Progestogens

Progestogens are synthetic forms of progesterone.

Progesterone was first isolated in 1934 by Butenandt. Progestogens were developed because progesterone could not be absorbed orally, although a method of processing progesterone via micro-ionising is now available (Utrogestan®). It has been suggested that micronised progesterone may be safer than synthetic progestogens.[1]

Main groups[2]

Synthetic progestogens are divided into two main groups:

- **Progesterone analogues:**
  - Dydrogesterone.
  - 17-OH progesterone group: medroxyprogesterone acetate and cyproterone acetate.
  - 19-nor progesterone group: nomegestrol acetate (NOMAC), trimegestone, promegestone.

- **Testosterone analogues:**
  - Estranes: norethisterone.
  - Estrane/pregnane: dienogest.
  - Gonanes: norgestrel and levonorgestrel (the active isomer of norgestrel), desogestrel, norgestimate and gestodene.

Progesterone and its synthetic analogues are less androgenic than the testosterone analogues.

Dienogest is referred to as a hybrid progestogen. It is a testosterone derivative but, like drospirenone which is derived from spironolactone, has no androgenic effect but partial anti-androgenic activity.

Division according to generation

Based on time since market introduction:

- First generation: norethynodrel.
- Second generation: norethisterone and its metabolites and levonorgestrel (active component of norgestrel) and its derivatives.
- Third generation: desogestrel and its derivative etonogestrel, gestodene, norgestimate and norelgestromin.
- Fourth generation: drospirenone, nomegestrol acetate (NOMAC) and dienogest.

Methods of administration

- Tablets (often in combination with an oestrogen).
- Depot: medroxyprogesterone acetate (DMPA) is available as an intramuscular (Depo-provera®) or subcutaneous (Sayana Press®) injection. Norethisterone enantate (Noristerat®) is rarely used.
- Implants - etonogestrol implant (Nexplanon®).
- Intrauterine systems (IUS) with slow-release levonorgestrel - Mirena® and Jaydess®.
Vaginal gel, suppositories and injections of progesterone may be used for a variety of indications, including infertility and heavy menstrual bleeding.

Progesterone cream: unregulated bio-identical progesterone is marketed in cream form; it is not licensed in the UK. Serious concerns regarding the use of progesterone cream include misleading claims of effectiveness and safety, as well as variable purity and potency.

Contra-indications

Progestogens should be avoided in patients with a history of liver tumours, those with genital or breast cancer (unless being used to treat these conditions), severe arterial disease, undiagnosed vaginal bleeding and acute porphyria, or if there is a history of idiopathic jaundice, severe pruritus or pemphigoid gestationis occurring during pregnancy.

When used for contraception, progestogens are usually contra-indicated in women with a history of breast cancer; it is a hormonally sensitive disease and prognosis may be affected by any hormonal method of contraception. A decision to initiate hormonal contraception should be made in consultation with the local oncology team.

Uses

Menstrual disorders

- Women with polycystic ovary syndrome who have four or fewer periods per year may be at increased risk of endometrial cancer; inducing a withdrawal bleed every month with cyclical progestogen (or the use of combined hormonal contraception (CHC) or a levonorgestrel-releasing IUS if contraception is desired) is advised.
- In heavy menstrual bleeding, a levonorgestrel-releasing IUS is first-line if pharmaceutical treatment is appropriate. Oral progestogens have been widely used for menorrhagia but are less effective compared with tranexamic acid or mefenamic acid.
- In dysfunctional uterine bleeding, progestogens may be used, with or without oestrogens. It may be necessary to ensure that the patient does not have atypical endometrial hyperplasia or a cervical lesion prior to having treatment for dysfunctional uterine bleeding, particularly in older women.
- To delay menses: norethisterone can be taken three days before the expected start date and continued. Normal menstruation will occur 2-3 days after stopping.

Contraception

Progestogens are used widely for contraception, as they provide an alternative form of hormonal contraception for patients deemed unsuitable for CHC. This makes them particularly suitable for women with a history of:

- Obesity
- Hypertension
- Diabetes mellitus
- Venous thromboembolism
- Migraine
- Heavy smoking

Progestogens are available in many forms:

- In combination with oestrogens in CHC, in oral, transdermal or intravaginal contraception when oestrogen isn't contra-indicated.
- Alone in oral contraception - progestogen-only pill (POP).
- Levonorgestrel-releasing IUS (see also below): Mirena® and Jaydess® provide contraception for five years and three years respectively.
Injections:
- Use of DMPA requires full counselling and warning regarding menstrual disturbances and possible delay in return to full fertility. Use beyond two years needs to be evaluated carefully, particularly in women aged under 18 years, due to its potential effects on bone density. DMPA (Depo-provera® and Sayana Press®) provides contraception for twelve weeks. See separate Progestogen-only Injectable Contraceptives article for more information.
- Norethisterone enantate (Noristerat®) provides contraception for eight weeks, which may be useful in certain scenarios.

