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► To cite this version:

Marie-Laure Ancelin, Jacqueline Scali, Karen A. Ritchie. Hormonal therapy and depression: are we overlooking an important therapeutic alternative?: Hormonal therapy and depression. *Journal of Psychosomatic Research*, 2007, 62 (4), pp.473-85. 10.1016/j.jpsychores.2006.12.019 . inserm-00138466

HAL Id: inserm-00138466

<https://inserm.hal.science/inserm-00138466>

Submitted on 1 Oct 2007

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**HORMONAL THERAPY AND DEPRESSION: ARE WE OVERLOOKING AN
IMPORTANT THERAPEUTIC ALTERNATIVE?**

***Running Title:* Hormonal therapy and depression**

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ABSTRACT

Objective: To examine evidence for the role of hormonal changes in the onset and course of depressive symptomatology and assess the possible future role of hormonal therapies in the treatment of depression.

Methods: A Medline and PsychINFO search of the literature published between 1965 and 2006 was made of studies of depressive symptoms and hormonal treatment in women at all stages of reproductive life.

Results: The cyclic fluctuation of gonadal steroids at menarche coincides with the beginning of gender-based differences in depression rates which continue throughout reproductive life until menopause. Modifications in hormonal status, whether related to endogenous or exogenous exposure or to hormone deprivation, appear to be associated with affective disorder in a subgroup of women. For these women, a growing body of evidence indicates a biological pattern of vulnerability to mood disorders in response to hormonal fluctuations. This could have three major implications: that women vary in vulnerability to mood disorder when abrupt change in steroid levels occur, that these effects could be cumulative across the female lifespan, and that women do not arrive at menopause with equal risk of mood disorders, or equal susceptibility to the effects of hormonal replacement therapy as has been assumed by current clinical research and practice.

Conclusion: While hormonal therapies could have positive effects in the treatment and prevention of depressive disorders, further research is required to differentiate hormone-responsive subgroups of women for whom specific hormonal treatments may be most beneficial. To this end we suggest that a multifactorial model of cumulative vulnerability, which takes into account hormonal exposure throughout life, genetic vulnerability and environmental factors, may provide better prediction of treatment response.

Key words: Biological vulnerability; cumulated lifelong exposure to steroids; depression; estrogens; female reproductive cycle; hormone therapy.

Abbreviations:

CEE: conjugated equine estrogens

CES-D: Center for Epidemiologic Studies-Depression

DES: diethylstilbestrol

ET: estrogen therapy

GnRH: gonadotropin releasing hormone

HERS: heart and estrogen/progestin replacement study

HT: hormone therapy

MPA: medroxyprogesterone acetate

MRD: menstrually related disorders

OC: oral contraceptive

PMDD: premenstrual dysphoric disorder

PMS: premenstrual syndrome

PPD: postpartum depression

RCT: randomized controlled trial

SSRI: selective serotonin reuptake inhibitor

SERM: selective estrogen receptor modulator

WHI: women's health initiative

INTRODUCTION

Numerous epidemiological studies have reported that mood disorders are more common in women [1-4]. While gender differences may in part be attributed to factors such as willingness to declare symptoms, hormonal factors are nonetheless believed to play an important role throughout life in relation to mental health. Given that estrogen receptors (ERs) are extensively present in the brain, and that estrogens appear to exert protective effects on neurotransmitter systems (see Refs. [5,6] for reviews), the question currently being raised is whether hormonal therapy (HT) may play a role in the management of psychiatric disorder. Studies of HT have focused principally on the reduction of menopausal symptoms and cognitive dysfunction, and little attention has been paid to psychiatric disorder although improvement in depressive symptomatology is one of the clinical reasons given by many women for maintaining HT. We examine current research on the impact of hormonal functioning on mental health throughout the life cycle, including endogenous endocrine fluctuations (*e.g.* menstrual cycle, pregnancy, peri-menopause), hormone deprivation (by castration or anti-hormone treatment), and exogenous endocrine exposure (*e.g.* oral contraceptives (OCs) or HT) with a view to examining the potential value of hormonal treatment of mood disorders in women.

