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A comparison of the central effects of different progestins used in hormone replacement therapy

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Abstract

Objective: To evaluate the central effect exerted by different progestins used for hormone replacement therapy. *Methods:* Randomised, placebo-controlled study. One hundred-twenty postmenopausal women on continuous hormonal replacement therapy with transdermal estradiol (50 μg per day) associated, for 10 days every 28 days, with four different progestins: dydrogesterone (DYD; 10 mg per day; $n = 20$), medroxyprogesterone acetete (MPA; 10 mg per day; $n = 20$), nomegestrol acetate (NMG; 5 mg per day; $n = 20$) or norethisterone acetate (NETA; 10 mg per day; $n = 20$). Other 40 women, 10 for each treatment group, were used as controls and were monitored for a single cycle of 28 days during the administration of transdermal estradiol plus placebo. Morning basal body temperature (BBT) was monitored for 28 days. Anxiety, by the state-trait anxiety inventory, and depression, by the self-evaluation depression scale of Zung, were evaluated just prior to and in the last 2 days of the 10-day progestins adjunct. *Results:* All progestins except DYD increased ($P < 0.0001$) BBT by 0.3–0.5 °C. Anxiety was decreased by DYD ($-2.3 + 1.1$; $P < 0.01$) and MPA ($-1.5 + 0.5$; $P < 0.01$), but not by NMG or NETA. Depression did not significantly increase during progestins and actually decreased during MPA ($-3.0 + 0.7$; $P < 0.01$). Only the effect of DYD on anxiety and that of MPA on depression were significant versus the control group ($P < 0.05$). *Conclusions:* Different progestins exert different central effects. DYD has the peculiarity of not increasing BBT and of decreasing anxiety, which is also decreased by MPA. Depression is not negatively affected by the tested progestins and it may be ameliorated by MPA. The present data may help to individualise the progestin choice of hormone replacement therapy.

Keywords: Mood; Psychological symptoms; Anxiety; Depression; Menopause; Progestins; Body temperature

1. Introduction

Progestins are used in hormone replacement therapy to counteract estrogen-induced proliferation of the endometrium. Aside from their local action, progestins act at different body sites including the central nervous system (CSN). In the CNS progestins may influence different functions among which the

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regulation of body temperature [1–3] and mood [4–6]. While the effect on body temperature may have metabolic implications, the effect on mood, particularly if negative, can be invalidating and induce non-acceptance or withdrawal from hormone replacement therapy. Accordingly, definition of the impact of different progestins on mood is mandatory in order to personalize hormone prescription. A recurrence of symptoms during progestin administration was observed in women having suffered from premenstrual dysphoria [7], while conflicting results were obtained in the studies investigating the effect of progestins on normal postmenopausal women. However, in most of the studies mood disturbances were evaluated by arbitrary scores [3–5,8–12], and in others no distinction was shown among the different progestins [6,13,14]. Indeed, progestins derive from different molecules [15,16] and by differently interfering with steroid receptors they may exert different central effects [12]. Only few studies have compared the effect of one progestin to that of another [17–21]. In this study, we investigated the effects on body temperature, anxiety and depression of four different progestins all associated with the same estrogenic compound.

2. Materials and methods

One hundred and twenty women in postmenopause for at least 1 year, were recruited at the Menopause Centre of our Institute. Each woman furnished an informed consent to participate in the study, which had been previously approved by the local ethics committee and Institutional Review Board. Women with a BMI (kg/m^2) below 30, had been not taking hormone replacement therapy for at least 6 months. Randomly and in a double blind fashion each woman was assigned to receive the continuous administration of estradiol via a transdermal patch rated to deliver 50 μg per day of the compound (Dermestril 50; Rottapharm, Monza, Italy) associated for 10 days every 28 days with one of the following four different progestins: the progesterone derivative dydrogesterone at the dose of 10 mg per day (DYD; $n = 30$; Dufaston, Solvay Pharma SpA, Grugliasco, Torino, Italy); the 17-hydroxyderivative medroxyprogesterone acetate at the dose of 10 mg per day (MPA; $n = 30$) (Farlutal, Pharmacia & Upjohn, Milano, Italy); the 19-norprogesterone derivative nomegestrol acetate at the dose of 5 mg per day (NMG; $n = 30$; Theramex SpA, Milano, Italy); the 19-nortestosterone derivative, norethisterone acetate at the dose of 10 mg per day (NETA; $n = 30$; Primolut-nor, Schering SpA, Segrate, Milano, Italy). At the initial randomisation 10 women within each of the four treatment groups, were blindly assigned to receive in the evaluation cycle placebo instead of the active progestin, and were considered as the control group. Evaluations were performed between the 6th and 7th cycle of treatment. At entry, all patients were instructed that they may or may not experience a menstrual bleeding at the end of each cycle, but that this pattern may not be consistent.

