Newer progestogens

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Abstract

Objective. *To review the literature on the most recent progestogens to be developed, to provide clinical comparisons with older progestogens and to look at the potential of products not yet marketed.*

Data sources. *Searches of Medline and Popline together with requests for bibliographies from the Population Council, Wyeth-Ayerst Research and Schering Health Care.*

Study selection. *Information from technical papers was used to ascertain the metabolic characteristics and receptor binding affinities of the compounds. Previous reviews were scrutinised in order to make comparisons with older compounds. Any available trials were examined to ascertain efficacy, bleeding patterns and tolerability, more weight being given to comparative trials.*

Discussion. *Five progestogens have been developed in the last decade. They are all devoid of androgenic activity; some have antiandrogenic activity. Combined oral contraceptive (COC) pills containing dienogest and drospirenone are already marketed. Nomegestrol and nestorone have been extensively studied as subdermal implants.*

Conclusions. *Newer progestogens used in combination with oestrogen behave very similarly to existing products. Progestogen-only products using new progestogens have potential for significantly better tolerability due to their lack of androgenic activity.*

Key message points

- Combined oral contraceptive pills containing newer progestogens have not been shown so far to have appreciable advantages over existing formulations.
- Nestorone has the potential advantage when used during lactation that it is not significantly absorbed by the suckling infant.
- Nestorone implants have the highest amenorrhoea rate of any implant so far produced.
- Nomegestrol implants do not appear to have acne as a side effect.
- More than half of nomegestrol implant users have a bleeding pattern similar to their normal menstrual cycle.

Introduction

It is now 50 years since the first progestogens were synthesised. New progestogens are being produced in order to develop novel positive attributes, enhance positive attributes of existing progestogens or to reduce or eliminate undesirable attributes. In the last decade five progestogens have been developed; these are indicated in italic type in Table 1.

Research into new progestogens has been driven by the thought that combined oral contraceptive (COC) pills tend to alter lipid metabolism in an adverse direction due to a preponderance of androgenic properties of the progestogen component. Effects on lipids may increase the risk of arterial disease, although clinical studies have not confirmed this. Even though high-density lipoprotein (HDL)-cholesterol is decreased and triglycerides and low-density lipoprotein (LDL)-cholesterol are increased by treatment with COCs containing 'androgenic' progestogens, the strong direct effect of ethinylestradiol on the arterial wall is thought to protect against atheroma formation, probably by preventing oxidation of LDL.[1] Also, the effect of COCs on carbohydrate metabolism is mainly dependent on the action of ethinylestradiol, modulated only slightly by the progestogen component.

The majority of women settle well on the traditional levonorgestrel or norethisterone monophasic COCs. (Norgestimate is largely metabolised to levonorgestrel and so is not such a novel progestogen as first thought.) If monophasic pills are thought to be causing progestogenic side effects, transferring to a triphasic formulation reduces total progestogen dose per cycle. But for those who still do not settle, the alternative pills containing desogestrel or gestodene have been helpful. The strong potency of these latter progestogens has allowed a reduction in ethinylestradiol dosage to 20 µg without loss of efficacy and this can be useful when an individual is thought to be suffering from estrogen side effects and has theoretical advantages in possibly reducing venous thromboembolism risk.

Table 1 *Classification of progestogens*

19-Nortestosterone derivatives		17α -OH-Progesterone derivatives	19-Norprogesterone derivatives	17α -Spirolactone derivative
Estranes	Gonanes	Pregnanes		
Norethisterone *Dienogest*	Levonorgestrel Desogestrel Gestodene Norgestimate (norelgestromin)	Medroxyprogesterone Cyproterone	*Nomegestrol* *Nestorone* *Trimegestone*	*Drospirenone*

Italic type is used to indicate those progestogens developed within the last 10 years.

Levonorgestrel and etonogestrel progestogen-only subdermal implants have the disadvantages of androgenic side effects and unpredictable bleeding patterns. Progestogens without androgenic activity used in implants would be a significant advance.

The newer progestogens discussed in this review are all devoid of androgenic activity; indeed some have antiandrogenic activity. Are there particular women who will benefit from these formulations? The COC containing drospirenone purports to have benefits from its antimineralocorticoid activity. How do implants containing new progestogens compare with existing products? Is there a future for vaginal rings using new progestogens?

This review concerns use for contraception only. All the progestogens mentioned have been developed with a view to use in hormone replacement therapy (HRT) products also.[2]

Classification of progestogens

The classification of progestogens according to biochemical grouping is shown in Table 1. For clinicians this is not helpful as very minor changes to the steroid skeleton can produce major metabolic changes, for instance halogenation of C-6 or removal of the C-19 methyl radical results in compounds with much higher progestational activity. Categorisation according to 'generations' will not be used in this review.