EFFECTS OF ENDOGENOUS ENDOCRINE FLUCTUATION

Reproductive-cycle-related mood disorders share some common symptoms, whether they be observed before menstruation (menstrually related disorders MRDs), after childbirth (postpartum depression PPD; postpartum psychosis) or during the perimenopausal transition (see Refs. [7,8] for recent reviews). These disorders include mood instability, changes in sleep and appetite, fatigue, irritability, anxiety, and concentration difficulties. Symptoms specific to a given reproductive phase are also reported, for example, somatic symptoms (breast tenderness, bloating, headaches), food cravings, anger associated with MRD, profound social isolation and obsessive ruminations with PPD, and tearfulness occurring with MRD and perimenopausal depression, the latter being also associated with excessive worry or somatic complaints, such as vasomotor symptoms [7-10]. With regard to MRD, several terms have been used not only as a function of the severity but also as part

of *DSM* classification. Premenstrual syndrome (PMS) was first described. In 1987, the *DSM-III-R* included criteria for late luteal phase dysphoric disorder (LLPDD), which was changed to premenstrual dysphoric disorder (PMDD) in *DSM-IV* (with an additional item compared to LLPD), but PMDD was described as an example of depressive disorder that was not otherwise specified. PMDD was considered as a distinct clinical entity in 1999. PMDD may be distinguished from PMS by symptom severity, predominance of mood symptoms, and dysfunction in interpersonal relationships [11]. Throughout the article we will now refer to MRD as recently suggested [12].

Menstruation

The menarche heralds the beginning of gender-based differences in depression rates which continue throughout reproductive life, decreasing only after the menopause [2,13]. MRD are frequent, occurring in approximately 80% of women, with 3-9% in the most severe form, PMDD. They are characterized by recurrent physical and emotional symptoms that generally occur during the late luteal phase of the menstrual cycle (when ovarian hormone levels decrease progressively to the minimal levels observed at the onset of the menarche) and remit within a few days after menstruation (see Ref. [14] for review). During the premenstrual and menstrual phases women are observed to be at increased risk for both onset of a new depressive episode and worsening of existing depressive symptoms [15-17]. Women already receiving anti-depressant therapy are also commonly observed to have a recurrence of symptoms during this phase of the cycle [18,19].

Neither progesterone blockade nor the truncation of the luteal phase (by mifepristone) appears to alter symptoms in women with MRD, suggesting that they are triggered by hormonal changes before the late luteal phase, especially in women with a history of depression [20]. This is also consistent with reports that the suppression of ovulation could result in the prevention of cyclic mood disturbance and the remission of MRD. It is also interesting to note that some of the women taking mifepristone did not have MRD when the menstrual cycle started again, indicating the existence of distinct subgroups of treatment vulnerability.

Gonadotropin-releasing hormone (GnRH) agonists (leuprolide) used to suppress ovarian function in gynecological disorders, have been found to produce hypo-estrogenic side effects, for example vasomotor instability and vaginal dryness [21]; however, findings relating to mood response are inconsistent, with some women reporting the onset of major depression, and some women with pre-existing MRD experiencing remission of symptoms [21-24]. Schmidt et al. [25] further observed that adding estradiol or progesterone to leuprolide, led to a recurrence of symptoms or an increase in depressive symptomatology in women with MRD compared to controls. This suggests that there is a selective sensitivity of women with menstrual cycle-related mood disorders (compared to controls) to the effects of gonadal steroids, and that in women with MRD the occurrence of affective disorder could represent an abnormal response to normal hormonal fluctuations.

Reduction in progesterone metabolites, especially 3α -pregnane neuroactive steroids has recently been associated specifically with mood disorder (see Refs. [26,27] for reviews). Both, 3α , 5α -THP (allopregnanolone) and 3α , 5β -THP were found to be decreased in patients suffering from major depression, whereas an increase was observed in 3β , 5α -THP which may act as a functional antagonist for these GABA-agonistic steroids. Levels could be normalized by successful treatment with antidepressants. Regarding MRD, lower luteal phase allopregnanolone levels has been associated with increased symptom severity [28,29], and an increase in allopregnanolone and 5α -dihydroprogesterone (5α -DHP) has been associated with improved symptom ratings in patients with MRD [30]. Bicikova et al. have also reported low concentrations of allopregnanolone in patients with MRD but in the follicular phase only [31]. On the other hand, other studies have reported no variation of allopregnanolone in the luteal phase of patients with MRD [30,32], or even greater luteal phase allopregnanolone [33] and decreased allopregnanolone following treatment and improvement in symptomatology [34]. Several methodological differences may underlie these inconsistent findings, for example, failure to employ strict *DSM* diagnostic criteria [32] and to assess prior psychiatric disorders in MRD and control subjects [30,32], duration of MRD, absence of cycle phase evaluation or differences in blood sampling procedures and assay sensitivity [33], as well as difference in pharmacokinetic properties (see below). Another recent small study does not