Morning basal body temperature (BBT) was self-monitored by each woman, for 28 consecutive days, starting from the first day of progestin administration. BBT measured every morning at the same hour prior to getting up from the bed by a vaginal thermometer, was recorded on a chart. States of anxiety and depression were evaluated twice; i.e. just prior to the initiation (days 15–17 from the last progestin pill of the previous cycle) and in the last 2 days of the 10-day progestin adjunct (days 26–28 from the last progestin pill of the previous cycle). The order of the evaluation performed in the only estradiol phase and in the estradiol–progestin phase was randomised. Anxiety was evaluated by the form Y-1 of the State–Trait–Anxiety–Inventory (STAI) [22] and depression by the self-evaluating depression score of Zung (SDS) [23]. Both scales, administered as a validated Italian translation, have 20 items with four choices (score 1–4). Patients were requested to answer each question by themselves. Total scores of both scales range between 20 and 80, higher scores indicating a higher prevalence of symptoms. The two scales represent a sensitive index for the evaluation of depression and anxiety states.

At baseline and in the evaluation cycle, after 5 months of treatment, hot flushes were analysed in each woman in accordance to a vasomotor score. An arbitrary value was assigned to each flush on the basis of its intensity (1: slight; 2: moderate; 3: severe). The sum of these values for periods of 24 h, constituted the vasomotor score [24].

2.1. Statistical evaluation

Statistical analysis was performed with the statistical package StatView for Apple Macintosh (SAS Institute, Inc., 1998). By setting the difference higher than 1 standard deviation of the difference, eight subjects were sufficient for each group in order to detect a significant difference. Scores were blindly calculated by one of the authors. Scores observed during progestin administration were compared to those observed during estrogens by paired test. Net modifications induced by the different scores were compared with those observed in controls using one factor analysis of variance (ANOVA) followed by the post hoc test of Dunnett. BBT values recorded in the 28-day period were compared using two-factors ANOVA for repeated measures followed by the post hoc test of Dunnett, considering BBT registered immediately before progestin administration as the reference value. For each analysis, a *P*-value below 0.05 was chosen to reject the null hypothesis.

All the results are expressed as the mean ± standard error (S.E.).

3. Results

In the 5 months preceding the evaluation cycle we had eight drop-outs. Drop-outs were equally distributed among the four progestin groups: two in the DYD group, three in the MPA group, one in the NMG group and two in the NETA group. Six of them dropped-out for the occurrence of skin reactions to the patch and two of them were lost at the follow-up. Analyses were performed only on women undergoing the evaluation cycle. Accordingly analyses were performed in 19 women with DYD, 18 women with MPA, 19 women with NMG, 18 women with NETA and 38 women as controls. The vasomotor score of investigated women was 16.2 ± 2.3 at baseline. This was markedly reduced to 1.3 ± 1.2 ($P < 0.0001$) after 5 months of transdermal estradiol. No difference was observed depending on the progestin adjunct.

Characteristics of investigated subjects are reported in Table 1. No difference was observed among the four groups.

