Review Use of the new progestogens in contraception and gynaecology

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Key content:

- There has been a continuing drive to develop 'cleaner' and more progesterone receptor-specific progestogens in the hope of enhancing certain qualities and minimising others, such as androgenic properties.
- In the last five to 10 years several new progestogens have become available, including: dienogest, drospirenone, nomegestrol acetate, nestorone and trimegestone.
- These new progestogens do offer more therapeutic choice but the real way forward appears to lie in the development and incorporation of these in novel delivery systems.

Learning objectives:

- To learn about the new progestogens available and how they act.
- To learn about the uses of the new progestogens in contraception, gynaecological disorders and hormone replacement therapy.

Keywords contraception / ethinylestradiol / hormone replacement therapy / new progestogens / progesterone

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Introduction

In recent years, a number of new hormonal products for use in gynaecology have been launched. Some, using progestogens familiar to us, offer real advantages to users by utilising novel, innovative delivery systems such as implants, patches, intrauterine systems and vaginal rings. However, over the last five to 10 years several new progestogens have become available. Are these really different and do they offer additional benefits for women who require effective contraception, treatment for gynaecological disorders and menopausal vasomotor symptom relief? In this article this is explored further but complex descriptions of different steroid molecules are avoided and information is factual and clinically relevant.

The action of progestogens

Progesterone is rapidly metabolised and requires frequent dosing regimens if given by injection, vaginally or orally. Synthetic progestogens offer the advantage of less frequent administration but, like progesterone, they mediate their effects by intracellular progesterone receptors to ensure endometrial protection and, depending on the particular progestogen, suppression of ovulation. The mechanism of action in target tissues is complex but different chemical configurations have the potential to act on (stimulate or inhibit) other receptors, such as androgen, oestrogen, glucocorticoid and mineralocorticoid receptors.

Classification of progestogens

Most progestogens are derived from testosterone or progesterone, although drospirenone, a newly launched progestogen, is derived from 17 α-spirolactone.[1] It has been common practice to place each progestogen (particularly those contained in combined oral contraceptives) into groups related to the year/decade of introduction – hence, first, second and third generation compounds **(Table 1)**. This is unhelpful because it may infer that those in each generation are chemically similar and have related properties. A preferred option is to classify progestogens according to their biochemical families **(Box 1)**. This, again, is not ideal as minor changes to the steroid molecule can result in major metabolic alterations in steroid receptor affinity conferring markedly different actions.[2]

There has been a continuing drive to develop 'cleaner' and more progesterone receptor-specific progestogens in the hope of enhancing certain qualities and minimising others, such as androgenic properties. These newer progestogens are thought to have enhanced attributes and fewer associated side effects **(Table 2)**.

New progestogens

Several new progestogens have been synthesised in the last two decades. These include dienogest, drospirenone, nestorone, nomegestrol acetate and trimegestone. These new progestogens have been designed to have no androgenic or oestrogenic actions and to be closer in activity to the physiological hormone progesterone. Trimegestone and nestorone are thought to have the most progestational activity, followed by two of the older progestogens: 3-keto-desogestrel and levonorgestrel. The anti-ovulatory potency of these progestogens also varies.[1] These newer progestogens may offer additional beneficial effects for women if used in combined hormonal contraceptive preparations, hormone replacement therapy (HRT) or for treatment of gynaecological disorders such as endometriosis. Dienogest, drospirenone and trimegestone, for example, have anti-androgenic activity. This paper looks at these therapeutic areas more closely to investigate whether published data support the growing enthusiasm for prescribing the newer progestogens.

The role of new progestogens in combined hormonal contraceptives

In modern combined oral contraceptive pills the standard oestrogen component is ethinylestradiol, a potent synthetic derivative of estradiol, which has replaced mestranol to ensure adequate cycle control. In addition to this, progestogens are added to suppress ovulation and prevent endometrial hyperplasia.

