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Micronized progesterone, progestins, and menopause hormone therapy

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ABSTRACT

Treatment with estrogens alone in women without a uterus or in combination with progestins (PG) in women with a uterus is the most effective treatment for vasomotor symptoms in the peri or postmenopausal period. However, PGs differ by their biological activities, and it is likely that not all PGs will display a class effect. The type of PG is important regarding tolerance and cardiovascular and breast cancer risk. Some studies indicate that micronized progesterone (P) is safer than synthetic PGs with an acceptable metabolic profile. For that purpose, we conducted a narrative review on the balance between benefit/risk using P versus PGs in menopause hormone therapy (MHT) to aid clinician to choose the best regimens, specifically the PG component of hormone therapy, for women with bothersome menopausal symptoms and with a uterus.

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Introduction

Treatment of severe and moderate vasomotor symptoms (VMS) is the main indication for menopause hormone therapy (MHT). Treatment with estrogens alone in women without a uterus or in combination with PGs or micronized P in women with a uterus is the most effective treatment for VMS in the postmenopausal period and is particularly indicated for symptomatic women under 60 years and less than 10 years of menopause (The hormone therapy position statement of The North American Menopause Society 2017; Gompel 2012). PGs differ in their chemical structures and their biological activities; it is likely that not all PGs will display beneficial effects and side-effects to the same extent (Toit et al. 2017). It is thus crucial to improve our understanding of the risk/benefit profile of PGs used in hormone therapy. This review focuses on the different types and use of PGs in women with an intact uterus using MHT.

PGS – classification

PGs are a class of synthetic compounds that have been developed to mimic the biological action of P. These PGs have many therapeutic applications and are used in place of progesterone because they have better bioavailability and half-lives. They are generally characterized by a stronger affinity for the P receptor (PR) and/or by a slower catabolism than that of P (Toit et al. 2017). They can induce other effects, making it possible to characterize each molecule, by their antiestrogenic/estrogenic, antiandrogenic/androgenic, antimineralocorticoid and glucocorticoid properties (Toit et al. 2017).

There are several pharmacological classes of PGs (Stanczyk et al. 2013) (Figure 1):

- retroprogesterone, derived from natural P: dydrogesterone (DYD);
- 17OH progesterone derivatives: pregnanes and norpregnanes;

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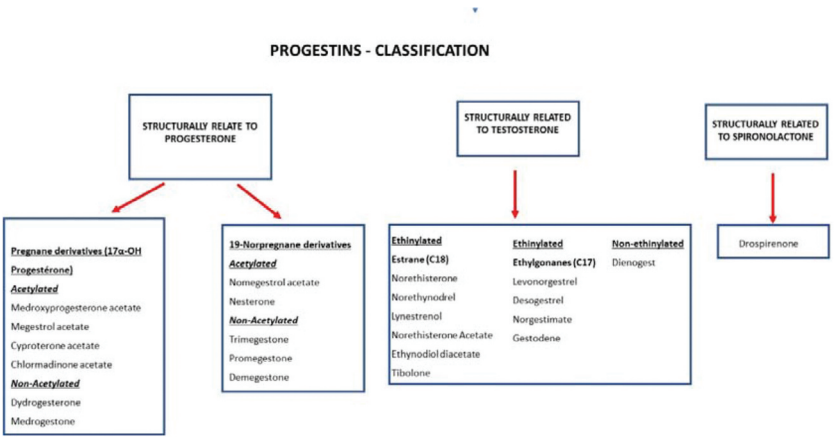

Figure 1. Classification of progestins.

- derivatives of normethyltestosterone (19-nortestosterone): estrane and gonanes;
- the spironolactone derivative: drospirenone (DRSP);
- a mixed derivative of both nor-steroid and pregnane: dienogest (DNG).

PG can be structurally parent to P, testosterone or spironolactone. Nor-steroid PGs are also classified according to their generation. The first generation includes norethisterone (NET) and its derivatives; the second generation includes norgestrel and levonorgestrel (LNG); and the third generation: desogestrel (DSG), gestodene (GSD) and norgestimate (NRG). By analogy, contraceptives containing derivatives from pregnanes and spironolactone, DRSP, chlormadinone acetate (ACM), acetate cyproterone (ACP), are called (improperly)" fourth generation" (Toit et al. 2017).