In the control group, BBT did not vary during the 28 days of evaluation (Table 2). Mean BBT values observed in the four groups of treatment are reported in Fig. 1. In the DYD group, BBT did not increase (−0.0003 ± 0.04 °C; P = ns) (Table 2; Fig. 2). In the MPA group, BBT increased from the estradiol only to the estradiol/MPA phase by 0.34 ± 0.04 °C ($P < 0.0001$) (Table 2; Fig. 2). In the NMG group, BBT increased from the estradiol only to the estradiol/NMG phase by 0.52 ± 0.06 °C ($P < 0.0001$) (Table 2; Fig. 2), and in the NETA group, BBT increased from the estradiol only to the estradiol/NETA phase by 0.43 ± 0.05 °C ($P < 0.0001$) (Table 2; Fig. 2). Net BBT increases induced by MPA, NETA and NMG were not significantly different among each other, but all three were significantly higher than the variation observed in the control group ($P < 0.0001$ by ANOVA) (Fig. 2). Time course of the BBT increase was different among the three tested progestins. The increase of BBT during MPA and NETA was present after 1 day while during NMG it was evident after 2 days of progestin administration (Fig. 1). Furthermore, BBT returned to baseline in 3 days after NETA withdrawal, while 10 and 14 days were necessary after MPA or NMG withdrawal (Fig. 1).

Anxiety did not significantly vary between the two evaluations performed in the control group (+0.3 ±

Table 1
Mean ± standard error (S.E.) characteristics of postmenopausal women studied during 28 days of treatment with transdermal estradiol alone or associated for 10 every 28 days with dydrogesterone (DYD; 10 mg per day), medroxyprogesterone acetate (MPA; 10 mg per day), nomegestrol acetate (NMG; 5 mg per day) or norethisterone acetate (NETA; 10 mg per day)

	Control ($n = 38$)	DYD ($n = 19$)	MPA ($n = 18$)	NMG ($n = 19$)	NETA ($n = 18$)
Age (year)	51.0 ± 1.3	50.8 ± 1.6	51.2 ± 1.5	51.1 ± 1.6	50.7 ± 1.5
Months of menopause	15.0 ± 2.5	14.0 ± 2.5	18.0 ± 2.9	17.1 ± 3.0	16.0 ± 2.3
BMI (kg/m^2)	25.5 ± 1.7	25.8 ± 2.1	26.9 ± 1.8	26.3 ± 1.7	25.6 ± 2.0
Months of HRT	–	5.8 ± 0.5	5.9 ± 0.8	5.0 ± 0.2	5.3 ± 0.5

Table 2
Mean ± standard error (S.E.) values of basal body temperature (BBT), score of anxiety, evaluated by STAI, and score of depression, evaluated by Zung, observed in postmenopausal women treated with transdermal estradiol alone (controls) or associated for 10 days every 28 days with dydrogesterone (DYD; 10 mg per day), medroxyprogesterone acetate (MPA; 10 mg per day); nomegestrol acetate (NMG; 5 mg per day) or norethisterone acetate (NETA; 10 mg per day)

	BBT		Anxiety		Depression	
	E	E/P	E	E/P	E	E/P
Controls ($n = 38$)	36.31 ± 0.05	36.33 ± 0.02	42.1 ± 1.4	42.7 ± 1.4	33.1 ± 1.5	34.1 ± 1.6
DYD ($n = 19$)	36.29 ± 0.02	36.29 ± 0.05	43.01 ± 1.3	40.6 ± 1.0*	34.5 ± 1.6	35.5 ± 1.9
MPA ($n = 18$)	36.22 ± 0.04	36.56 ± 0.04§	40.6 ± 0.99	39.1 ± 0.7§	35.0 ± 1.8	32.0 ± 1.4§
NMG ($n = 19$)	36.38 ± 0.07	36.90 ± 0.04§	39.0 ± 1.8	38.5 ± 1.9	31.0 ± 2.0	31.7 ± 2.4
NETA ($n = 18$)	36.53 ± 0.09	36.96 ± 0.09§	43.4 ± 1.6	43.2 ± 1.5	34.3 ± 2.3	34.7 ± 2.5

Evaluations were performed at the end of the estradiol (E) and estradiol/progestin (E/P) phase.
* $P < 0.05$.
§ $P < 0.01$ vs. E.