Newer progestogens have high progestogen potency and additional effects, such as anti-androgenic or anti-mineralocorticoid activity. The combination of these progestogens with ethinylestradiol leads to the unique properties found in individual combined oral contraceptives. The 19-norprogesterone molecules plus drospirenone and dienogest are not androgenic and, therefore, have no negative effect on the lipid profile. Unlike the older 19-nortestosterone

Table 1
Examples of different generations of progestogens

Progestogen	Date of introduction	Generation	Product
Norethynodrel	1950s	First	Enovid (150 μg mestranol plus 9.58 mg norethynodrel) in 1959
Norethisterone	Early 1960s	Second	Anovlar (50 μg ethinylestradiol plus 4 mg norethisterone) in 1961
Levonorgestrel	Early 1970s	Second	Microgynon in 1973
Norgestimate	Late 1980s	Second/third	Cilest in late 1980s
Gestodene	Mid-1980s	Third	Femodene in 1980s
Desogestrel	Mid-1980s	Third	Marvelon in early 1980s
Drospirenone	Early 2000	Fourth	Yasmin in 2001

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derivatives the new progestogens may have neutral effects on metabolic or vascular risks but further studies are required to confirm this. Several pharmaceutical companies are also investigating the potential use of 'natural' oestrogens with the newer progestogens to formulate a more acceptable contraceptive pill.

Combined pills containing drospirenone

Drospirenone, derived from 17 α-spirolactone, has a pharmacological profile similar to natural progesterone in showing anti-mineralocorticoid activity, which causes moderately increased sodium and water excretion. Drospirenone is 8–10 times more effective in this respect than spironolactone[3] **(Table 2)**. Its anti-androgenic potency is about a third of cyproterone acetate.[4]

In the UK, a 30 μg ethinylestradiol/3 mg drospirenone combined oral contraceptive (Yasmin®, Schering Health Care, Burgess Hill, West Sussex) is available and a 20 μg combined oral contraceptive is going to be launched soon. Yasmin is an effective contraceptive and is well tolerated. When compared with a 30 μg ethinylestradiol/150 μg levonorgestrel combined oral contraceptive (Microgynon®, Schering Health Care) there was a lower rate of increased body weight and blood pressure in the Yasmin group over a six-month period.[5]

The anti-androgenic effects of the Yasmin combined oral contraceptive were demonstrated in a nine-month trial and similar beneficial effects on acne were obtained when compared with a 35 μg ethinylestradiol/2 mg cyproterone acetate pill (Dianette®, Schering Health Care).[6] Most combined oral contraceptives (even those containing 20 μg of ethinylestradiol) have been shown to reduce acne and seborrhoea[7] and the benefits of the anti-androgenic progestogens in them may only be obvious with long-term use.

Some premenstrual symptoms improve when Yasmin is taken cyclically.[8] A further study found a 20 μg ethinylestradiol/3 mg drospirenone combined oral contraceptive, given for 24 days of a 28 day cycle, to be superior to placebo for improving symptoms associated with premenstrual dysphoric disorder as defined by a 50% decrease in daily symptom scores.[9]

Box 1
Classification of progestogens[2]

Progestogen	Examples
Progesterone	Natural progesterone
Retroprogesterone	Dydrogesterone
Progesterone derivative	Medrogestone
17α-hydroxyprogesterone derivatives (pregnanes)	Medroxyprogesterone acetate Megestrol acetate Chlormadinone acetate Cyproterone acetate
17α-hydroxynorprogesterone derivatives (norpregnanes)	Gestonorone caproate Nomegestrol acetate
19-norprogesterone derivatives (norpregnanes)	Demegestone Promegestone Nestorone Trimegestone
19-nortestosterone derivatives (estranes)	Norethisterone Norethisterone acetate Lynestrenol Etynodiol diacetate
19-nortestosterone derivatives (gonanes)	Norgestrel Levonorgestrel Desogestrel Etonogestrel (3-keto-desogestrel) Gestodene Norgestimate Norelgestromin (17-deacetyl-norgestimate) Dienogest
Spirolactone derivatives	Drospirenone