- Implant: etonogestrel (Nexplanon®) provides contraception for up to three years when implanted subdermally.
- Emergency contraception.

In addition to anovulation, progestogens also lead to thickening of the cervical mucus, making it hostile to sperm. Furthermore, prolonged progestogen exposure leads to reversible atrophy of the endometrium, which reduces the chance of implantation of a fertilised ovum.

IUS
- Progestogen is delivered directly into the uterus, using a T-shaped device which slowly releases levonorgestrel over a three-year or five-year period.
- In addition to its use as a contraceptive, Mirena® may be used for endometrial protection in hormone replacement therapy (HRT), when the licence is for four years, and to treat heavy menstrual bleeding.

See separate Intrauterine System article.

HRT[9]
See also separate Hormone Replacement Therapy article.

- Postmenopausal women who have not had a hysterectomy and take oestrogens for HRT require progestogen, either on a cyclical or a continuous basis, to prevent hyperplasia of the endometrium and the possible development of endometrial cancer.
- Continuous combined HRT is recommended for any women requiring HRT once she is postmenopausal, ie a year after her last period or after she has been on cyclical HRT for one year.
- There have been reports of endometrial cancer in postmenopausal women who have used unregulated progesterone cream for endometrial protection, thought to be due to inadequate progesterone dose[3].

Endometriosis
See also separate Endometriosis article. A commonly used progestogen in endometriosis is medroxyprogesterone acetate but use of a levonorgestrel-releasing IUS is increasingly advocated[10].

- Progestogens have been shown in several studies to reduce pain from endometriosis, with minimal side-effects.
- Some theories suggest that progestogens have an anti-inflammatory effect on ectopic endometrium.
- Progestogens have no effect on fertility rates in endometriosis.

Acne[11, 12]
Some progestogens in combined oral contraceptives (COCs) are anti-androgenic.

- COCs block androgen receptors and 5-alpha reductase which converts testosterone to the more potent dihydrotestosterone.
- Androgen blockade occurs in the sebaceous glands of the skin, leading to reduction in seborrhoea and improvement in acne.
- They can also reduce hirsutism.
- Progestogen types appear to differ in the degree to which they prevent testosterone production, conversion or bioavailability.
- COC should be considered for women with acne who also want oral contraception.
Premenstrual syndrome

Progestogen alone is not recommended for women with premenstrual syndrome (PMS), due to insufficient evidence to support its effectiveness\cite{13}.

- PMS consists of mental and physical symptoms which are related to the menstrual cycle.
- The aetiology is unclear.
- It is not seen in anovulatory cycles.
- Psychotropics or the suppression of ovulation are the main pharmacological treatments.

Anticancer hormonal therapy

- Megestrol - breast cancer and endometrial cancer (advanced disease). Efficacies of progestogens are not proven and current practice is to combine progestogens with platinum or taxane chemotherapeutic agents.
- Medroxyprogesterone - renal cell cancer and prostate cancer.
- Cyproterone acetate - prostate cancer.

Palliative role in neoplastic disease\cite{14}

Progestogens stimulate appetite and lead to weight gain in cancer-associated anorexia-cachexia. Megestrol acetate is widely used for this indication but the mechanism is largely unknown. There may be a risk of phlebitis and pulmonary embolism.

Side-effects

The risk and types of side-effects and adverse effects vary between different progestogens, their dosage and different modes of delivery.

- Unscheduled bleeding
- Constipation
- Vaginal dryness
- Breast tenderness
- Acne
- Weight gain (DMPA)

Other adverse effects

- Ovarian cysts.
- HDL cholesterol can be suppressed among users of DMPA.
- Decreased glucose tolerance.
- Cardiovascular disease - limited evidence suggests that in women with concomitant risk factors, particularly hypertension, there is a small increase in cardiovascular events\cite{5}.
- Hirsutism (rare).
- Jaundice (rare - contra-indicated in hepatic impairment).

Further reading & references

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- Long-term Consequences of Polycystic Ovary Syndrome; Royal College of Obstetricians and Gynaecologists (November 2014)
- Heavy menstrual bleeding - assessment and management; NICE Clinical Guideline (August 2016)
- Contraception - progestogen-only methods; NICE CKS, February 2015 (UK access only)

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