PGS and the breast

Breast tissue contains large amounts of glucocorticoid receptors (GR), androgen receptors (AR) and mineralocorticoid receptors (MR). Different PGs can bind to one or more receptors, AR, MR, and GR with low or high affinity; they can be agonists or antagonists toward these receptors (Hapgood et al. 2014; Kuhl 2011; Schindler et al. 2008; Wiegratz and Kuhl 2006) (Table 1) (Hipolito and Gompel 2018); furthermore, several nor-steroids are partially metabolized in estrogenic derivatives with low affinity for the estrogen receptor (ER) (Gompel and Plu-Bureau 2012). These different activities in their respective receptors could explain the different results regarding the risk of breast cancer in MHT.

Combined MHT including a synthetic PG have been linked to an increased risk of breast cancer in many epidemiological studies (Gompel and Plu-Bureau 2012). In the Women Health Initiative (WHI) study, a randomized trial comparing a treatment with conjugated equine estrogens (CEE) combined with medroxyprogesterone acetate (MPA), after an average of 11.3 years, out of 2236 breast cancers, the incidence was higher in users than in never-users (0.60% versus 0.42%, annualized rate, respectively, with a hazard ratio [HR] of 1.55; confidence interval [CI] 95%: 1.41–1.70; p <001) (Chlebowski et al. 2013).

Data from observational studies strongly suggest that PG are not equivalent in terms of risk of breast cancer associated with their use, as micronized P and DYD, do not appear to increase, as much as PG, the risk of breast cancer. A cohort study in France, analyzed different types of PGs and different routes of estrogen administration, and the risk of breast cancer. A total of 54,548 postmenopausal women with an average follow-up of 5.8 years were analyzed (Fournier et al. 2014). The relative risk (RR) for breast cancer was 1.2 (95% CI: 1.1–1.4) for users of MHT compared to never-users. When

Table 1. Spectrum of hormonal activity of progestins and natural progesterone (Hipolito and Gompel 2018).

Progestogen	Antigonadotrope	Anti Estrogenic	Estrogenic	Androgenic	Antiandrogenic	Glucocorticoid	Antiminéralocorticoid
Progesterone	+	+	-	-	+	+ (in vitro)	+
Dydrogesterone	-	+	-	-	(+)	-	-
Pregnanes							
Chlormadinone acetate	+	+	-	-	+	+	-
Cyprotérone acetate	+	+	-	-	++	+	-
Megestrol	+	+	-	(+)	+	+	-
MPA	+	+	-	(+)	-	+	-
Medrogestone	+	+	-	-	(+)	-	-
19-norpregnanes							
Nomegestrol acetate	+	+	-	-	(+)	-	-
Promegestone	+	+	-	-	-	+	-
Trimegestone	+	+	-	-	(+)	-	(+)
Nestorone		+	-	-	-	-	
19-nortestosterone derivatives							
Norethisterone	+	+	+	+	-	-	-
Lynestrenol	+	+	+	+	-	-	-
Norethynodrel	+	(+)	+	(+)	-	-	-
Levonorgestrel	+	+	-	+	-	-	-
Norgestimate	+	+	-	+	-	-	-
3Keto-desogestrel	+	+	-	+	-	-	-
Gestodene	+	+	-	+	-	+	+
Tibolone		+	+	++	-	-	-
Metabolites							
Dienogest	+	(+)	(+)	-	+	-	-
Spironolactone derivative							
Drospirenone	+	+	-	-	+	-	+

++: strongly effective; +: effective; (+): weakly effective; –: not effective; ?: unknown;
MPA: medroxyprogesterone acetate