General characteristics of newer progestogens

Newer progestogens have high progestogen potency, with no androgenic activity. Some have antiandrogenic activity but not as much as cyproterone acetate has. None of them bind to sex hormone-binding globulin (SHBG).

Progestational activity is usually tested using the McPhail Index in immature rabbits, and also the pregnancy maintenance and the ovulation inhibition tests in rats.[2] Using these in vivo tests, nestorone appears to be the most potent progestogen, being 10 times more potent than levonorgestrel and 100 times more potent than progesterone itself when the molecules are administered subcutaneously.[3] When given orally, norethisterone, medroxyprogesterone and drospirenone are more potent than progesterone but less potent than levonorgestrel. These relative potencies are summarised in Table 2. However, it should be noted that the strength of binding affinity does not necessarily correlate with the degree of agonistic or antagonistic effect.[1] When newer progestogens are combined with ethinylestradiol, the formulation is estrogen-dominant as far as metabolic effects are concerned. The effects of the progestogens on the endometrium and cervix outweigh those of ethinylestradiol and contribute to the high contraceptive efficacy.

Dienogest

Dienogest exhibits weak binding affinity for the progesterone receptor and negligible affinity for the estrogen, glucocorticoid and mineralocorticoid receptors.[4] Nevertheless, dienogest shows a pronounced progestogenic effect on the endometrium. There is low competitive binding to the androgen receptor. After oral administration, dienogest is five times as active as levonorgestrel and 10 times as active as medroxyprogesterone acetate by the McPhail test. Compared to levonorgestrel, dienogest has a considerably higher fraction of free, non-protein-bound compound in plasma. This large fraction of biologically active steroid contributes to the strong progestational effect of dienogest. Antigonadotrophic actions, e.g. inhibition of follicle-stimulating hormone (FSH) and luteinising hormone (LH), are weak. Dienogest inhibits ovulation primarily via peripheral actions, rather than via a central action on gonadotrophin secretion. Antiandrogenic activity is approximately 30% that of cyproterone acetate.[1]

A COC containing dienogest 2 mg with ethinylestradiol 30 µg has been available in Germany since 1991. Efficacy is satisfactory and cycle control good.[5] In a randomised, double-blind comparison of dienogest 2 mg/ethinylestradiol 30 µg with cyproterone acetate 2 mg/ethinylestradiol 35 µg, both formulations caused increases in SHBG of 250–300%, reductions in free testosterone of around 70% and reductions of androstanediol glucuronide of 50–60%. Metabolic effects were not significantly different between the two formulations and beneficial effects on acne were equal.[6]

Drospirenone

Drospirenone on its own produces a small negative sodium balance when compared to placebo.[7] Drospirenone has antimineralocorticoid activity very much like progesterone; the only other COC with similar activity, but much weaker, is gestodene. When compared to conventional COCs, a drospirenone COC results in a much greater rise in plasma aldosterone[8,9] and a rise in plasma renin activity[9] which is presumed to be compensatory to the antimineralocorticoid effect of drospirenone.

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

	Progestational activity[2]	Androgenic activity	Antiandrogenic activity	Antimineralocorticoid 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 to 10, 10 being most potent. These numbers are a rough guide only.
–, No effect; (+), weak effect; +, effect; ++, strong effect; +++, very strong effect.

It was thought worth investigating the potential of a COC whose natriuretic effect might actually have a beneficial effect on weight and blood pressure. Such a product is now marketed widely: it contains drospirenone 3 mg and ethinylestradiol 30 µg. Randomised comparative trials making a comparison with desogestrel 150 µg/ethinylestradiol 30 µg showed similar efficacy and cycle control between the two formulations.[10,11]

There is a suggestion that women on the drospirenone COC show a small but significant loss of weight. In a 1-year randomised comparison with a monophasic desogestrel COC, weight fell slightly in both groups, but marginally more with the drospirenone COC.[10] In a 2-year randomised comparison with a monophasic desogestrel COC, weight in the drospirenone COC group was significantly lower than in the desogestrel COC group throughout the study.[11] In a 6-month randomised study with very small numbers making a comparison with a levonorgestrel COC, there was a small mean weight loss with the drospirenone COC and small mean weight gain with the levonorgestrel COC.[9]

The drospirenone COC increases levels of SHBG considerably with a corresponding decline in total testosterone, free testosterone, dehydroepiandrosterone and androstendione levels. These metabolic effects are analogous to those brought about by the product cyproterone acetate 2 mg/ethinylestradiol 35 µg and similar beneficial effects on acne are seen.[12] In the 1-year trial, similar beneficial effects on acne were seen in the drospirenone COC group as in the desogestrel COC group.[10]

