from 19-nortestosterone are used as **hormonal contraceptives** (see p.2069), either alone or combined with an oestrogen. The progesterone derivative medroxyprogesterone acetate is also used, and progesterone itself has been used.

Progestogens, and sometimes progesterone, are used with oestrogens for **menopausal HRT** (p.2076) to reduce the increased risk of endometrial hyperplasia and carcinoma that occurs when long-term oestrogen therapy is unopposed.

Similarly, drugs with progestogenic actions may be used in **menstrual disorders** such as dysmenorrhoea (p.6) and menorrhagia associated with dysfunctional uterine bleeding (below). Progestogens may also be used in the management of endometriosis (p.2091). Although progestogens and progesterone have been used for the management of the premenstrual syndrome (below), such a practice is of debatable value.

Progestogens may be valuable in advanced **endometrial cancer** (p.663) and have been tried in some other malignancies. The progestogens typically used for malignant disease include medroxyprogesterone acetate, megestrol, and norethisterone. Some progestogens such as megestrol and medroxyprogesterone are used for the **cachexia** or wasting associated with severe illness including cancer and AIDS (p.2115).

Progestogens have been widely advocated for either the prevention of **recurrent miscarriage** or the treatment of threatened miscarriage (below). However, there is little evidence of any benefit from such a practice and the use of progestogens in early pregnancy is not now generally advised, with the exception of the use of progesterone or a progesterone derivative in women who are progesterone deficient (see also Precautions, above). Progesterone is, however, the preferred drug for luteal support in women undergoing **assisted reproductive techniques** such as IVF (see Infertility, p.2080).

USES AND ADMINISTRATION OF PROGESTERONE. Progesterone is usually given as an oily intramuscular injection, a vaginal gel or pessaries, or as suppositories. Preparations containing micronised progesterone are also available for oral and vaginal use.

In dysfunctional uterine bleeding or amenorrhoea 5 to 10 mg daily of progesterone may be given by intramuscular injection for about 5 to 10 days until 2 days before the anticipated onset of menstruation. Alternatively, progesterone may be given for amenorrhoea as a vaginal gel at a usual dose of 45 mg on alternate days for up to 6 doses; the dose may be increased to 90 mg in those who do not respond to the lower dose. An oral dose of 400 mg given daily at bedtime for 10 days may also be used for amenorrhoea.

In women with a history of recurrent miscarriage and proven progesterone deficiency, twice weekly intramuscular injection (increased to daily if necessary) of 25 to 100 mg of progesterone, from about day 15 of the pregnancy until 8 to 16 weeks, has been used. The dose may be increased to 200 mg daily if necessary. Vaginal doses of micronised progesterone 200 to 400 mg daily, in 2 divided doses, have also been given until week 12 of pregnancy. A similar intramuscular schedule has been used for luteal support in IVF or gamete intra-fallopian transfer techniques with treatment beginning on the day of transfer of embryo or gametes. Alternatively, progesterone may be given vaginally in assisted reproduction, but doses can vary widely depending on the preparation. A vaginal gel may be given at a dose of 90 mg daily; it is given for 30 days if pregnancy occurs, and may be continued until there is placental autonomy (up to 10 to 12 weeks). A dose of 90 mg twice daily has been used in women with ovarian failure. A vaginal tablet containing micronised progesterone 100 mg may be given 2 or 3 times daily; treatment is started at oocyte retrieval and continued for up to 10 weeks. Some soft capsules containing micronised progesterone may also be suitable for intravaginal use in a dose of 400 to 600 mg daily, in 2 or 3 divided doses, from the day of gonadotrophin administration until week 12 of pregnancy.

Progesterone may be given vaginally or rectally in doses of 200 mg daily to 400 mg twice daily for the management of the premenstrual syndrome. Treatment usually starts on day 12 to 14 of the menstrual cycle and continues until the onset of menstruation. Similar vaginal or rectal doses have also been used in the treatment of puerperal (post-natal) depression.

Progesterone has been given as the progestogen component of menopausal HRT. Soft capsules containing micronised progesterone are available in some countries for oral use, given in a dose of 200 mg daily at bedtime for 12 to 14 days of each month. Alternatively, a dose of 100 mg daily may be given from day 1 to 25 of each cycle, resulting in less withdrawal bleeding.

A progesterone-releasing intra-uterine device has been used as a hormonal contraceptive; the device contains 38 mg of progesterone and is effective for up to 12 months. A vaginal ring device that releases 10 mg of progesterone daily is used in some countries for contraception in lactating women. The first ring is inserted 6 weeks after delivery, then replaced every 90 days.