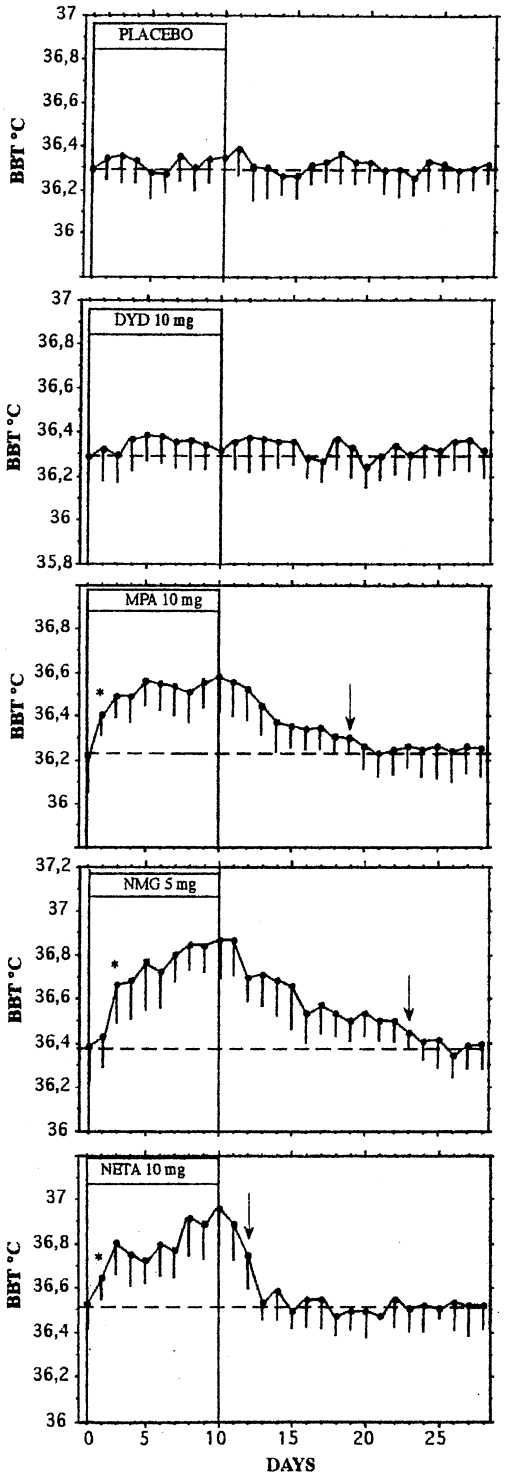
1.1; P = ns) (Table 2; Fig. 2). In comparison to the values observed in the estradiol only phase, anxiety decreased during the adjunct of DYD (-2.3 ± 1.1; $P < 0.05$) or MPA (-1.5 ± 0.5; $P < 0.01$), but not NMG (-0.5 ± 0.4; P = ns) or NETA (-0.22 ± 1.4; P = ns) (Table 2; Fig. 2). Only the decrease induced by DYD was significant compared with the variations observed in the control group ($P < 0.05$ by ANOVA) (Table 2; Fig. 2).

Depression did not vary between the two evaluations performed in the control group ($+1.02 \pm 0.98$; P = ns) (Table 2; Fig. 2). In comparison to the variations observed in the estradiol only phase, depression did not significantly vary during the adjunct of DYD ($+1.0 \pm 0.9$; P = ns), NMG ($+0.7 \pm 0.7$; P = ns) or NETA ($+0.4 \pm 2.5$; P = ns), while it significantly decreased during MPA (-3.0 ± 0.7; $P < 0.01$) (Table 2; Fig. 2). Only the decrease of depression induced by MPA was significant compared with the variation observed in the control group ($P < 0.05$ by ANOVA) (Fig. 2).

4. Discussion

Beside binding to progesterone receptors A and B, progestins may exert different effects by interfering with estrogen, androgen, glucocorticoids and mineralcorticoid receptors [25]. Accordingly, the final effect of each single molecule will emerge by the combination of these multiple activities. The present study indicates that different progestins exert different central effects. Among the four progestins herein tested, DYD appeared to have the most peculiar effects. DYD is a retrosteroid, derived from progesterone and metabolized in almost 20 metabolites, all maintaining the retrosteroid and the chetone structure [26]. These structural characteristics are likely responsible for the peculiar effect of this progestin in the control of body temperature. Indeed, among all progestins herein and previously tested [1–3,15], DYD is the only one that does not increase BBT. Whether this peculiarity of DYD furnishes any benefit to the woman is presently unknown. Modifications of BBT were induced by all the other three progestins. The effects were similar, but the time course of the BBT modifications appeared to be different, likely reflecting the different pharmacokinetic properties of the administered molecule [16]. In this respect, measurement of BBT may be useful to monitor and check the time of exposure to progestins with hyperthermic properties.