Until there are some comparative studies with large enough sample sizes, there can be no valid comment on whether the drospirenone COC can be useful in the treatment of severe premenstrual syndrome as has been suggested.[13] As for an effect on premenstrual symptoms while taking the drospirenone COC, in a non-comparative study, only 2/23 menstrual distress parameters (negative affect and water retention) were affected favourably.[14] In a comparison of the drospirenone COC with a monophasic desogestrel COC, there was no difference between the formulations with respect to premenstrual symptoms.[11]

Nomegestrol

Initially known as TX066, nomegestrol has been developed in France. It is one of the most potent progestogens, exerting a strong effect on the endometrium.[1] Given orally it is four times more potent than medroxyprogesterone acetate by the McPhail test and half as potent as medroxyprogesterone acetate in the inhibition of estradiol-induced uterotropic action.[15] Its binding affinity to the progesterone receptor is 2.5 times higher than that of progesterone and higher than that of medroxyprogesterone acetate. Its antiandrogenic effect is not quite as high as cyproterone acetate. The compound does not bind to the estrogen receptor, the aldosterone receptor or the glucocorticoid receptor. Also, it does not induce sodium retention or exert antidiuretic activity. It inhibits ovulation effectively at a dose of 1.25 mg/day when given orally and at much lower doses in the form of a 1-year single-rod subdermal implant.[16] A multicentre trial in > 1500 women showed a low pregnancy rate (almost as low as for Norplant), 56% of women experiencing bleeding patterns similar to normal menstruation and a discontinuation rate of only 16% at the end of the first year.[17] Headache and weight gain are infrequently reported non-menstrual side effects in nomegestrol implant users, as for users of other progestogen implants.[18] Acne was not reported in the trials. This is in contrast to levonorgestrel implants (Norplant-6), the levonorgestrel intrauterine system and the etonogestrel implant which all show an overall increase in the frequency of acne in users.[19,20] Nomegestrol implants are not currently marketed.

Nomegestrol has a much longer half-life than medroxyprogesterone acetate. No clinically important effects on lipoproteins, carbohydrate metabolism, insulin levels or on hepatic function were observed in women using nomegestrol 55 mg implants over 2 years.[21] Users of nomegestrol implants showed no change in SHBG levels over 2 years;[22] there are no comparative studies of nomegestrol implants.

Nestorone

Nestorone (formerly known as ST-1435) has only a 10% oral bioavailability but has a slow elimination rate when given in sustained release delivery systems.[15] Its progestational activity is higher than that of levonorgestrel but lower than that of etonogestrel.[3] It shows no glucocorticoid activity. Nestorone implants do not appear to alter liver function, carbohydrate metabolism or lipid metabolism.[23]

Single-rod subdermal implants with a lifespan of 2 years and releasing various amounts of nestorone have been developed by the Population Council and have proved highly effective contraceptives.[24] Nearly 4000 woman-months of exposure have been accumulated in non-lactating women. No ovulation occurred when mean serum nestorone levels were higher than 40 pg/ml. Bleeding patterns are characterised by the highest incidence of amenorrhoea or oligomenorrhoea of any implant so far developed,[25] much higher than that with Norplant and approaching that of depot medroxyprogesterone acetate. Adverse events cited by users that led to implant removal were those usually seen with progestogens, i.e. headache, dizziness, weight gain, mood changes, mastalgia, acne and alopecia. Published comparative trials with other implants so far are of limited size.

As nestorone is virtually inactive orally, nestorone implants have great potential for use in breastfeeding women. One trial indeed confirms the safety for the infant.[24]

Rings containing nestorone alone or in combination with ethinylestradiol have been extensively evaluated.[25–27] Nestorone is also absorbed readily transdermally;[28] both gels and patches are being investigated. Comparisons will be needed with existing levonorgestrel vaginal rings, etonogestrel 120 µg/ethinylestradiol 15 µg vaginal rings and norelgestromin 150 µg/ethinylestradiol 20 µg patches. It will take some years to bring products other than implants to the market as studies are not that far advanced.

Trimegestone

Trimegestone is still under development. It is a potent progestogen that has greater selectivity for progesterone receptor than medroxyprogesterone acetate.[29] It is devoid of androgenic activity and has some antiandrogenic and antimineralocorticoid activity at higher doses.[30]

Conclusions

Massive amounts of time and energy are put into the development of new products, not to mention money. Products may take more than a decade to bring to the market. Many compounds fall by the wayside.