Combined pills containing dienogest

Dienogest is often called a hybrid progestogen as it has a pharmacological profile combining the properties of 19-nortestosterone and progesterone derivatives. Dienogest has a pronounced progestogenic effect on the endometrium with little affinity for oestrogen, glucocorticoid and mineralocorticoid receptors. Its anti-androgenic activity is approximately 30% of that exhibited by cyproterone acetate.[10]

Since the early 1990s there has been a combined oral contraceptive available in Europe (but not in the UK) containing 30 μg ethinylestradiol/2 mg dienogest (Valette®). In a head-to-head study with a 35 μg ethinylestradiol/2 mg cyproterone acetate pill

Table 2
Metabolic effects of progestogens (based on relative binding affinity to sex steroid receptors)[4]

	Progestational activity	Androgenic activity	Anti-androgenic activity	Anti-mineralocorticoid activity	Glucocorticoid activity	SHBG↓
Progesterone	1	–	(+)	+	–	–
Cyproterone acetate	4	–	+++	–	(+)	–
Norethisterone	4	+	–	–	–	–
Medroxyprogesterone	4	+	–	–	(+)	+
Levonorgestrel	6	++	–	–	–	++
Desogestrel	8	+	–	–	–	–
Gestodene	9	+	–	(+)	–	+
Norgestimate	4	+	–	–	–	–
Drospirenone	4	–	+	+	–	–
Dienogest	4	–	+	–	–	–
Nomegestrol	5	–	+	–	–	–
Nestorone	10	–	–	–	–	–
Trimegestone	10	–	(+)	(+)	–	?

Progestational activity graded 1–10: 10 being most potent (these numbers are a rough guide only)
– no effect, (+) weak effect, + effect, ++ strong effect, +++ very strong effect
SHBG = sex hormone binding globulin

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(Dianette®, Schering Health) both reduced free testosterone by approximately 70%, raised sex hormone-binding globulin (SHBG) by 250–300% and produced a similar improvement in acne.[4]

Combined hormonal vaginal rings containing nestorone

Nestorone is a 19-norprogesterone derivative which is only active when administered parenterally because of its rapid hepatic metabolism. It has a high binding affinity to the progesterone receptor but negligible binding to androgen and oestrogen receptors, which results in strong anovulatory properties.[11] Nestorone has high potency and very small doses are required, which can be delivered via long-term sustained-release delivery systems.

A vaginal ring releasing 15 μg ethinylestradiol/150 μg nestorone per day can effectively suppress ovulation and gives an acceptable bleeding pattern for users.[12] There is no study comparing this new vaginal ring with the already licensed 15 μg ethinylestradiol/120 μg etonogestrel ring (NuvaRing®, Organon, Cambridge, Cambs).

The role of new progestogens in progestogen-only contraceptives

Low doses of progestogens such as norethisterone and levonorgestrel are effective oral contraceptives even though they may not reliably suppress ovulation (which has been reported in about half of treatment cycles using these traditional progestogens). Their mechanism of action probably relies upon changes in cervical mucus which reduce sperm viability and penetration.[13] Oral desogestrel (Cerazette®, Organon), however, metabolises to 3-keto-desogestrel (etonogestrel), which has a strong affinity for the progesterone receptor, thereby suppressing ovulation in up to 99% of cycles and offering greater contraceptive reliability.[14]

Demonstration that diffusion of steroids could be controlled at a constant rate through a silicone membrane resulted in the development of Norplant® (withdrawn from the UK market in 1999), the system of six subdermal capsules containing levonorgestrel. These early implant studies have more recently been extended to produce effective systems using only one or two silicone rods: Implanon® (Organon) and Jadelle® (Schering AG). Implanon is available in the UK and some European countries, while Jadelle is available in some European countries but not the UK.