analyzing different types of PGs, an increased risk of breast cancer was observed in users of estradiol (E2) associated with a PG (RR: 1.3; 95% CI: 1.1–1.5). However, this increased risk was limited to the use of synthetic PG (RR: 1.4; 95% CI: 1.2–1.7) and, without risk when using micronized P (RR: 0.9; 95% CI: 0.7–1.2) (Fournier et al. 2014). This study played a key role in providing evidence that PGs are not equal in terms of risk for breast cancer. Similarly, the study from Lyytinen and colleagues, based on registers and reporting on 221 551 postmenopausal women using MHT, showed a RR of 1.22 (95% CI 0.83–1.72) for use of DYD up to 5 years (Lyytinen, Pukkala, and Ylikorkala 2009). Further, The French cohort study E3N, during follow-up (mean duration 8.1 postmenopausal years) reported that combined hormone therapy with micronized P (RR 1.00, 95% CI 0.83–1.22) or DYD (RR 1.16, 95% CI 0.94–1.43) was not associated with any increase in the risk of breast cancer, whereas synthetic PGs were associated with a significant increase in the RR of 1.69 (95% CI 1.50–1.91) (Fournier, Berrino, and Clavel-Chapelon 2008). The results of these studies and others examining the effects of MHT on natural P or DYD are presented in Table 2 (Hipolito and Gompel 2018) showing that the use of micronized P and DYD is associated with a lower risk of breast cancer compared to synthetic PGs (Cordina-Duverger et al. 2013; Espié et al. 2007; Fournier, Berrino, and Clavel-Chapelon 2008; Lyytinen, Pukkala, and Ylikorkala 2009; Schneider, Jick, and Meier 2009). These results are corroborated in a recent meta-analysis, involving 86,881 postmenopausal women (average age of 59 years) and whose follow-up varied from 3 to 20 years, progesterone was associated with a lower risk of breast cancer than synthetic PGs when combined with estrogens (RR: 0.67; 95% CI: 0.55–0.81) (Asi et al. 2016).

The consensus is that MHT exerts a promoter effect, i.e. MHT promotes an existing breast tumor (occult lesions) rather than initiating one. This consensus is based on the decreased risk of breast cancer observed after discontinuation of MHT (Gompel 2012; Santen et al. 2020). There are no data from clinical trials showing that P is associated with a definite increase in the relative risk of breast cancer (Gompel and Plu-Bureau 2012).

This is corroborated by a study measuring proliferation (and apoptosis) of MHT in normal breast tissue in women treated by various menopause treatment. Biopsies from women treated either by CEE + MPA or by transdermal estradiol + P, demonstrated different proliferation measured by Ki67. Proliferation was significantly increased in the group of women treated with CEE + MPA but not in women treated with estradiol+ P, emphasizing different actions of progesterone and PGs (MPA) in breast tissue and the highest safety of P (Murkes, Conner, and Leifland et al. 2011).

Another important concept is that the level of breast cancer risk of the woman must be evaluated before discussing with her the indication of MHT. The amplitude of the increase in the risk of breast cancer is a function of the level of the baseline risk (Santen et al. 2020).

PGS and the endometrium

It is well established that unopposed estrogen prescribed to postmenopausal women induces a dose-related stimulation of the endometrium associated with an increased risk of hyperplasia and endometrial cancer. Further, there is considerable debate about whether and at which dosage P or PG provide an effective endometrial protection. P acts physiologically to counteract the proliferative effects of estradiol during the menstrual cycle. During the luteal phase, progesterone suppresses the epithelial and stromal expression of estrogen receptors (α and β) in the functional layer of the endometrium and not in the basal (Mote et al. 2000).

In MHT, PG protect the endometrium against the proliferative effects of estrogens. Furthermore, various publications have shown that the proliferative activity upon estradiol stimulation is dose and time-dependent. The duration of the PG sequence to avoid the risks associated with taking estrogens alone has been estimated to be at least 10 to 14 days per month according to the duration of estrogens (Whitehead et al. 1982). The sequential addition of a PG virtually eliminates any risk of hyperplasia, provided that the PG sequence is sufficiently long, greater than or equal to 12 days (Van Gorp and

Table 2:. Principal studies on the risk of breast cancer and menopause hormone therapy (MHT) with micronized progesterone (P) or dydrogesterone (DYD) (Hipolito and Gompel 2018).