Products that have antimineralocorticoid properties are novel and interesting. But it must be borne in mind that weight gain, although of major importance as a perceived difficulty for users, is not in fact a significant side effect

when placebo-controlled studies are performed.[31] So, the launch of a product that does not cause weight gain is aimed at consumers who may be reluctant to initiate or continue the COC on account of fear of side effects such as weight gain; if this encourages uptake and continuation rates then it will have been a helpful development.

Due to their absent androgenic activity, combinations with ethinylestradiol show an estrogen dominance with respect to their effects on clotting factors, lipid metabolism and hepatic serum proteins. It remains to be seen whether the risk of arterial and venous diseases during long-term treatment with newer formulations differs from older preparations.

Androgen levels do not correlate with acne severity among people with acne,[32] so that acne is not necessarily part of a hyperandrogenic state. On balance, most COCs result in an improvement in acne, mainly by reducing sebum excretion rate under the influence of relative estrogen-dominance.[33] COCs with antiandrogenic activity are no better than the existing cyproterone/ethinylestradiol formulation in improving acne.[6,12] In turn, a biphasic desogestrel COC is as good as cyproterone/ethinylestradiol in its effect on acne.[34] Use of progestogens for true hyperandrogenic conditions is beyond the scope of this review.

Implants containing nomegestrol and nestorone have already been shown to have potential advantages over existing products. One- and 2-year implants without androgenic activity would be useful contraceptives to be able to offer. Nestorone is the only progestogen so far produced with virtually absent oral activity and is eminently suitable in the form of an implant for lactating women; it has a high amenorrhoea rate. Nomegestrol implants have the most 'natural' bleeding pattern of any implant so far developed, with over half of women having a bleeding pattern like a normal cycle; they appear not to cause acne.

With nestorone vaginal rings and transdermal delivery systems there is so far only limited data; large-scale clinical trials would be needed before consideration could be given to marketing.

