

# PROGESTOGEN USE IN THE MENOPAUSE

*The use of progestins in the menopause is being re-evaluated in the light of recent research findings.*



**MIKE DAVEY**

MB BCh, FCOG (SA)

**Gynaecologist in private practice**

Westville Hospital  
Durban

*Mike Davey practises mainly in the fields of menopause and osteoporosis. He is a founder member and the present Vice-President of the South African Menopause Society. He qualified at the University of the Witwatersrand, and has been in private practice for the past 18 years.*

The past two years have seen increasing attention being focused on the progestogens. The findings, as regards breast cancer, from the two arms of the Women's Health Initiative (WHI)<sup>1,2</sup> study supported the findings of previous observational studies that the addition of a progestin increased the risk of breast cancer above that of oestrogen alone. The lack of protection against ischaemic heart disease afforded by menopausal hormone therapy as shown in the WHI and HERS<sup>3,4</sup> studies also led to questions being asked about the influence of the progestin used. A re-evaluation of progestogen use in the menopause is occurring.

**CLASSIFICATION OF THE PROGESTOGENS**

The term progestogen applies to both natural progesterone and the synthetic progestins. Natural progesterone, even in the micronised form, shows a wide variation in absorption in the individual patient.

The synthetic progestins are far more rapidly absorbed, reaching a peak serum level in 2 - 5 hours. The progestins used in menopausal hormone therapy preparations were chosen primarily for their ability to protect the endometrium. The one effect they have in common is their ability to turn an oestrogen-primed endometrium from a proliferative into a secretory pattern. They vary widely in their other effects, including oestrogenicity, androgenity, glucocorticoid and mineralocorticoid effects.

Table 1. **Progestogens available in South Africa**

Parent compound	Progestogen
Progesterone	Micronised progesterone
Retroprogesterone	Dydrogesterone
Progesterone derivative	Medrogestone
17 $\alpha$ -OH-progesterone derivatives (Pregnanes C21)	Medroxyprogesterone acetate
	Cyproterone acetate
19-nor-progesterone derivatives (19-nor-pregnanes C20)	Promegestone
	Trimegestone
19-nor-testosterone derivatives	
Estranes (C18)	Norethisterone
	Norethisterone acetate
Gonanes (C17)	Norgestrel
	Levonorgestrel
	Norgestimate
	Dienogest
	Desogestrel
	Gestodene
Spirolactone derivatives	Drospirinone

*The term progestogen applies to both natural progesterone and the synthetic progestins. Natural progesterone, even in the micronised form, shows a wide variation in absorption in the individual patient.*

*The findings of increased risk of breast cancer with the use of a progestin have prompted a review of the need for their use.*

*Oral oestrogen therapy has a beneficial effect on both LDL cholesterol and HDL cholesterol, lowering the former and raising the latter.*

*In all likelihood, in the patient at low risk for either breast or cardiovascular disease, it will make no difference which progestogen is used and the choice will often be based on patient tolerance.*

The progestins are classified according to their derivation from a particular parent compound. Table I lists some of the progestogens available for use in menopausal patients in South Africa. The 19 nor-progesterone derivatives are not available in South Africa at this stage but are included because of their potential for future use due to their high specificity for the progesterone receptor, allowing adequate progestogenic effect at low doses.

### THE NEED FOR PROGESTOGEN USE IN MENOPAUSAL HORMONE THERAPY

The findings of increased risk of breast cancer with the use of a progestin have prompted a review of the need for their use. The sole reason for using a progestin is endometrial protection. The authors of the Million Women Study,<sup>5</sup> a large observational study that confirmed the increased risk of breast cancer with the use of progestogen combined with oestrogen, suggested that there may be no place for the use of a progestogen because the increased risk of endometrial cancer was outweighed by the comparatively decreased risk of breast cancer in unopposed oestrogen users. They calculated that 10 years' use of unopposed oestrogen would produce 5 extra breast cancers and 10 extra endometrial cancers per 1 000 women compared with 19 extra breast cancers and no extra endometrial cancers using a combined oestrogen-progestin preparation for the same duration. It should however be realised that these figures applied only to the patients in the 50 – 64-year age group and that even after oestrogen is discontinued, the risk for endometrial cancer remains increased for the next 10 years.<sup>6</sup> The numbers as calculated by the Million Women Study would therefore be an under-estimate.