support the hypothesis that neurosteroid suppression (consecutive to low-dose OC administration) could engender mood effects, at least in psychologically healthy women [35]. One possibility is that altered neurosteroids provoke adverse mood symptoms only in women predisposed to affective disorders. There is currently no conclusive evidence to suggest that the normalization of neuroactive steroid levels is essential for the clinical response, or that a lack of effect on neuroactive steroid concentrations (as observed after non-pharmacological treatment) precludes antidepressant efficacy (see Ref. [36] for recent review). Clearly additional studies are needed to ascertain the clinical significance of reduced progesterone metabolites.

Hence, despite the evidence for a role of the gonadal hormones in the pathophysiology of MRD, it is generally agreed that neither a deficiency nor an excess in estradiol, progesterone or its reduced metabolites is etiologically relevant to these disorders. On the other hand, there is some indication that some women may be more sensitive to the mood modulatory effects of gonadal hormones and their neuroactive metabolites, and that this metabolism could be altered in MRD.

Pregnancy

Serum levels of estrogens (estrone, estradiol and estriol) as well as progesterone and most of its reduced metabolites [37,38] increase rapidly during pregnancy, although smoking may lower estriol levels by 20% or more. After parturition, levels of all steroids drop sharply, especially progesterone and its reduced metabolite, 5 α DHP, as well as estrogen whose levels decrease dramatically while maintaining a level sufficient for prolactin secretion for two days. During lactation, estradiol levels decrease to postmenopausal levels (see Ref. [39] for review). With regard to associated mood changes, longitudinal studies suggest a high risk of depression (14-18%) between 32-weeks of pregnancy and 13 weeks postpartum [40-42]) (**Table 1**). Pregnancy rather than childbirth appears to be the factor that triggers depression in nondepressed women, with childbirth appearing more likely to be followed by improvement in depressed women [42]. As for MRD, the role of progesterone reduced metabolites has been investigated in depression related to pregnancy and postpartum. A tendency for increased concentrations of 5 α DHP, and progesterone, has been reported in women

with depression during the latter half of pregnancy, and in women with depressive symptomatology at 3 days postpartum compared with nondepressed women [37,38], as well as low levels of 3α , 5α -THP [45] although not systematically [38].

Hence, peak depression rates are reported during the last 3-6 weeks of pregnancy, when steroid levels are high, and in the early postpartum period, when steroid levels are low. The lowest rates are observed at the beginning of pregnancy or in the late postpartum period when levels are stabilized [41,42]. Rate of change in hormonal levels rather than absolute values may in fact be the key determinant as well as other factors linked to hormonal variability such as breastfeeding. It is interesting to note that while breastfeeding has been linked to the onset of major depression [40], bottle-feeding has been associated with depressive symptoms and major depression [17,46-48]. Although little is known from these follow-up studies about previous treatment, it would appear that women with recurrent major depression appear to be at especially high risk for relapse during pregnancy, especially those who discontinue antidepressant medication around the time of conception, with relapse rates of up to 75% [49,50].

A small double-blind trial [51] involving 16 euthymic women (with and without a history of PPD) treated with a GnRH agonist, followed by transient addition of estradiol and progesterone, concluded that estrogen and progesterone may be involved in the development of PPD in a subgroup of women (women with a history of PPD have a differential vulnerability to gonadal steroids compared to women without a history of PPD).