Study	Population	Mean follow-up (years)	Risk of breast cancer
Fournier, Berrino, and Clavel-Chapelon (2008)	Cohort study; 80 377 French postmenopausal women, mean age 53.1 years	8.1 ans	Estrogen alone: RR 1.29 (95% CI 1.02–1.65) Estrogen + P: RR 1.00 (95% CI 0.82– 1.22) Estrogen + DYD: RR 1.16 (95% CI 0.94–1.43) Estrogen + synthetic progestins: RR 1.69 (95% CI 1.50–1.91)
Espié et al. (2007)	Cohort study; 4949 French women, mean age: 64.2 years, women with MHT 60.6 years, women without MHT	2.5 ans	Without MHT 0.70% E2 alone 0.28% E2þP 0.40% E2þsynthetic progestin 0.94% No increase in risk
Cordina-Duverger et al. (2013)	Case–control study; 1555 French women:739 cases, 816 controls. Mean age of cases: 35–54 years (16.5%); 55–64 years (47.0%); >65 years (36.5%). Mean age of controls: 35–54 years (17.6%); 55–64 years (43.6%); >65 years (38.7%)		E2 alone: OR 1.19 (95% CI 0.69–2.04) E2 + P: OR 0.80 (95% CI 0.44–1.43) E2 + synthetic progestin: OR 1.57 (95% CI 0.99–2.49) E2 + nortestosterone derivative: OR 3.35 (95% CI 1.07–10.4)
Schneider, Jick, and Meier (2009)	Case–control study; 1261 cases and 7566 controls; mean age 51.3 years	6.0 ans	E2 + DYD: OR 0.68 (95% CI 0.38–1.20) CEE+ norgestrel, 2–4 years: OR 1.50 (95% CI 1.11–2.04); ≥5 years: OR 1.34 (95% CI 0.71–2.54)[a] E2+ NET, 2–4 years: OR 1.19 (95% CI 0.86–1.63); ≥5 years: OR 2.85 (95% CI 1.87–4.36) CEE+ MPA: OR 0.78 (95% CI 0.50–1.20) Significantly less breast cancer with DYD
Lyytinen	221 551 postmenopausal women using MHT from register, 6211 cases		E2 transdermal vs. oral: no difference E2 + NET: increase with duration: 3–10 years, RR 1.34 (95% CI 1.17–1.51); 5–10 years, RR 2.03 (95% CI 1.88–2.18); >5 years, RR 3.15 (95% CI 2.44–4.00) E2 + MPA: 3–10 years, RR 1.27 (95% CI 1.09–1.48); 5–10 years, RR 1.64 (95% CI 1.49–1.79); >5 years, RR 1.90 (95% CI 1.07–3.07) E2 + DYD: 3–5 years, RR 1.22 (95% CI 0.83–1.72); 5–10 years, RR 1.13 (95% CI 0.49–2.22); >5 years, no cases and very few controls In NET group: RR with continuous treatment > sequential

aBased on five cases

NET, norethisterone; MPA, medroxyprogesterone acetate; DYD, dydrogesterone; CEE, conjugated equine estrogens; E2, estrogen/estradiol; OR, odds ratio; RR, relative risk.

Neven 2002), except in the case of a sequence short estrogenic, 21 days, 10 days of PG then is enough. The dosage of PG needed to avoid virtually any risk of hyperplasia depends on the potency of the product used (Table 3) (Kuhl 2011; Schindler et al. 2008; Stanczyk et al. 2013; Wiegratz and Kuhl 2006). Comparing the potencies of PG on the endometrium, the authors concluded that normethyltestosterone derivatives had the greatest potency, followed in order by MPA, dydrogesterone and micronized P (King and Whitehead 1986).

Several observational and randomized studies have looked at the frequency of endometrial hyperplasia in women treated by estrogens and PG. Sequential use is associated with a higher risk than continuous combined MHT. In the WHI study, continued use of CEE + MPA was associated with a risk of endometrial cancer similar to that of placebo (relative risk (RR): 0.81; 95% confidence interval

Table 03. Usual doses of progesterone and progestins administered orally in MHT theoretically protecting the endometrium (Kuhl 2011; Schindler et al. 2008; Stanczyk et al. 2013; Wiegratz and Kuhl 2006).

Progestogen	Sequential treatment (mg/day)	Continuous treatment (mg/day)
Micronized progesterone	200–300	100/200
Dydrogesterone	10 or 20	5–10
Medrogestone	10	5
Chlormadinone acetate	10	5
Medroxyprogestrone acetate	5–10	2.5
Cyproterone acetate	1	-
Promegestone	0.5	0.250
Nomegestrol acetate	5	2.5
Trimegestone	0.25–0.5	-
NET ou NETA	1	0.5

NET: norethisterone; NETA: norethisterone acetate.