Anxiety and depression were evaluated at the end of the progestin phase, when the progestin exposure is maximal, and at the end of the only estradiol phase, in a situation of absolute progestin clearance, as also confirmed by BBT monitoring. The data show that DYD exerts clear anxyolitic effect. This confirms a previous study on DYD in which an arbitrary score of anxiety and depression was used [8], and is at variance with another study in which DYD administered in a dose twice as high as the present one, exerted neutral effect on anxiety evaluated with the same psychiatric scale [17]. The possibility that a reduction in dose brings a better effect on mood has already been



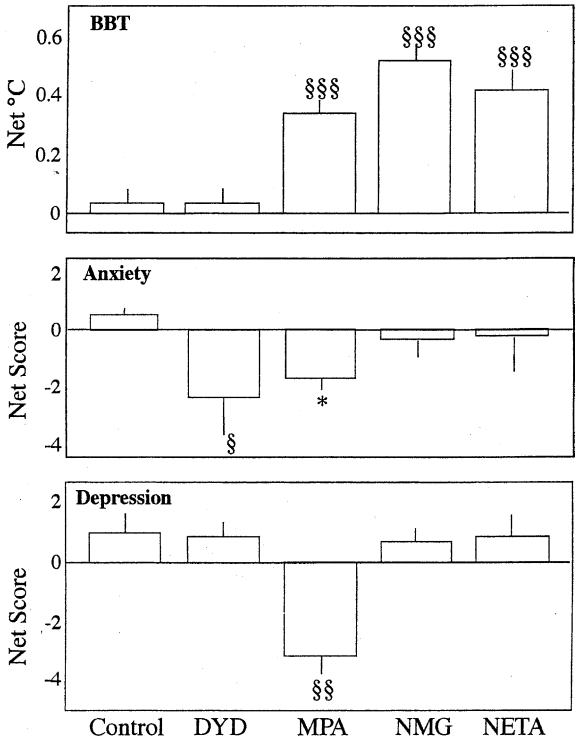


Fig. 2. Mean (±S.E.) net modification between the progestogenic and estrogenic phase, of basal body temperature (BBT; top panel), STAI score of anxiety (middle panel), and Zung score of depression (lower panel) evaluated in postmenopausal women receiving transdermal estradiol (50 μg per day) and sequential dydrogesterone (DYD; 10 mg per day; $n = 19$), medroxyprogesterone acetate (MPA; 10 mg per day; $n = 18$), nomegestrol acetate (NMG; 5 mg per day; $n = 19$), or norethisterone acetate (NETA; 10 mg per day; $n = 18$). $^{*}P < 0.01$ vs. the estrogenic phase; $^{\S}P < 0.05$ vs. the estrogenic phase and vs. controls; $^{\S\S}P < 0.01$ vs. the estrogenic phase and $P < 0.05$ vs. controls; $^{\S\S\S}P < 0.0001$ vs. the estrogenic phase and vs. controls.

Fig. 1. Mean (±S.E.) basal body temperature values, measured in postmenopausal women receiving transdermal estradiol (50 μg per day) and sequential administration of placebo (control), dydrogesterone (DYD; 10 mg per day; $n = 19$), medroxyprogesterone acetate (MPA; 10 mg per day; $n = 18$), nomegestrol acetate (NMG; 5 mg per day; $n = 19$), or norethisterone acetate (NETA; 10 mg per day; $n = 18$). Recordings started on the first day of progestin adjunct. Asterisks identify the first point significantly higher than BBT registered prior to progestin administration (reference value). Arrows identify the end of the significant BBT elevation in comparison to the reference value.

reported for MPA [27]. The anxyolitic effect of DYD resembles that described for progesterone, whose effect is likely mediated by the activation of GABAergic receptors [28,29]. Accordingly, the structural modifications of the progesterone molecule leading to DYD do not seem to impair the anxyolitic effect of the original molecule, although they impede the effect on BBT. Also MPA exerted anxyolitic effects, but they were less pronounced than those of DYD and not significant versus the control group. NETA and NMG, which are molecules less similar to the progesterone structure, failed to reduce anxiety.