Administration. A number of progesterone creams for *topical* application to the skin are promoted in various countries for the management of menopausal symptoms and conditions associated with progesterone deficiency. These are sometimes described as containing 'natural' progesterone or phytoprogesterone from plant sources. However, many of these products are available without prescription or medical consultation and there has been some concern about their safety and efficacy. Reviews[1,2] have found early studies reporting that absorption of progesterone from these creams was minimal. However, a later study[3] using liquid chromatography-tandem spectrometry of whole blood reported that steady-state progesterone exposure was similar for women given either oral micronised progesterone or topical cream.[3] The authors suggested that the differences between their results and previous studies were likely to have been caused by the use of different analytical techniques, and that women using these creams may in fact be exposed to higher systemic concentrations of progesterone than previously thought. Some proponents of topical progesterone therapy have questioned the importance of using serum concentrations as a marker for absorption. A review[4] concluded that available serum-progesterone concentrations probably remain low after topical use and that further studies on the pharmacokinetics of topical progesterone are needed. In terms of efficacy, a number of small controlled studies have not shown progesterone cream to be any better than placebo for the management of menopausal vasomotor symptoms or the prevention of bone loss, and mixed results have been reported regarding the prevention of endometrial proliferation associated with oestrogen therapy.[1,2,4]

1. Anonymous. 'Natural' progesterone creams for postmenopausal women. *Drug Ther Bull* 2001; **39:** 10–11.
2. Wren BG. Transdermal progesterone creams for postmenopausal women: more hype than hope? *Med J Aust* 2005; **182:** 237–9.
3. Hermann AC, *et al.* Over-the-counter progesterone cream produces significant drug exposure compared to a Food and Drug Administration-approved oral progesterone product. *J Clin Pharmacol* 2005; **45:** 614–19.
4. Elshafie MAA, Ewies AAA. Transdermal natural progesterone cream for postmenopausal women: inconsistent data and complex pharmacokinetics. *J Obstet Gynaecol* 2007; **27:** 655–9.

Menorrhagia. Menorrhagia, or excessive menstrual bleeding, is usually defined as a blood loss exceeding 80 mL per menstrual period,[1,2] compared with a normal loss of about 30 mL. However, many women consider losses below 80 mL to be excessive particularly if 'flooding' occurs. Although not life-threatening, menorrhagia can lead to iron deficiency anaemia and considerably impair quality of life. Menorrhagia may be associated with pelvic disorders such as fibroids or endometriosis, the use of copper IUDs, or some systemic disorders.[1-3] However, most commonly it is associated with dysfunctional uterine bleeding;[1] a term used to denote frequent, prolonged or heavy uterine bleeding for which no specific cause is found (essential, idiopathic, or primary menorrhagia). Both ovulatory (regular) and anovulatory cycles may give rise to dysfunctional uterine bleeding.[2] In general, medical treatment is used initially in women with no underlying uterine abnormalities.[3] The most commonly used drugs are NSAIDs, tranexamic acid, combined oral contraceptives, and progestogens, and choice of therapy may be influenced by the contraceptive needs of the patient.[1-3] Surgery can be used if medical management is ineffective, and may be considered for first-line treatment in selected patients.[3]

NSAIDs such as mefenamic acid, ibuprofen, and naproxen have been widely used. They reduce menstrual blood loss by about 20 to 50%, and there does not seem to be evidence to suggest that one NSAID is more effective than another.[1] They are taken only during the menstrual phase, which reduces adverse effects, and probably improves patient compliance; they also have the benefit of relieving dysmenorrhoea (p.6).[1] Systematic review[4] suggests that NSAIDs are less effective than tranexamic acid, danazol, and intra-uterine levonorgestrel in reducing bleeding. NSAIDs are considered a suitable option when hormonal therapy is not acceptable. They should be stopped if symptoms do not improve within three menstrual cycles, but can be used for as long as the patient finds them to be beneficial.[3]

Given during menstruation *tranexamic acid* reduces menstrual blood loss by about half;[1] the benefits of tranexamic therapy have been confirmed by systematic review.[5] Like NSAIDs, tranexamic acid is considered a suitable option when hormonal therapy is not acceptable. It should be stopped if symptoms do not

improve within three menstrual cycles, but can be used for as long as the patient finds it to be beneficial.[3] *Etamsylate* has been used for menorrhagia, but it is less effective than NSAIDs and tranexamic acid, and is no longer recommended.[1,3]