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References

1 Kuhl H. Comparative pharmacology of newer progestogens. *Drugs* 1996; **51**: 188–215.
2 Sitruk-Ware R. Progestogens in hormonal replacement therapy: new molecules, risks, and benefits. *Menopause* 2002; **9**: 6–15.
3 Kumar N, Koide SS, Tsong Y-Y, et al. Nestorone: a progestin with a unique pharmacological profile. *Steroids* 2000; **65**: 629–636.
4 Oettel M, Holz C. Hybrid progestins: the example of dienogest. In: Sitruk-Ware R, Mishell DR (eds), *Progestins and antiprogestins in clinical practice*. New York, NY: Marcel Dekker, 2000; 163–178.
5 Zimmermann T, Dietrich H, Wisser K-H, et al. The efficacy and tolerability of Valette®: a postmarketing surveillance study. *Eur J Contracept Reprod Health Care* 1999; 4: 155–164.
6 Moore C, Luderschmidt C, Moltz L, et al. Antiandrogenic properties of the dienogest-containing oral contraceptive Valette®. *Med Actual* 1999; **35**(Suppl. C): 69–78.
7 Oelkers W, Berger V, Bolik A. Dihydrospirenone, a new progestogen with antimineralocortcoid activity: effects on ovulation, electrolyte excretion, and the renin-aldosterone system in normal women. *J Clin Endocrinol Metab* 1991; **73**: 837–842.
8 Oelkers W, Helmerhorst FM, Wuttke W, et al. Effect of an oral contraceptive containing drospirenone on the renin-angiotensin-aldosterone system in healthy female volunteers. *Gynecol Endocrinol* 2000; **14**: 204–213.
9 Oelkers W, Foidart JM, Dombrovicz N, et al. Effects of a new oral contraceptive containing an antimineralocorticoid progestogen, drospirenone, on the renin-aldosterone system, body weight, blood pressure, glucose tolerance, and lipid metabolism. *J Clin Endocrinol Metab* 1995; **80**: 1816–1821.
10 Huber J, Foidart JM, Wuttke W, et al. Efficacy and tolerability of a monophasic oral contraceptive containing ethinylestradiol and drospirenone. *Eur J Contracept Reprod Health Care* 2000; **5**: 25–34.
11 Foidart JM, Wuttke W, Bouw GM, et al. A comparative investigation of contraceptive reliability, cycle control and tolerance of two monophasic oral contraceptives containing either drospirenone or desogestrel. *Eur J Contracept Reprod Health Care* 2000; **5**: 124–134.
12 van Vloten W, van Haselen CW, van Zuuren EJ, et al. The effect of 2 combined oral contraceptives containing either drospirenone or cyproterone acetate on acne and seborrhea. *Cutis* 2002; **69**(Suppl. 4): 2–15.
13 Freeman EW, Kroll R, Rapkin A, et al. Evaluation of a unique oral contraceptive in the treatment of premenstrual dysphoric disorder. *J Womens Health Gend Based* Med 2001; **10**: 561–569.
14 Brown C, Ling F, Wan J. A new monophasic oral contraceptive containing drospirenone: effect on premenstrual symptoms. *J Reprod Med* 2002; **47**: 14–22.
15 Sitruk-Ware R, Sundaram K. Pharmacology of new progestogens: the 19-norprogesterone derivatives. In: Sitruk-Ware R, Mishell DR (eds), *Progestins and antiprogestins in clinical practice.* New York, NY: Marcel Dekker, 2000; 153–161.
16 Barbosa I, Coutinho E, Hirsch C, et al. Effects of a single contraceptive Silastic implant containing nomegestrol acetate on ovarian function and cervical mucus production during 2 years. *Fertil Steril* 1996; **65**: 724–729.
17 Coutinho EM, de Souza JC, Athayde C, et al. Multicenter clinical trial on the efficacy and acceptability of a single contraceptive implant of nomegestrol acetate, Uniplant. *Contraception* 1996; **53**: 121–125.
18 Brache V, Faundes A, Alvarez F, et al. Nonmenstrual adverse events during use of implantable contraceptives for women: data from clinical trials. *Contraception* 2002; **65**: 63–74.
19 Urbancsek J. An integrated analysis of nonmenstrual adverse events with Implanon. *Contraception* 1998; **58**: 109S–115S.
20 Andersson K, Odlind V, Rybo G. Levonorgestrel-releasing and copper-releasing (Nova T) IUDs during five years of use: a randomised comparative trial. *Contraception* 1994; **49**: 56–72.
21 Barbosa I, Coutinho E, Athayde C, et al. The effects of nomegestrol acetate subdermal implant (Uniplant) on carbohydrate metabolism, serum lipoproteins and on hepatic function in women. *Contraception* 1995; **52**: 111–114.
22 Barbosa I, Coutinho E, Athayde C, et al. Androgen levels in women using a single implant of nomegestrol acetate. *Contraception* 1996; **53**: 37–40.
23 Dorflinger LJ. Metabolic effects of implantable steroid contraceptives for women. *Contraception* 2002; **65**: 47–62.
24 Sivin I, Moo-Young A. Recent developments in contraceptive implants at the Population Council. *Contraception* 2002; **65**: 113–119.
25 Fraser IS, Weisberg E, Minehan E, et al. A detailed analysis of menstrual blood loss in women using Norplant® and Nestorone® progestogen-only contraceptive implants or vaginal rings. *Contraception* 2000; **61**: 241–251.
26 Brache V, Mishell DR, Lahteenmaki P, et al. Ovarian function during use of vaginal rings delivering three different doses of Nestorone®. *Contraception* 2001; **63**: 257–261.
27 Laurikka-Routti M, Haukkamaa M, Heikinheimo O. A contraceptive vaginal ring releasing ethinylestradiol and progestin ST-1435: bleeding control, serum steroid concentrations, serum lipids and serum chemistry. *Contraception* 1990; **42**: 111–120.
28 Haukkamaa M, Laurikka-Routti M, Heikinheimo O. Transdermal absorption of the progestin ST-1435: therapeutic serum steroid concentrations and high excretion of the steroid in saliva. *Contraception* 1991; **44**: 269–276.
29 Zhang Z, Lundeen SG, Zhu Y, et al. In vitro characterization of trimegestone: a new potent and selective progestin. *Steroids* 2000; **65**: 637–643.
30 Philibert D, Bouchoux F, Degryse M, et al. The pharmacological profile of a novel norpregnane progestin (trimegestone). *Gynecol Endocrinol* 1999; **13**: 316–326.
31 Coney P, Washenik K, Langley RGB, et al. Weight change and adverse event incidence with a low-dose oral contraceptive: two randomized, placebo-controlled trials. *Contraception* 2001; **63**: 297–302.
32 Levell MJ, Cawood ML, Burke B, et al. Acne is not associated with abnormal plasma androgens. *Br J Dermatol* 1989; **120**: 649–654.
33 Pye RJ, Meyrick G, Pye MJ, et al. Effect of oral contraceptives on sebum excretion rate. *BMJ* 1977; **2**: 1581–1582.
34 Vartiainen M, de Gezelle H, Broekmeulen CJH. Comparison of the effect on acne with a combiphasic desogestrel-containing oral contraceptive and a preparation containing cyproterone acetate. *Eur J Contracept Reprod Health Care* 2001; **6**: 46–53.