An increase of depressive mood during progestin administration has been suggested by several studies with the use of arbitrary mood scores [4,5,20,27,30] or with different estro-progestinic compounds [13]. This data was not confirmed by studies with MPA [3,11,19,21,27] and DYD [8,17]. Single studies also failed to show depressive effect of NETA [17], cyproterone acetate [18] or norgestrel [18]. The results of the present study, confirm that progestins, at least those herein studied, do not induce depression, and indeed MPA may actually improve it. The reason for this different effect occurring from MPA is unknown, but needs to be replicated by other studies.

The central effects herein shown are likely not dependent on modifications of other parameter as hot flushes or vaginal bleeding. Indeed, after 5 months of therapy hot flushes were negligible, and during the 2 days in which anxiety and depression were evaluated, vaginal bleeding was not present in any of the investigated subject. Limitations of the present study are that the central effect of progestins was evaluated with only two scales that although validated for anxiety and depression, may give results different from those obtained with other scales. Physical symptoms as bloating or breast tenderness were not among the items investigated. Finally the dose of NETA (10 mg) was higher than that commonly used in combined estrogen–progestin formulations (1 or 2 mg). Accordingly, the present data can not be applied to the formulations with lower NETA, but the central neutral effect of NETA, even at the high doses herein tested, is rather reassuring.

In any case, the present data does not seem to support a negative effect from the four different progestins herein tested. Vice versa, few positive effects emerged. Further investigations are needed to elucidate the mood impact of different estrogens/progestin combinations in order to identify the most efficacious and tolerated molecules for hormone replacement therapy.

References

[1] Cagnacci A, Melis GB, Soldani R, Paoletti AM, Fioretti P. Effect of sex steroids on body temperature in postmenopausal women. Role of endogenous opioids. Life Sci 1992;50:515–21.
[2] Cagnacci A, Elliott JA, Yen SSC. Modification of circadian body temperature rhythm during the luteal menstrual phase: role of melatonin. J Appl Physiol 1996;80:25–9.
[3] Prior JC, Alojado N, McKay DW, Vigna YM. No adverse effects of medroxy-progesterone treatment without estrogen in postmenopausal women: double-blind, placebo-controlled, cross-over trial. Obstet Gynecol 1994;83:24–8.
[4] Pearlstein TB. Hormones and depression: what are the facts about premenstrual syndrome, menopause, and hormone replacement therapy? Am J Obstet Gynecol 1995;173:646–53.
[5] Sherwin BB. The impact of different doses of estrogen and progestin on mood and sexual behavior in postmenopausal women. J Clin Endocrinol Metab 1991;72:336–43.
[6] Zweifel JE, O'Brien WH. A meta-analysis of the effect of hormone replacement therapy upon depressed mood. Psychoneuroendocrinology 1997;22:189–212.
[7] Scmidt PJ, Nieman LK, Danaceau MA, Adams LF, Rubinow DR. Differential behavioral effects of gonadal steroids in women with and in those without premenstrual syndrome. N Engl J Med 1998;338:209–16.
[8] Siddle NC, Fraser D, Whitehead MI, Jesinger DK, Endacott J, Prescott P, et al. Endometrial, physical and psychological effects of postmenopausal oestrogen therapy with added dydrogesterone. Br J Obst Gynaecol 1990;97:1101–7.
[9] Hammarback S, Bacstrom T, Holst J, von Schoultz B, Lyrenas S. Cyclical mood changes as in the premenstrual syndrome during sequential estrogen–progestagen postmenopausal replacement therapy. Acta Obstet Gynecol Scand 1985;64:393–7.
[10] Magos AL, Brewster E, Singh R, O'Dowd T, Brincat M, Studd JWW. The effect of norethisterone in postmenopausal women on estrogen replacement therapy: a model for the premenstrual syndrome. Br J Obstet Gynaecol 1986;93:1290–6.
[11] Kirkham C, Hahn PM, Van Vugt DA, Carmichael JA, Reid RL. A randomized, double-blind, placebo-controlled, cross-over trial to assess the side effects of medroxyprogesterone acetate in hormone replacement therapy. Obstet Gynecol 1991;78:93–7.
[12] Greendale GA, Reboussin BA, Hogan P, et al. For the postmenopausal estrogen/progestin interventions trial investigators. Symptom relief and side effects of postmenopausal hormones: results from the postmenopausal estrogen/progestin intervention trial. Obstet Gynecol 1998;92:982–8.