In women who require contraception, a *combined oral contraceptive* appears to be effective,[1,3] although good evidence of this is actually lacking.[6] It has been suggested that extended-cycle regimens should be considered for women with menorrhagia, as there are fewer bleeding episodes per year of treatment.[2] Traditional therapy with *progestogens* such as norethisterone or medroxyprogesterone given during the luteal phase appears to be ineffective in women with normal ovulatory cycles,[1,3,7] although cyclical therapy may be of benefit in anovulatory patients as it imposes a cycle.[2] Progestogen therapy for 21 days of the cycle results in a significant reduction in menstrual blood loss,[1,3,7] but is associated with adverse effects that may limit its acceptability. Long-acting injectable progestogens, such as medroxyprogesterone acetate, reduce menstrual blood loss or induce amenorrhoea when they are used as contraceptives. They have therefore been used for menorrhagia, although specific studies for this indication are lacking.[1,3]

More recently, a contraceptive *levonorgestrel-containing IUD* has been shown to be very effective in reducing menstrual blood loss in menorrhagia.[1,2] UK guidelines[3] suggest that it should be considered first when either hormonal or non-hormonal treatment is acceptable and long-term use is anticipated, although comparative data are scanty.[8] There is also some evidence that it may be an effective alternative to surgery, but data from long-term follow-up are needed.[9] As there can be changes in bleeding pattern associated with this device, particularly in the first few cycles, use for at least 6 months is advised to enable full assessment of benefit.[3]

Danazol is also effective,[10] producing about a 50% reduction in menstrual blood loss,[1] but has significant adverse effects and treatment is usually limited to 3 to 6 months. *Gonadorelin analogues* are effective for menorrhagia associated with fibroids (p.2107).[1] When used pre-operatively for endometrial thinning, they produce more consistent results than danazol.[11] Gonadorelin analogues may therefore be considered before surgery or when other options for fibroids are contra-indicated, but 'add-back' hormone replacement is recommended for the management of adverse effects from oestrogen deficiency or if they are used for more than 6 months.[3]

In patients who fail to respond to drug treatment, or in whom such therapy is inappropriate, various *surgical options* exist. Conservative surgical techniques, where the endometrium is ablated or resected, are increasingly being used, and are an effective alternative to hysterectomy.[3,12] Hysterectomy is the ultimate therapy, but is associated with significant morbidity.

1. Roy SN, Bhattacharya S. Benefits and risks of pharmacological agents used for the treatment of menorrhagia. *Drug Safety* 2004; **27:** 75–90.
2. Nelson AL, Teal SB. Medical therapies for chronic menorrhagia. *Obstet Gynecol Surv* 2007; **62:** 272–81.
3. National Collaborating Centre for Women's and Children's Health/NICE. Heavy menstrual bleeding (issued January 2007). Available at: http://www.nice.org.uk/nicemedia/pdf/CG44FullGuideline.pdf (accessed 27/06/08)
4. Lethaby A, *et al*. Nonsteroidal anti-inflammatory drugs for heavy menstrual bleeding. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 27/06/08).
5. Lethaby A, *et al*. Antifibrinolytics for heavy menstrual bleeding. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2000 (accessed 27/06/08).
6. Iyer V, *et al*. Oral contraceptive pills for heavy menstrual bleeding. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 1997 (accessed 27/06/08).
7. Lethaby A, *et al*. Cyclical progestogens for heavy menstrual bleeding. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 27/06/08).
8. Lethaby AE, *et al*. Progesterone or progestogen-releasing intrauterine systems for heavy menstrual bleeding. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 27/06/08).
9. Marjoribanks J, *et al*. Surgery versus medical therapy for heavy menstrual bleeding. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 27/06/08).
10. Beaumont H, *et al*. Danazol for heavy menstrual bleeding. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 27/06/08).
11. Sowter MC, *et al*. Pre-operative endometrial thinning agents before endometrial destruction for heavy menstrual bleeding. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2002 (accessed 27/06/08).
12. Lethaby A, *et al*. Endometrial resection and ablation versus hysterectomy for heavy menstrual bleeding. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 1999 (accessed 27/06/08).

Miscarriage. Threatened miscarriage is a common complication of pregnancy that presents before 20 weeks of gestation as vaginal bleeding, with or without abdominal pain, while the cervix is closed and the fetus is viable. Endogenous progesterone is normally produced by the corpus luteum to maintain pregnancy, and low concentrations have been associated with pregnancy loss. Progestogen therapy has therefore been widely used in the treatment of threatened miscarriage,[1] but there is a paucity of clinical study data to support routine use.[2] Similarly, progestogens have been used prophylactically to prevent miscarriage, but studies have suffered from various limitations.[3] A systematic review[4] found no evidence to support routine use, but there was limited evidence to suggest that women with a history of recurrent miscarriage (3 or more consecutive miscarriages) might gain some benefit. The *BNF* advises that progestogen prophylaxis in women with a history of recurrent miscarriage is not recommended. (See also Pregnancy, above, for reports of hypospadias in the offspring of women given hormonal support therapy.)