Menopause

Variability in study designs, sample subjects, definitions of menopausal status, and absence of standardized assessment of psychiatric symptoms has led to some inconsistent findings regarding the association between the menopausal transition and concomitant vulnerability to depressive symptoms. However, the most recent longitudinal, community-based studies suggest perimenopausal transition rather than menopause itself to be the point of increased vulnerability for depressive episodes [52-57] even in the absence of a history of depression [58,59] or in

asymptomatic women [59]. Vasomotor symptoms (directly attributable to menopausal estrogen withdrawal) have been observed to increase the risk of depressive symptoms in perimenopausal women but not in pre- or postmenopausal women in primary care [60] and also in a population sample, but they were not shown to be independently associated with diagnosed depressive disorder in population [57,58]. In addition, the observation that estrogen therapy (ET) may improve depressive symptoms even in women without menopausal symptoms [61-63] also suggests that perimenopausal vulnerability to depression may be independent of vasomotor symptoms.

Lifetime history of depression has been associated with early perimenopause [54,64] and women undergoing natural menopause before age 47 are two to three times more likely to have been treated for depression. Recent findings also suggest a relationship between episodic alterations in ovarian function and depressive symptomatology in some perimenopausal women, with improvements in ovarian function being associated with remission of depressive symptoms [65]. The question, however, remains as to whether depression is the result of lifelong low exposure to steroid hormones due to early decline in ovarian function or if depression permanently alters hypothalamic-pituitary-gonadal axis regulation to stressful events [65].

Reports of depression following surgical menopause are inconsistent, possibly due to the difference in delay between surgery and the psychiatric examination [66]) or the type of surgery, with bilateral oophorectomy causing rapid depletion of estrogens and androgens to lower than natural menopause levels [67]. In a recent prospective study focusing on the menopause transition (with a 11-year follow-up), a higher depressive symptomatology has been reported for women who have undergone surgical menopause (after hysterectomy and/ or oophorectomy) [55]. In oophorectomized women the risk of depression may be higher compared with women who underwent natural menopause, with depression onset occurring rapidly after the ovariectomy [68,69]. Maintaining the ovaries of premenopausal women who have had a hysterectomy may protect against subsequent mood disorder [68,70] although hysterectomy may also cause premature ovarian failure. Being the result of prolonged heavy periods, chronic pelvic pain, and severe MRD, depressed mood is, however,

also observed in women before hysterectomy [71-74]. Hysterectomy may thus improve mood, except for women with preexisting psychiatric illness or predisposing personality problems, in whom depressed mood may persist or re-occur in response to the stress associated with surgery [72,74]. Finally, thirty eight percent of women experiencing induced menopause due to treatment of breast cancer have been observed to develop major depression and 95% dysphoria within the first 6 months of treatment [75].

IMPACT OF EXOGENOUS ENDOCRINE EXPOSURE

Oral contraceptives

A recent review concluded that OC users experience less variability in mood across the menstrual cycle, and fewer depressive symptoms during menstruation [76]. A minority of women do, however, experience negative mood changes. Potential mediators of the relation between OCs and mood are age, preexisting psychiatric disorder, history of depression or hormonal-related symptoms (related to premenstrual phase, dysmenorrhoea, pregnancy, or postpartum), and OC type (dosage and content). A lower ratio of progesterone to estrogen is associated with more negative mood change in women with a history of MRD, and a higher ratio is associated with increased negative mood in women without such a history, suggesting a distinct biological vulnerability for women with a history of MRD. Major depression and anxiety disorder have been observed in women with no prior psychiatric history 1-3 months after Norplant insertion (a long-acting subdermal implant with progesterone-like effects). Symptoms were found to worsen over time but disappeared 1-2 months after Norplant removal [77].

In a nested case-control study within a community-based cohort of 976 premenopausal women [78], 16.3% of OC users reported premenstrual mood deterioration, while 12.3% reported improvement. An adjusted regression model found previous depression to be the only significant predictor of OC-related mood deterioration while early-onset premenstrual mood disturbance and dysmenorrhea were observed to be significant predictors of OC-related mood improvement. Using estradiol, progestins or OC may thus be therapeutic for patients with MRD [79,80]. Treatment may, however,

be less effective for women suffering from severe MRD, for whom selective serotonin reuptake inhibitors (SSRIs) may be preferable [81]. Randomized controlled trials (RCTs) are clearly needed in this area, especially for the more recent OCs.