There is also the issue of the abnormal bleeding patterns that will inevitably develop with unopposed oestrogen and the increased intervention in the form of endometrial biopsies, hysteroscopy and dilatation and curettage that would be required for endometrial assessment in patients on unopposed oestrogen. Very-low-dose oestrogen replacement has been shown to adequately suppress bone resorption, has a favourable effect on blood lipids,<sup>7</sup> and will control vasomotor symptoms in most patients. However, although the incidence of endometrial hyperpla-

sia is low with this type of therapy, there is still an increased risk compared with opposed therapy, even after only 2 years.<sup>6</sup>

Other methods of administering progestogen have been considered. Long-term sequential therapy results in a small increased risk of endometrial cancer compared with continuous combined therapy.<sup>8</sup> The same problem would therefore apply to long-cycle therapy.

An alternative that has been proposed is the use of intrauterine progestin in the form of the progestin-containing intrauterine contraceptive device (Mirena). This is available in South Africa in a 20 µg form, and a 10 µg form (not yet available in South Africa) has been developed especially for use in menopausal patients. This is an attractive option that has been shown to control bleeding and although long-term observational studies are not yet available, it would appear to adequately suppress the endometrium. The amount of progestin released into the circulation is much lower than with oral administration.<sup>6</sup> However, there is still a significant amount of progestin absorbed and there is no evidence at this stage that the effect on the breast or cardiovascular system would be any different. Further research is needed on this promising mode of therapy.

There has even been the suggestion that there should be a move back towards hysterectomy to allow unopposed oestrogen. With the advent of less invasive means of controlling dysfunctional uterine bleeding, there has been a move away from hysterectomy. The incidence of morbidity associated with hysterectomy is high, and there would appear to be no justification at this stage for a move back towards this invasive and potentially dangerous procedure purely to avoid using progestogens in the menopause. Patients who have had endometrial ablation still require endometrial pro-

Table II. Differential effects of progestogens

Progestogen	mineralocorticoid	Oestrogenic	Androgenic	Anti-androgenic	Glucocorticoid	Anti-mineralocorticoid
Progesterone		-	-	+/-	+	+
Didrogesterone		-	-	+/-	-	+/-
Medrogestone		-	-	+/-	-	-
<b>17<math>\alpha</math>-OH-derivatives</b>						
Medroxyprogesterone acetate		-	+/-	-	+	-
Cyproterone acetate		-	-	++	+	-
<b>19-nor-progesterone derivatives</b>						
Promegestone		-	-	-	-	-
Trimegestone		-	-	+/-	-	+/-
<b>19-nor-testosterone derivatives</b>						
Norethisterone		+	+	-	-	-
Levonorgestrel		-	+	-	-	-
Norgestimate		-	+	-	-	-
Dienogest		+/-	-	+	-	-
Desogestrel		-	+	-	-	-
Gestodene		-	+	-	+	+
<b>Spirolactone derivatives</b>						
Drosperinone		-	-	+	-	+

tection with a progestogen as pockets of endometrium may remain.

**THE USE OF DIFFERENT PROGESTINS**

If we therefore accept that at present the balance of evidence is that we need to use a progestogen, we need to look at whether the use of a different progestogen may have resulted in a different outcome, as regards breast disease and cardiovascular disease, in studies such as WHI and HERS. These studies used a combination of conjugated equine oestrogen (CEE) and medroxyprogesterone acetate (MPA). The progestins used in current preparations were chosen more for their ability to suppress oestrogen-induced thickening of the endometrium rather than for other effects and, as stated above, they differ in many aspects, as seen in Table II.<sup>9</sup>

There are no long-term observational studies or randomised control trials comparing the effects of these different

progestogens. We therefore have to rely on indirect evidence in order to decide if there is potential advantage in using alternative progestogens.

**CARDIOVASCULAR SYSTEM**

The different progestins differ in their effect on intermediate markers of cardiovascular risk such as blood lipid levels. Oral oestrogen therapy has a beneficial effect on both LDL cholesterol and HDL cholesterol, lowering the former and raising the latter. The more androgenic progestogens, such as norethisterone acetate (NETA), MPA and levonorgestrel, oppose both of these effects. This is not seen with the less androgenic progestogens such as dydrogesterone, drosperinone and micronised progesterone. However the more androgenic progestogens oppose the potentially adverse increase of triglyceride seen with oral oestrogen administration. The increase in triglyceride is however generally within normal limits and its significance is debatable.<sup>9</sup>

A difference is also seen in the effect on insulin resistance, with androgenic progestins increasing insulin resistance and therefore decreasing glucose tolerance.<sup>10</sup> Progesterone, dydrogesterone and drosperinone have no adverse effects in this regard. The adverse effect of decreased glucose tolerance on the cardiovascular system is well established.