1. Sotiriadis A, *et al*. Threatened miscarriage: evaluation and management. *BMJ* 2004; **329:** 152–5.
2. Wahabi HA, *et al*. Progestogen for treating threatened miscarriage. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 27/06/08).
3. Walch KT, Huber JC. Progesterone for recurrent miscarriage: truth and deceptions. *Best Pract Res Clin Obstet Gynaecol* 2008; **22:** 375–89.
4. Haas DM, Ramsey PS. Progestogen for preventing miscarriage. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 27/06/08).

Premature labour. Recommendations have been made regarding progesterone therapy for the prevention of premature birth in women at risk of preterm delivery (see under Hydroxyprogesterone Caproate, p.2110).

Premenstrual syndrome. Progestogen therapy was once popular for premenstrual syndrome, but beneficial responses have not been universally achieved and the theory that progesterone was necessary to correct a hormone imbalance is now losing ground (see p.2099). Progesterone has been given orally, vaginally, and rectally, in continuous and luteal phase regimens. However, systematic reviews[1,2] have found no convincing evidence to support its use.

1. Wyatt K, *et al*. Efficacy of progesterone and progestogens in management of premenstrual syndrome: systematic review. *BMJ* 2001; **323:** 776–80.
2. Ford O, *et al*. Progesterone for premenstrual syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 27/06/08).

Preparations

BP 2008: Progesterone Injection;
USP 31: Progesterone Injectable Suspension; Progesterone Injection; Progesterone Intrauterine Contraceptive System; Progesterone Vaginal Suppositories.

Proprietary Preparations (details are given in Part 3)
Arg.: Crinone; Faselut†; Gester; Mafel; Progest; Proluton; Utrogestan; ***Austral.:*** Crinone; Proluton; ***Austria:*** Utrogestan; ***Belg.:*** Crinone; Progestogel; Utrogestan; ***Braz.:*** Crinone; Evocanil; Utrogestan; ***Canad.:*** Crinone; Prometrium; ***Chile:*** Crinone†; Hormoral; Progendo; Progering; ***Cz.:*** Agolutin; Crinone; Utrogestan; ***Denm.:*** Crinone; ***Fin.:*** Crinone; Lugesteron; ***Fr.:*** Estima; Evapause†; Progestogel; Utrogestan; ***Ger.:*** Crinone; Progestogel; Utrogest; ***Gr.:*** Crinone; Promenorea; Utrogestan; ***Hong Kong:*** Crinone; Cyclogest; Endometrin; Progestogel; Utrogestan; ***Hung.:*** Utrogestan; ***India:*** Crinone; Dubagest; Naturogest; Profine†; Progest†; Remens; Uterone; ***Indon.:*** Crinone; ***Irl.:*** Crinone; Utrogestan; ***Israel:*** Crinone; Endometrin; Gestone; Utrogestan; ***Ital.:*** Crinone; Esolut; Lutogin†; Progeffik; Progestogel†; Progestol†; Prometrium; Prontogest; ***Malaysia:*** Crinone; Cyclogest; Utrogestan†; ***Mex.:*** Crinone; Cuerpo Amarillo Fuerte; Gepromi; Geslutin; Gestageno; Premastan; Prosphere; Utrogestan; ***Neth.:*** Progestan; ***Norw.:*** Crinone; ***NZ:*** Crinone; Gestone; ***Philipp.:*** Crinone; ***Pol.:*** Luteina; ***Port.:*** Crinone; Progenar†; Progestogel; Utrogestan; ***Rus.:*** Crinone (Крайнон); Progestogel (Прожестожель); Utrogestan (Утрожестан); ***S.Afr.:*** Crinone; Cyclogest; Utrogestan; ***Singapore:*** Crinone; Cyclogest; Utrogestan†; ***Spain:*** Crinone; Darstin; Progeffik; Progestogel†; Progestosol; Utrogestan; ***Swed.:*** Crinone; ***Switz.:*** Crinone; Progestogel; Utrogestan; ***Thai.:*** Crinone; Cyclogest; Gestone†; Progestogel; Utrogestan; ***Turk.:*** Crinone; Cyclogest; Progestan; ***UK:*** Crinone; Cyclogest; Gestone; Utrogestan; ***USA:*** Crinone; Endometrin; Prochieve; Progestasert†; Prometrium; ***Venez.:*** Crinone; Progendo; Progestogel; Utrogestan.