(CI): 0.48–1.36); with a significant reduction in risk after a median cumulative follow-up of 13 years in their population where the prevalence of obesity was high (Manson et al. 2013). Interestingly, the Million Women Study (MWS) conducted in the UK highlighted a different risk in normal, overweight, and obese women using MHT. Whereas sequential therapy was associated with a higher risk in lean women compared to non-users, it was beneficial in obese women (RR: 0.76, 95% CI 0.49–0.91) (Beral, Bull, and Reeves 2005). This protective effect of MHT on the uterus of obese women was even more important with continuous combined treatment (RR 0.28; 95% CI 0.14–0.45) (see Table 3).

Observational cohort study, the European Prospective Investigators into Cancer and Nutrition (EPIC), involving 115,474 menopausal women gathered ten cohorts from different countries including France, followed for 9 years. They reported an increased risk of cancer of the endometrium in a group of women (from the E3N cohort) with oral micronized P (HR: 2.42; 95% CI 1.53–3.83), but not in women receiving synthetic PG or testosterone derivatives (Allen et al. 2010); this increase was based on only 26 cases of endometrial cancer. In this part of the study, the follow-up was 8 years and MHT was only reported at inclusion. The French cohort study E3N (Fournier, Berrino, and Clavel-Chapelon 2008) then published more detailed data and reported an over-risk with P and beyond 5 years of use also with dydrogesterone. In the E3N, information on the regimen of treatments (sequential or continuous) and on the dose of PG used is lacking. Additionally, most of the women used more than one type of MHT regimens: estradiol with micronized P or DYD or pregnane and nor-steroid derivative. Given the fact that there was no difference observed between estradiol-only treatment (HR 1.80, 95% CI 1.31–2.49) and estradiol + micronized P treatment (HR 1.80, 95% CI 1.38–2.34), this finding may be due to lack of compliance with micronized P and dydrogesterone in part of the population, since P does not exist in association with E2 (Lyytinen, Pukkala, and Ylikorkala 2009). Since these publications, it is recommended to use rather 100/200 mg/day of micronized P in continuous treatment and 200/300 mg/day in sequential treatment.

The first randomized trial to look at the effect of micronized P was The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. The endometrial histology obtained from 596 subjects (2418 endometrial biopsies) was predominantly atrophic or hypotrophic in women treated with micronized P 200 mg/day for 12 days/month (The Writing Group for the PEPI trial 1996).

Several other studies have not shown an incidence of higher hyperplasia with micronized P orally plus estradiol applied now by transdermal route. In a 6-month open study of 101 women who used percutaneous estradiol (1.5 mg/day) plus micronized P (100 mg/day), for 21/28 days or 25 days/calendar month (n = 98), or estradiol (3 mg/day) for 25 days associated with MP (300 mg/day), from day 16 to day 25 (n = 3), no hyperplasia was found by any pathologist (Gillet et al. 1994). Another study examined findings from 157 women who regularly used a combination of transdermal estradiol

(21–25 days per month) and micronized P (10–14 days per month). The use of micronized P, 200 mg/day, for 14 days/cycle after 7 days of estradiol was associated with the highest incidence of subatrophic endometrium and amenorrhea in more than 80% of the women compared to the use of 300 mg/day during 10 days of P. Neither endometrial hyperplasia nor carcinoma was observed. These findings are in line with a randomized French study (Jondet et al. 2002) where 336 early postmenopausal women used percutaneous estradiol (1.5 mg/day) for 24 days of 28-day cycles plus PG: chlormadinone acetate (10 mg once daily) or micronized P (200 mg once daily) taken orally from the 11th to the 24th day. Not a single case of endometrial hyperplasia was reported in either treatment group and a majority of the biopsies performed in women using P showed a hypotrophic endometrium.

The vaginal route may have advantages over oral. Whether vaginal micronized P use provides adequate protection of the endometrium was demonstrated on The Early versus Late Intervention Trial with Estradiol (ELITE). In this randomized trial, the authors compared 1 mg/day oral E2 or placebo with 45 mg/day of cyclical vaginal P gel (10 days/cycle); no significant difference for endometrial cancer was found between E2/P vs. placebo (Hodis et al. 2016).