Post-partum HT

The use of HT as a modulator of PPD has been reported in the register of clinical trials maintained and updated by the Cochrane Pregnancy and Childbirth Group [82]. Synthetic progestogens given within 48 hours of delivery and over 8-12 weeks are associated with significantly higher depressive symptomatology than placebo, whereas ET in severely depressed women led to improvement. A positive and rapid (2-13 weeks) effect for ET has also been reported for severe PPD and postpartum psychosis [83,84]. Improvement is generally rapid, with one RCT of 61 women with PPD reporting statistically and clinically significant reductions in depressive symptoms after 1 and 3 months of HRT consisting of 17 β -estradiol with added dydrogesterones (for 12 days each month) [83]. The treatment response was sustained over the next 5 months. However, half of the women were also taking antidepressants; hence, it remains uncertain as to whether estrogen should be used as monotherapy or as an ancillary therapy. A more recent study evaluated 23 women with a major depressive disorder with postpartum onset. Depressive symptoms diminished rapidly with oral 17 β -estradiol, and after 2 weeks depression scores indicated clinical recovery in 83% of patients [84]. As for MRD and perimenopausal depression, the positive effects on puerperal depression are mostly reported with transdermal estradiol [85].

Menopausal HT

A large number of studies have shown a significant amelioration of mood in perimenopausal and postmenopausal women treated with HT, although not systematically. The discrepancies probably result from differences in HT use [86]; cohorts [87,88]; methods used to determine menopausal and hormonal status [89]; clinical features of the menopause that is, whether symptomatic [90,91], natural or following oophorectomy [92]; and criteria for the target psychiatric disorders [93,94].

Interstudy variability is further amplified by differences in sample size, methods of statistical analysis, and variable reliability of retrospective reporting of symptoms (e.g. recall bias, healthy user bias, compliance bias, expectancy effects, and influence of previous psychiatric disorder) [88].

Despite methodological limitations and contradictory reports regarding the beneficial effect of HT on depression, a meta-analysis of 38 RCTs or cohort studies found that the overall effect size (ES) for HT was 0.68 [87] indicating that even if interstudy differences and potential confounders were considered, that HT lowered the rate of depressed mood by 76%. Estrogen [mostly oral conjugated equine estrogen [CEE]) was found to have a moderate to large effect in reduction of depressed mood (ES=0.69), while progesterone alone, or combined with estrogen, was associated with smaller reductions (ES=0.39 and 0.45, respectively). Androgen alone, or combined with estrogen was associated with the greatest reduction in depressed mood (ES=1.37 and 0.90, respectively). ES was greater in perimenopausal than in postmenopausal women (1.81 vs. 0.9) and in natural compared to surgical menopause (1.52 vs. 0.77). Treatment longer than 8 months was associated with the greatest improvement. Although most of the studies included in this meta-analysis used depression measures with documented reliability and validity, few reported subjects with significant levels of depression. The true effectiveness of HT for patients with significant levels of depression may thus have been underestimated.

Two recent large RCTs investigating the long-term effect of HT on mood in postmenopausal women, the Heart and Estrogen/progestin Replacement Study (HERS) and the Women's Health Initiative (WHI) study. They evaluated the effect of a 36-month-treatment with CEE+ medroxyprogesterone acetate (MPA, which is probably not the most efficient in terms of neuroprotection) in older post-menopausal women (who are probably not the most sensitive targets). In both studies, quality of life or "psychiatric distress" (rather than depressive symptoms) was assessed using the Burnam screen [95]. In HERS, HT had mixed effects among 2763 postmenopausal women depending on the presence of menopausal symptoms. Women without flushes had greater declines in physical measures, while women with flushes improved in quality-

of-life items relating to mood [90]. Flushes are more common in thin women, and after menopause peripheral aromatization of androgens in adipose tissue is the primary source of endogenous estrogen. This could thus reflect a threshold in the level of biologically significant doses of estrogens beyond which additional exogenous estrogens would have negligible effects on measures of mood. In the WHI study, HT did not improve “psychiatric distress” in 16,608 postmenopausal women, most of them did not have menopausal symptoms [96]. The Burnam screen has, however, serious short-comings and is inadequate for this type of study; subjects frequently complained that the items were confusing, and the scale as a whole has very poor sensitivity and positive predictive value for major depression, dysthymia and mood disorder [97].