Progestogen-only contraceptive implants containing nestorone

The Population Council (based in the USA) is investigating a single-rod, subdermal nestorone implant which will be effective for two years. As nestorone is virtually inactive orally there is potential for its use in breastfeeding women. Initial studies suggest it is fairly effective and acceptable although side effects include menstrual disturbances, headache and weight gain.[15] Further studies are required following modification of the design in the hope of improving its effectiveness.

Progestogen-only implants containing nomegestrol acetate

Nomegestrol acetate is a potent progestogen which exerts strong effects on endometrium. When given orally it is four times more potent than medroxyprogesterone acetate and has a binding affinity for the progesterone receptor that is 2.5 times higher than natural progesterone. Nomegestrol acetate is anti-androgenic but not quite as potent as cyproterone acetate. It does not bind to oestrogen, aldosterone or glucocorticoid receptors.[4]

Studies have shown that a single-rod, contraceptive implant containing nomegestrol acetate (Uniplant®), which has been much researched but is not commercially available at the moment, is effective for one year's use, with no reported increase in acne, unlike levonorgestrel implants. Fifty-six percent of women using this implant experienced cycle patterns similar to normal menstruation and 16% discontinued its use at one year.[16] Implants containing nomegestrol acetate have little effect on carbohydrate, lipid or hepatic metabolism. It is still questionable whether there is a place for a contraceptive implant that requires replacement every year.

Progestogen-only contraceptive sprays containing nestorone

The Population Council and Acrux Ltd have undertaken phase I studies investigating a nestorone contraceptive spray for women. Results indicate that daily, metered doses of nestorone, delivered transdermally to the inside of the forearm, are safely absorbed through the skin and achieve the necessary plasma levels needed to block ovulation. A single dose of transdermal nestorone is not completely absorbed within 24 hours, so it may give greater flexibility over the timing of the doses. Such sophisticated delivery systems offer choice to potential users and decreased dosing regimens.

The role of new progestogens in gynaecology

Progestogenic compounds were initially used in the first oral contraceptives but it soon became apparent that they had an important role in the treatment of menstrual cycle problems, endometrial cancer, endometriosis, support of pregnancies in assisted reproduction therapy and,

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more controversially, premenstrual syndrome (PMS).

Newer progestogens in the treatment of menstrual bleeding problems

Progestogens are often used cyclically to regulate menstrual bleeding or continuously (for example, using the levonorgestrel intrauterine system) for the management of heavy menstrual blood loss. The regime, dose and type of progestogen used vary widely, with little consensus about the optimum treatment approach. There is no evidence to date suggesting that the newer progestogens offer any advantages.

Newer progestogens in the treatment of endometriosis

Endometriosis is a progressive disease affecting 5–10% of women. It can cause dyspareunia, dysmenorrhoea, low back pain and infertility. It is associated with a high rate of recurrence (there is a cumulative five-year recurrence rate of approximately 50% following medical therapy). High dose progestogens (like combined oral contraceptives) suppress follicle stimulating hormone (FSH) and luteinising hormone (LH) and they shrink/decidualize endometrial implants, along with reducing retrograde menstruation. Studies suggest that progestogens have a similar efficacy to other medical treatments but that they are significantly cheaper and may be better tolerated than either danazol or gonadotrophin-releasing hormone (GnRH) analogues. If effective, these agents can be used safely for long periods of time.

Some recent research has suggested that 1 mg of dienogest daily is as effective as 3.75 mg triptorelin given intramuscularly every four weeks over a 16-week period following surgical treatment of endometriosis.[17] It may, therefore, be a new therapeutic alternative to the GnRH analogues.[17]

Newer progestogens in the treatment of premenstrual syndrome

The rationale behind the use of progesterone and progestogens in the management of premenstrual syndrome is based on the idea that progesterone deficiency is the cause. There is no evidence to support this. Further, more results from recent meta-analyses do not recommend the use of progesterone or progestogens (old or new) in the management of premenstrual syndrome.[18]

The role of progestogens in hormone replacement therapy

Progestogens are added to oestrogen in HRT to provide endometrial protection, control bleeding patterns and reduce the risk of endometrial cancer. The addition of androgenic progestogens may exert deleterious metabolic effects (for example, on lipoproteins) by opposing the high density lipoprotein cholesterol-raising action of oestrogen.[19] Following published data from the Women's Health Initiative study[20] implicating progestogens as the 'bad guys' for increasing the risk of breast cancer in HRT users, there has been much speculation concerning different progestogens and their effects on target tissues. Whether any of the newer progestogens discussed here offer hope to potential future users is still open for debate.