Further, the REPLENISH study, a double-blind, placebo-controlled, multicenter trial, was the first, large, rigorous trial to demonstrate no endometrial hyperplasia with various doses of continuous oral E2 + P E2 doses (E2/P, respectively, at 1 mg and 100 mg, 0.5 mg and 100 mg, 0.5 mg and 50 mg, or 0.25 mg and 50 mg) for 12 months (Lobo et al. 2018).

Recently, a systematic review including 40 studies (Stute, Neulen, and Wildt 2016) detailed the literature available on P and endometrium in postmenopausal treatment. The international expert panel's stated that oral micronized P provides endometrial protection if applied sequentially from 12 to 14 days/month at 200 mg/day for up to 5 years; vaginal micronized P may provide endometrial protection if applied sequentially for 10 days/month at 4% (45 mg/day) or every other day at 100 mg/day for up to 3–5 years (off-label use) and finally, transdermal P does not provide endometrial protection. According to these results explained above, the vaginal route may offer a low dose, infrequent dosage and even lower systemic exposure than oral, but further studies are needed.

Hence, according to these series of publications, it was mandatory to use 10–14 days of PG when estrogen was concurrently used for at least 21 days per month or continuously to provide endometrial protection.

Recently, Gompel A (Gompel 2018) published that respecting simple rules the endometrium can be easily protected from the proliferative effects of estrogens:

(1) Adapt the dose of PG to dose/duration of estrogen treatment.
(2) Inform the woman of the importance of taking the PG pill.
(3) Check regularly woman's compliance on the PG.
(4) Adapt the dose to body mass index.
(5) Prefer continuous treatment rather than sequential.

PGS and cardiovascular function

Cardiovascular disease (CVD) is the leading cause of death among women around the world. The main risk factors for CVD in women include age, hypertension, dyslipidemia, diabetes mellitus (DM), family history of early CVD, smoking, sedentary lifestyle, obesity, and unhealthy nutrition. New risk factors for CVD include a history of pregnancy complicated by preeclampsia, gestational diabetes, or hypertension (Shifren and Gass 2014).

Some of the most widely prescribed PG have been shown to partially oppose the beneficial effects of estrogens on surrogate markers of cardiovascular disease (CVD) risk (Nath and Sitruk-Ware 2009). PGs with higher androgenic activity may interfere with lipid profile and glucose tolerance (The Writing Group for the PEPI trial 1996). P and its 17OH progesterone derivatives, if devoid of androgenic effects, have no negative impact on the beneficial effects of estrogens on the lipid profile (see above).

A randomized-controlled trial (RCT) showed that oral micronized P had fewer negative effects on high-density lipoprotein cholesterol (HDL-C) levels than MPA (The Writing Group for the PEPI trial 1996).

Additional studies comparing various hormone types and routes of administration have been published and demonstrated that P has a neutral effect on lipid metabolism. Clinical trial with 86 women receiving intranasal 17β estradiol- 3 mg/day or percutaneous 17β estradiol gel 1.5 mg/day plus 200 mg/day of micronized P by vaginal route 14 days/month (E2 + P) demonstrate the neutral or beneficial effects of combined MHT with micronized P. Glucose, insulin, high-density lipoprotein cholesterol (HDL-c), triglycerides, and the high-sensitivity C-reactive protein level remained constant after non-oral therapy with or without micronized P. Total cholesterol decreased after E2-only treatment, and the addition of P maintained this reduction (Casanova and Spritzer 2012). In a randomized, double-blind study, 20 postmenopausal women were tested before and after six weeks of treatment with micronized P (100 mg/d) and placebo. P given without estrogen has no effect on lipid levels (Honisett et al. 2003). A double-blind study of P (300 mg/day), placebo-controlled for 3 months, in 133 postmenopausal women, comparing P (n = 65) and placebo (n = 47) groups showed that the levels of total cholesterol (CT), low-density lipoproteins (LDL), triglycerides (TG) and high-density lipoproteins (HDL) were lower with P than with placebo (Prior et al. 2014). This study was the first randomized-controlled trial that assessed the short-term cardiovascular marker effects of oral micronized P treatment given alone (without estrogen) in healthy postmenopausal women. Retrospective studies from cohorts of postmenopausal women receiving E2 or E2 + P for 10 years showed that there were no significant differences between levels of TG, CT, HDL-C and LDL-C between both treatments (Prior et al. 2014).