Most recent robust RCTs in women with clinically diagnosed depression report a positive effect of ET (**Table 2**). A full or partial therapeutic response was mostly seen in women with perimenopause-related major or minor depression or dysthymia, who receive transdermal estradiol [61]. Complete remission of symptoms persisted after a 4-week washout period, although somatic complaints increased in frequency and intensity [62]. Evidence for an ET antidepressant response has, however, been found to be weaker in postmenopausal compared to perimenopausal women [63,98]. It is still unclear, however, as to whether postmenopausal women require higher doses and/or prolonged treatment to obtain a satisfactory antidepressant effect. They could also be unresponsive to the mood-enhancing effects of estradiol, suggesting the existence of a critical window of estrogen susceptibility in the perimenopausal period during which HT could have maximal antidepressant and neuroprotective effects [99,100].

It should be noted that effects vary according to the estrogen derivative used (CEE being less effective than 17- β -estradiol) and the administration mode, as oral (but not transdermal) drugs are metabolized by the liver, reducing brain concentrations. Addition of androgens allows the reduction of the dose of estrogen needed to control vasomotor symptoms or enhance mood improvement, whereas synthetic progestins (especially MPA) could be antagonistic to estrogen and mitigate its mood-enhancing effect [101,102]. Sequential HT may produce periodic increases in depressive and

anxiety symptoms (which has been related to the progesterone metabolite allopregnanolone [103]), and this may improve with continuous combined HT therapy. A negative effect on mood was reported in nondepressed postmenopausal women treated with cyclic progestagens in combination with estrogen, whereas no significant change or an improvement in mood was observed with estrogen alone [104-106]. This is also compatible with a recent large cross-sectional study of 6602 postmenopausal women in whom a decreased risk of depressive symptoms was reported in current estrogen users but not in combined estrogen plus progestin users [107].

Anti-hormone treatment and depressive symptomatology

Many estrogen-related diseases are treated with antiestrogenic drugs. Selective Estrogen Receptor Modulators (SERMs), such as tamoxifen, are synthetic, non-hormonal compounds acting as estrogen agonists on some tissues and antagonists on others. They are widely used as an adjuvant therapy for breast cancer. In a prospective clinical trial of 257 women with breast cancer, 15% of the women treated with tamoxifen had symptoms of depression compared to 3% in controls in the 6-12 months following treatment [108]. In a more recent multicenter study of 11,064 women treated for 5 years, no difference was found between tamoxifen and placebo groups with regard to depression and overall quality of life. However, tamoxifen subjects showed consistent increases in vasomotor and gynecological symptoms [109]. Hence, depressed symptoms appear to be related to short-term use, whereas long-term use is associated only with vasomotor symptoms. An RCT with another SERM, raloxifene, found lowered anxiety levels but no effect on quality of life or depressed mood in asymptomatic, post-menopausal women [110-112].

The xeno-estrogen, diethylstilbestrol (DES) which has been used in the treatment of breast and prostate cancer, frequently causes irritability and more rarely, depression. Although not well substantiated, there is some evidence to suggest that DES may modulate late-life vulnerability to depression. In a large RCT including 530 adult men and women exposed to DES in utero, an increased vulnerability (by twofold) was reported by general practitioners (unaware of DES status)

for depression, anxiety and eating disorders independently of genital anomalies and somatic complications of DES exposure [113]. An increased prevalence of major depression was also observed in 50 DES-exposed women compared to 50 unexposed sisters, although in a comparison with 43 women experiencing other gynecologic problems, the excess of risk of depression could not be attributed specifically to DES [114]. A smaller study also found a higher non-significant prevalence in major depressive disorder and a significant increase in recurrence of depressive episodes in 27 DES-exposed compared to nonexposed brothers (44 vs. 26%) [115]. On the other hand, no association was found with regard to self-reported mental illness in a study of 5686 women of whom 69% were exposed to DES [116]. Overall there is currently insufficient evidence to permit the drawing of any conclusions in relation to the effects of DES exposure.

ENDOCRINE FLUCTUATIONS AND DEPRESSION: A CONTINUUM MODEL

Is there a common pattern of vulnerability regarding reproductive cycle-associated depressive symptoms?