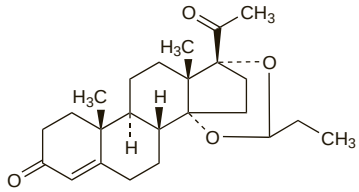
Multi-ingredient: ***Arg.:*** Cristerona; Fempack; Hosterona; Lubriderm; Menstrogen; Tropivag Plus; ***Braz.:*** Ginecoside†; Normomensil†; ***Fr.:*** Florgynal; Synergon; Trophigil; ***Ger.:*** Jephagynon†; ***Ital.:*** Biormon†; Menovis; ***Malaysia:*** Duogynon; ***Mex.:*** Damax; Genofort; Lutoginestryl F; Metrigen Fuerte; Ominol†; Primoson-F; Progediol†; Proger-F; ***Port.:*** Emmenovis†; ***Thai.:*** Duoton; Phenokinon-F; ***Turk.:*** Di-Pro; Synergon; ***Venez.:*** Cyclogesterin†; Ginecosid.

Proligestone *(BAN, rINN)*

Proligeston; Proligestona; Proligestoni; Proligestonum. 14a,17α-Propylidene dioxypregn-4-ene-3,20-dione.

Пролигестон

$C_{24}H_{34}O_4$ = 386.5.
CAS — 23873-85-0.
ATC Vet — QG03DA90.



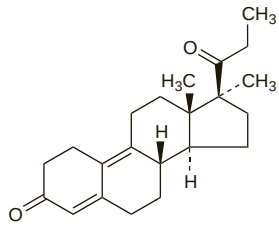
Profile
Proligestone is a progestogen used in veterinary medicine.

Promegestone *(rINN)*

Promegestona; Promégestone; Promegestonum; R-5020. 17α-Methyl-17-propionylestra-4,9-dien-3-one.

Промегестон

$C_{22}H_{30}O_2$ = 326.5.
CAS — 34184-77-5.
ATC — G03DB07.
ATC Vet — QG03DB07.



Profile
Promegestone is a progestogen structurally related to progesterone (p.2125). It has been given orally on a cyclical basis, in doses of 125 to 500 micrograms daily, in the treatment of menstrual disorders and mastalgia, and as the progestogen component of menopausal HRT.

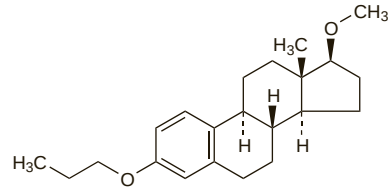
Preparations
Proprietary Preparations (details are given in Part 3)
Fr.: Surgestone; ***Port.:*** Surgestone.

Promestriene *(rINN)*

Promestrien; Promestrième; Promestrieno; Promestrienum. 17β-Methoxy-3-propoxyestra-1,3,5(10)-triene.

Проместриен

$C_{22}H_{32}O_2$ = 328.5.
CAS — 39219-28-8.
ATC — G03CA09.
ATC Vet — QG03CA09.



Profile
Promestriene is a derivative of estradiol (p.2097) that has been used topically in menopausal atrophic vaginitis, and in seborrhoea and acne.

Preparations
Proprietary Preparations (details are given in Part 3)
Arg.: Colpotrophine; ***Braz.:*** Colpotrofine; ***Cz.:*** Colpotrophine†; ***Hong Kong:*** Colpotrophine; ***Ital.:*** Colpotrophine; ***Mex.:*** Colpotrophine; ***Port.:*** Colpotrophine; ***Singapore:*** Colpotrophine; ***Spain:*** Colpotrofin; Delipoderm; ***Switz.:*** Colpotrophine; ***Turk.:*** Colpotrophine; ***Venez.:*** Colpotrofina†.

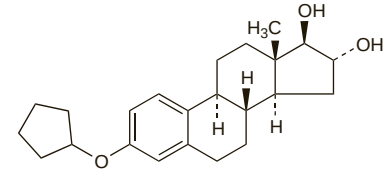
Multi-ingredient: ***Cz.:*** Colposeptine†; ***Hong Kong:*** Colposeptine; ***Port.:*** Trophoseptine; ***Turk.:*** Colposeptine.

Quinestradol *(BAN, rINN)*

Oestriol 3-Cyclopentyl Ether; Quinestradiol; Quinestradolum. 3-Cyclopentyloxyestra-1,3,5(10)-triene-16α,17β-diol.

Хинэстрадол

$C_{23}H_{32}O_3$ = 356.5.
CAS — 1169-79-5.



Profile
Quinestradol is a synthetic oestrogen that has been given orally for the treatment of menopausal vaginal symptoms.