That there is a difference in the direct effects of different progestogens on the vasculature is shown in a study by Thomas,<sup>11</sup> who looked at the acute vascular actions of progesterone, MPA, norethisterone, CEE and 17 $\beta$  oestradiol on peripheral and cerebral blood vessels of rats. Both MPA and norethisterone caused endothelial damage leading to inflammation and thrombosis. This was not seen with progesterone or the oestrogens. Although we must be careful about extrapolating this *in vitro* finding to the clinical situation, it is clear that there are differences in effect that could have significant clinical implications.

There are also differences as regards haemostasis. Oral oestrogen decreases antithrombin III (AT III), protein C and protein S. This increases coagulation and may partly explain the increase in incidence of thrombosis seen with oral oestrogen therapy. MPA also significantly decreases AT III activity whereas dydrogesterone has far less effect.<sup>12</sup>

**BREAST**

In order to understand the potentially adverse effects of progestogens on the breast, it is necessary to understand the effect of oestrogen on the breast in menopausal women.<sup>13</sup> Oestrogen results in an increase in proliferation of breast tissue. Oestradiol is the most biologically active oestrogen. Oestrone sulphate is the dominant circulating oestrogen in menopausal women. Oral oestrogen therapy results in increased levels of oestrone. There are various enzyme pathways that will determine the amount of oestradiol that accumulates in the breast tissue and therefore the potential for proliferative activity and stimulation of tumour growth. Oestrone sulphatase converts oestrone sulphate to oestrone. This is then reduced by 17β-OH steroid dehydrogenase to oestradiol. The significance of this is shown by the fact that sulphatase activity has been shown to be far more intense in malignant and benign breast tumours than in normal breast tissue.<sup>14</sup> Non-androgenic progestogens such as progesterone and dydrogesterone inhibit oestrone sulphatase activity. This benefit is also seen with tibolone. These non-androgenic progestogens also appear to favour the oxidative process whereby oestradiol is converted to the less biologically active oestrone rather than the reductive process, resulting in increased oestradiol levels. The androgenic 19-nor-testosterone derivatives do not have either of these effects, showing potential benefit for the use of a non-androgenic progestin. The

non-androgenic progestins have further potential benefit in that they encourage increased sulphatase activity that results in the conversion of oestradiol to the less biologically active oestradiol sulphate.

Apoptosis is an important and beneficial process in the removal of damaged and potentially malignant cells. Franke<sup>14</sup> looked at the apoptosis proliferation ratio of MCF-7 breast cancer cells exposed to progestins alone and in combination with oestradiol. Tibolone has the highest degree of apoptosis followed by the less androgenic progestogens. The more androgenic progestins had an apoptosis proliferation ratio well on the side of proliferation.

The previously mentioned effect of the androgenic progestins in increasing insulin resistance may also be significant as regards the breast as their effect of increasing both insulin and insulin-like growth factor I, which are potent mitogenic peptides, may play a role in breast cancer.<sup>15</sup>

**CONCLUSIONS**

Recent randomised control trials have shown that the use of progestogens may impair potentially beneficial effects and enhance adverse effects of oestrogen administration in menopausal women. Present evidence however still supports the use of a progestogen to protect the endometrium in menopausal women. There is no grade I evidence that the use of any other progestogen, different to that used in the currently available prospective randomised controlled trials, would have resulted in a different outcome. In all likelihood, in the patient at low risk for either breast or cardiovascular disease, it will make no difference which progestogen is used and the choice will often be based on patient tolerance. However, there is interesting indirect evidence

that different progestogens differ in their effects on both the breast and cardiovascular system and that there may be advantages in using less androgenic progestogens in patients at higher risk for breast or cardiovascular disease if the decision is taken to use menopausal hormone therapy. This further highlights the need for individualisation of therapy in menopausal women.

*References available on request.*

**IN A NUTSHELL**

Recent publications of prospective randomised controlled trials have called into question the role of progestogen use in menopausal women.

Progestogens are necessary to protect the endometrium from the hyperplastic effect of oestrogen.

Progestogens differ markedly in their effects on different organ systems.

In the cardiovascular system, the less androgenic progestogens have potential advantages as regards their effect on lipid profile, direct vascular effect, insulin resistance and haemostasis.

By virtue of their effect on breast tissue enzymes, progestogens may increase the concentration of oestradiol in breast tissue. Progestins differ in this effect.

Less androgenic progestogens have a favourable effect on the apoptosis proliferation ratio in breast tissue.

Individualisation of menopausal hormone therapy is important, especially in the high-risk patient.