Past history of depression is a strong predictor of subsequent depressive episodes (see Ref. [117] for meta-analysis). However, it is still uncertain as to whether hormone-related depression predicts subsequent hormone-related depression thus suggesting the existence of a continuum of hormonal vulnerability for reproductive-cycle-associated depressive symptoms. Small sample size, the limits of retrospective evaluation of MRD, the absence of measures of perimenopausal hormonal ovarian function and standardized diagnosis of depression, undoubtedly contribute to the observed inconsistency in results reported so far.

Numerous studies have shown that women who suffer from affective disorders following one reproductive event may be more vulnerable to relapse associated with others. Increased risk for postpartum depressive symptoms has been associated with MRD [118-122], psychiatric symptoms during pregnancy [121-125] or prior PPD [118,121,122,126,127], or, more rarely, mood instability at puberty [128,129] or secondary to OCs [121]. Women who report a high level of depressive symptomatology during menopause are also more likely to report past depression associated with

MRD, OC-related dysphoria, postnatal blues, and PPD, than those who did not report current psychiatric distress [55,56,130-132].

Nevertheless, although frequent, the presence of one episode of mood disorder related to reproductive endocrine functioning does not predict the uniform occurrence of depression during a subsequent period of hormonal change. Recent studies notably indicate that a high percentage of women experience their first depressive episode during perimenopause [57-59,133]. Richards et al. [133] also suggested that neither MRD cyclicality nor premenstrual dysphoria at the perimenopause was an invariant accompaniment of perimenopausal depression. However, they also reported a higher-than-expected rate of MRD cyclicality and premenstrual dysphoria in perimenopausal depressed women (26% of women experienced both conditions).

The fact that only some women who suffer from mood disorders in one phase of the reproductive cycle are also more likely to have a recurrence of symptoms in subsequent phases is suggestive of a specific inherent individual biological vulnerability. This also suggests that such vulnerability may constitute a stable trait [12,40,130,132], which may be expressed as symptoms in response to different triggers (biological or environmental). Individual variation in biological vulnerability and an intrinsic abnormal reaction to normal changes in reproductive hormones could, thus, contribute to a range of psychiatric symptoms in some subgroups of women even in the context of normal ovarian function [129,134].

If changes in gonadal steroid levels trigger hormone-associated depressive symptoms, why does this not occur in all women at every phase of change?

All women who have antecedents of hormone-sensitive depression have not systematically experienced depression at other periods of hormonal change. What is the underlying cause of this phenotypic response to a given biological stimulus? Although the context dependency of steroid action has been established, a further source of differences in response phenotype may also be attributed to genotype. Known polymorphisms in gonadal steroid receptors have been shown to alter receptor transcriptional efficiency but also to be associated with different hormone-related

pathologies, such as breast cancer, cardiovascular pathologies and osteoporotic fractures. This association has not, however, been fully explored in relation to mood disorders. At the present time, the role of ER polymorphisms in depression has only been investigated in two case control studies. A significant association was observed between depression and two distinct single-nucleotide polymorphisms of ER α in women with major depression but not in men [135,136]. ER polymorphisms may also be involved in HT response, a possibility which has not yet been evaluated. The importance of family or genetic factors in the etiology of MRD or postpartum mood disorders has already been suggested [137,138]. Recently, Rubinow and Schmidt [139] have also shown that a region of the ER α gene containing multiple polymorphic alleles was associated with MRD, thus supporting the hypothesis that the effects of multiple genes may interact in creating a dysphoric behavioral response to normal gonadal steroid levels.

Genetic polymorphism variability, interacting with lifetime hormonal exposure (see below) may determine systemic reactions to multiple environmental stressors and, hence, enhance or inhibit the onset of mood disorders. Within a multifactorial aetiological model, hormone-associated mood disorders may thus be construed as a clinical endpoint triggered by reproductive endocrine stimuli in persons susceptible to behavioral state changes due to the interaction of biological conditions, antecedent experimental events, vulnerability to depression (e.g. serotonergic dysregulation), and genetic as well as other environmental factors. Complex multi-factorial analyses incorporating detailed reproductive histories, the long-term effects of natural steroids, genetic vulnerability, and longitudinal observations of depressive symptomatology, are currently needed in order to adequately explore this hypothesis.