[13] Natale V, Albertazzi P, Zini M, Di Micco R. Exploration of cyclical changes in memory and mood in postmenopausal women taking sequential combined oestrogen and progestogen preparations. BJOG 2001;108:286–90.
[14] Girdler SS, O'Briant C, Steege J, Grewen K, Light KC. A comparison of the effect of estrogen with or without progesterone on mood and physical symptoms in postmenopausal women. J Womens Health Gender Based Med 1999; 8:637–46.
[15] Editorial. Progestins: present and future. J Steroid Biochem Molec Biol 1996;59:357–63.
[16] Stanczyk FZ. Structure-function relationships, potency, and pharmacokinetics of progestogens. In: Lobo RA, editor. Treatment of the postmenopausal woman: basic and clinical aspects. New York: Raven Press; 1994. p. 69–89.
[17] Cagnacci A, Volpe A, Arangino S, Mamlmusi S, Draetta FP, Matteo ML, et al. Depression and anxiety in climacteric women: role of hormone replacement therapy. Menopause 1997;4:206–11.
[18] McCarthy T, Dramusic V, Carter R, Costales A, Ratnam SS. Randomized cross-over study of a 21-day versus 28-day hormone replacement therapy (HRT). Maturitas 1995;22:13–23.
[19] Saadat P, Boostanfar R, Poysky J, Munevar CM, Stanczyk FZ, Buckwalter G, et al. A randomized prospective study comparing the effects of micronized progesterone and medroxyprogesterone acetate on mood and libido. Fertil Steril 2002;77(Suppl 3):s21.
[20] Bjorn I, Bixio M, Nojd KS, Nyberg S, Backstrom T. Negative mood changes during hormone replacement therapy: a comparison between two progestogens. Am J Obstet Gynecol 2000;183:1419–26.
[21] Cummings JA, Brizendine L. Comparison of physical and emotional side effects of progesterone or medroxyprogesterone in early postmenopausal women. Menopause 2002;9: 253–63.
[22] Spielberg CD, Gorsuch RL, Lusehene RE, Manual for the state-trait anxiety inventory (self-evaluation questionnaire). Palo Alto, CA: Consulting Psychologists Press; 1970.
[23] Zung WWK. A self-rating depression scale. Arch Gen Psych 1965;12:63–70.
[24] Cagnacci A, Melis GB, Soldani R, Paoletti AM, Gambacciani M, Spinetti A, et al. Neuroendocrine and clinical effects of transdermal 17 β-estradiol in postmenopausal women. Maturitas 1991;13:283–96.
[25] Sitruk-Ware R. Progestogens in hormonal replacement therapy: new molecules, risks, and benefits. Menopause 2002; 9:6–15.
[26] van Amsterdam PH, Overmars H, Scherpenisse PM, de Bree H, Post LC. Dydrogesterone: metabolism in man. Eur J Drug Metab Pharmacok 1980;5:173–84.
[27] Bjorn I, Bixio M, Nojd KS, Collberg P, Nyberg S, Sundstrom-Poromaa I, et al. The impact of different doses of medroxyprogesterone acetate on mood symptoms in sequential hormonal therapy. Gynecol Endocrinol 2002;16:1–8.
[28] Smith SS. Hormones, mood and neurobiology. A summary. In: Berg G, Hammar M, editors. The modern management of the menopause. A perspective for the 21st century. London: Parthenon Publishing Group; 1994, p. 257–68.
[29] de Lignières B, Vincens M. Differential effects of exogenous estradiol and progesterone on mood in post-menopausal women: individual dose/effect relationship. Maturitas 1982;4: 67–72.
[30] Holst J, Backstrom T, Hammarback S. Progestogen addition during oestrogen replacement therapy. Effects on vasomotor symptoms and mood. Maturitas 1989;11:13–20.