While the route of estrogen administration is now well recognized as an important determinant of VTE risk, there is also increasing evidence that PGs may modulate the estrogen-related VTE risk. The Estrogen and Thromboembolism Risk study group (ESTHER), a case–control study conducted in France, showed, in addition to a significantly increased risk of VTE for oral E2 versus transdermal estrogen, that there was no significant association of VTE with micronized P and pregnanes, but a four-fold increased risk of VTE when norpregnanes, such as nomegestrol acetate, were used in combination with MHT (Canonico et al. 2007). The Study of Norpregnanes Coagulation (SNAC) was a cross-sectional study carried out in France between 2006 and 2007 in postmenopausal women aged 45 to 70 years who were treated with transdermal E2 combined with norpregnanes or micronized P. While micronized P does not affect hemostasis, norpregnanes can induce resistance to protein C (APC) and activate coagulation (Canonico et al. 2010).

Data on the impact of different pharmacological classes of PGs on the risk of stroke are sparse. A case–control study of ischemic stroke conducted between 2009 and 2011 in French women, aged 51 to 62 years without a personal history of CVD or contraindication to hormone therapy, showed that the risk of ischemic stroke differed according to the type of PG (see in Table 4) (Canonico et al. 2016). Although P, pregnane derivatives, and nortestosterone derivatives were not associated with ischemic stroke (OR: 0.78; 95% CI: 0.49–1.26; OR: 1.00; CI 95%: 0.60–1.66; OR: 1.26; 95% CI: 0.62–2.58,

Table 04. Odds Ratio of ischemic stroke in relation to MHT by route of estrogen and pharmacological classes of progestogens (Canonico et al. 2016).

Characteristics	Cases	Controls	OR adjusted*
Nonusers	2950 (93.8)	11 331 (93.2)	1 (référence)
Current users of oral estrogens	90 (2.9)	243 (2.0)	1.58 (1.01–2.49)
Current users of transdermal estrogens	104 (3.3)	584 (4.8)	0.83 (0.56–1.24)
No progestogens	42 (1.5)	177 (1.4)	NA
Current users of progesterone	60 (1.9)	380 (3.1)	0.78 (0.49–1.26)
Current users of pregnane derivatives	58 (1.8)	197 (1.6)	1.00 (0.60–1.66)
Current users of norpregnane derivatives**	17 (0.5)	27 (0.2)	2.25 (1.05–4.81)
Current users of nortestosterone derivatives	17 (0.5)	46 (0.4)	0.62–2.58)

CI indicates confidence intervals; HT, hormone therapy; NA, not applicable; and OR, and odds ratio.

*Adjusted for antidiabetic medication, antihypertensive medication, antidyslipidemia medication, and long-term, chronic disease.

** 85% of the subjects used nomegestrol acetate.

respectively), users of norpregnane derivatives had a higher risk (OR: 2.25; CI 95%: 1.05–4.81). In this group, 85% of subjects used nomegestrol acetate, and a restrictive analysis of this molecule led to similar results (OR: 2.85; 95% CI: 1.15–7.06). Although there was no significant association between ischemic stroke and the use of P, pregnane derivatives and nortestosterone derivatives, norpregnane derivatives were at higher risk (Canonico et al. 2016).

An important point of debate in the cardiovascular risk assessment after the publication of the WHI results relates to the window of opportunity to start MHT. MHT started in the first years after menopause does not increase the risk of CVD whereas started in women far from menopause, the risk of plaque coming off is increased. In this context, the early versus late intervention trial, with 17β -E2 1 mg/d oral, plus P in vaginal gel (45 mg) administered sequentially for women with a uterus, reduced the progression of the thickness of carotid intima media after a median of 5 years when MHT was initiated in the first 6 years after menopause, but not when it was initiated 10 years or more after (Hodis et al. 2016).