Hormone replacement therapies containing drospirenone

A continuous combined HRT containing 2 mg drospirenone combined with 1 mg 17 β-estradiol is available in the UK (Angeliq®, Schering Health). It controls menopausal vasomotor symptoms effectively and may have a small positive effect on blood pressure. Data from two recent studies[21,22] have demonstrated this. In a small subgroup of mildly hypertensive women with an initial blood pressure reading of more than 140/90 mmHg, the mean decrease in systolic blood pressure after 28 weeks of treatment was 9 mmHg and the mean decrease in diastolic blood pressure was 5.7 mmHg.[22] Further studies are required to confirm these findings using greater patient numbers for a longer duration.

Hormone replacement therapy containing dienogest

An oral continuous combined HRT formulation containing 2 mg estradiol valerate/2 mg dienogest (Climodien®, Schering AG; this is not available in the UK but is marketed in some parts of Europe) has been shown to relieve menopausal symptoms. Limited evidence from a randomised, placebo-controlled trial showed that it might help women with mild to moderate depression.[23]

Hormone replacement therapy containing nomegestrol acetate

Transdermal cyclical HRT formulations containing 50 μg/day 17 β-estradiol/5 mg/day nomegestrol acetate have been investigated and compared with other HRT preparations. Women taking HRT containing nomegestrol acetate had a more regular bleeding pattern compared with those receiving cyclical medroxyprogesterone acetate or natural progesterone HRT patches.[24] HRT preparations containing nomegestrol control menopausal vasomotor symptoms, but whether they offer anything new to users is still under question.

Hormone replacement therapy containing trimegestone

Trimegestone is a potent progestogen with some anti-androgenic and anti-mineralocorticoid activity at high doses.[4] When compared to similar HRT combinations, trimegestone containing formulations are equally effective in relieving

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menopausal symptoms. Studies over 12 months have suggested that continuous combined HRT containing trimegestone provides endometrial protection and exhibits a more favourable bleeding pattern than preparations with norethisterone acetate.[25] The properties of this new progestogen may produce some beneficial metabolic effects, with high density lipoprotein and apolipoprotein A1 rising, compared with an HRT containing norethisterone.[26]

Conclusions

This paper has concentrated on the therapeutic role of progestogens in contraception and gynaecology with particular reference to five new progestogens: dienogest, drospirenone, nomegestrol acetate, nestorone and trimegestone. There is no doubt that these progestogens have their own unique properties, but do they offer additional benefits for women who require effective contraception, treatment for gynaecological disorders and menopausal symptom relief? After studying the published evidence to date it is not certain. Drospirenone, whether in a combined oral contraceptive or HRT preparation, is well accepted and its anti-androgenic and anti-mineralocorticoid effects may aid compliance. Dienogest is also anti-androgenic, but does it have advantages over formulations containing drospirenone? Nestorone, nomegestrol acetate and trimegestone are potent progestogens producing some beneficial metabolic changes, but data about menstrual bleeding are still a little disappointing. A number of these studies, however, suffer from being underpowered and may be methodologically flawed as they deal with subjectively evaluated outcomes.

It must be remembered that the progestogen dose, route of administration and its combination with oestrogen will alter overall acceptance by individual women and further 'fine tuning' of these particular steroid molecules might prove impossible. These new progestogens do offer more therapeutic choice but the real way forward appears to lie in the development and incorporation of these in novel delivery systems.

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