Recently, The American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE) Position Statement stated that micronized P is considered the safer alternative. Micronized P as compared with MPA may have better outcomes with respect to cardiovascular effects, blood pressure, VTE, probably stroke and breast cancer (Cobin and Goodman 2017). According to this position Statement, the most recent clinical guidelines recommend transdermal estrogens combined with P for symptomatic women requiring treatment, especially at high VTE risk (The NAMS 2017Hormone Therapy Position Statement Advisory panel 2017; Baber, Panay, and Fenton 2016; Stuenkel, Davis, and Gompel et al. 2015; Tremollieres et al. 2011).

PGs and central nervous system (CNS)

P has been classified as a neurosteroid and is synthesized from cholesterol in the brain, spinal cord, and peripheral nerves, and its actions can be mediated by the local metabolism of allopregnanolone (Stanczyk et al. 2013). Oral P has slight sedative effects, reducing wakefulness without affecting daytime cognitive functions, possibly through a GABA agonist effect (Schüssler et al. 2008). The P metabolite primarily active on GABA receptors is 3α-hydroxy-5α-pregnan-20-one (pregnanolone), which can be generated by glial cells in the CNS. Therefore, in summary, P has anxiolytic, hypnotic, and anticonvulsant properties. Other interactions between P and neurotransmitters include stimulation of dopamine release in the striatum, stimulation of release of gonadotropin-releasing hormone (GnRH) from hypothalamic neurons, inhibition of receptor binding, and activation opioids (Gruber and Huber 2003).

Clinical experience shows that the substitution of P in perimenopausal women can help promoting duration and quality of sleep. This effect appears to be most prominent for vaginal P and less pronounced with pregnanes, such as MPA, or oral gonanes (Gruber and Huber 2003). Some studies showed improvement in sleep parameters in MHT containing micronized P. In a small polysomnography study, micronized P at 200 mg/day, but not with cyclic 5 mg/day MPA significantly improved sleep efficiency, and decreased time spent awake after sleep onset from baseline (Montplaisir et al. 2001). Improved sleep parameters were also shown in The RESPLENISH Trial with different doses of estradiol plus micronized P (Kagan et al. 2017). Further, a randomized, double-blind, placebo-controlled study, investigate the effects of P administration on sleep architecture (subjects took daily a capsule of either 300 mg of P or placebo). P restored normal sleep when sleep was disturbed, acting as a "physiologic" regulator rather than as a hypnotic drug (Caufriez et al. 2011).

There is no epidemiological evidence of a protective effect of P on cognitive impairment, although preclinical studies suggest it. In the WHI memory study, greater brain atrophy was observed with CEE with or without MPA compared to the placebo group, although this is more apparent in women with cognitive abnormalities before initiating MHT (Resnick et al. 2009).

Finally, a cross-sectional study in 176 postmenopausal women formerly treated with estrogen plus MPA reported significant improvements in depression, anxiety, vasomotor symptoms, after they were substituted for estrogen plus micronized P during a period of one to 6 months (Prior 1990).

Bone effects

Estrogens are well known for preventing bone loss due to their physiological inhibitory effect on bone resorption linked to osteoclasts. Norethisterone acetate has been shown to prevent bone resorption in postmenopausal women without the addition of estrogen. High doses of MPA cause a partial reduction in bone resorption (The NAMS 2017Hormone Therapy Position Statement Advisory panel 2017; Stanczyk et al. 2013). Some have reported a beneficial effect of P and MPA on the bone (Prior 1990).

In a KEEPS sub-study (n = 76), oral CEE or transdermal E2 associated with cyclic oral micronized P for 4 years prevented the cortical volumetric bone mineral density (BMD) decline and cortical porosity increase at the distal radius seen with placebo (Farr et al. 2013). Other studies showed BMD improvements with similar regimens of MHT with micronized P (Prestwood et al. 2003; Riis et al. 1987).

Summary

Existing evidence from clinical studies on the use of micronized P in MHT, for the most part, shows favorable outcomes, without deleterious effects. Micronized P is able to prevent endometrial hyperplasia in combination with estrogens, does not increase the risk of VTE and stroke when used with transdermal estrogens. Micronized P does not seem to attenuate the cardiovascular benefits of estrogens and is likely safer than PGs. The breast cancer issue is of great concern, and according to observational studies, MHT regimens containing micronized P are associated with a significantly lower risk of breast cancer than those containing PGs.

Disclosure statement

No potential conflict of interest was reported by the authors.

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