Is it possible to identify women at risk of hormone-related depression?

Direct observation of circulating hormonal levels is not likely to be an useful biological marker for a number of reasons. In animals, ovarian steroids have higher concentrations in brain than plasma,

and the turnover rate of brain sequestration of blood-borne sex steroids is also high [140]. Serum levels are not very informative with regard to the etiology of disorders associated with decline in circulating estrogen levels due to the difference in estrogen, progesterone and testosterone kinetic diffusion rates across the blood brain barrier; the possibility of distinct affinity binding and steroid receptor content in the brain; the presence of localized brain neurosteroids and localized metabolism via aromatase [141,142]. The rate of change of hormonal levels rather than the absolute value might be more relevant to psychiatric outcome as suggested by the prevalence of depression during pregnancy, postpartum and following surgical menopause. More clinically relevant measures of endogenous steroid effects at the level of specific tissues are needed. Studies of other hormone-dependent pathologies such as osteoporosis and breast cancer, have already identified clinical markers that reflect increased lifelong estrogen exposure for example, earlier age at menarche, nulliparity, late menopause, climacteric obesity, and exogenous endocrine exposure.

Fluctuations in estrogen levels linked to these specific markers have been associated with the risk of developing hormone-dependent pathologies leading to the now widely-used concepts of ‘cumulative hormonal exposure’ and ‘hormonal windows’. For example, studies of the impact of reproductive factors on the etiology of hormone-sensitive breast cancer have increasingly relied on mathematical models that combine multiple markers into a single equation; these combined indices providing greater predictive power than individual markers [143,144]. This methodology has produced what is now a well-established model incorporating positive endogenous risk factors (early age at menarche, nulliparity, late age at first full-term pregnancy, late age at any birth, low parity among parous women and late age at menopause), and certain exogenous risk factors (notably OCs and HT) (see Refs. [145,146] for reviews). This model has also been widely used for osteoporosis to demonstrate that higher bone density is associated with a longer endogenous or exogenous hormonal exposure [147,148].

While the utility of global clinical markers of estrogen has been firmly established for other hormone dependent disorders, we do not currently know whether they may contribute to our understanding of the effects of estrogens on brain functioning. This methodology is now being

applied in the area of cognitive ageing where it has been suggested that no individual marker is as potent as a combined index for prediction of cognitive dysfunction, indicating that the effects of steroids on brain may be more apparent when the cumulative effects of exposure are evaluated (see for review [149]). No such study has as yet applied such a cumulative model to psychiatric disorder, although life-long low exposure to steroid hormones has been reported to be associated with lifetime history of depression [54,64].

THE USE OF HORMONAL THERAPIES IN CLINICAL PRACTICE

A growing body of literature attests to the significant impact of hormonal exposure on central nervous system functioning throughout the life course in women and raises the question of whether hormonal therapies may be useful in treating depression. Most studies reported that postmenopausal women appear to be more commonly nonresponsive to serotonergic antidepressant therapy than younger women [150-154], although not systematically [155,156]. Some studies have investigated the possible effect of estrogen as an adjunct treatment for postmenopausal depression. Whereas an early small study failed to show any benefit when CEE was added to the tricyclic antidepressant imipramine in pre- and post-menopausal women with major depression [157], subsequent reports have suggested that the antidepressant effect of SSRIs may be improved by concurrent estrogen treatment [158-161]. One retrospective non-controlled study did not reproduce this finding. However, 37% of the women in the HT group were also using intermittent progesterone [162]. The effectiveness of ET requires further validation in large RCTs before its routine use in clinical practice can be recommended. Research in this area has, however, recently stagnated due to the side effects of hormonal treatments observed in the WHI study [163]. While the hormonal treatments used in the American WHI study do not necessarily correspond to current European practice, and because the subjects were treated as a group and not according to their individual health profiles, there has been a general reticence to continue with this type of treatment. There is also an underlying assumption that a small increase in the risk of hormone-dependant cancer or cardiovascular disorder (but not on mortality rates [164]) is inevitably a far greater health concern

than major depression.

In terms of screening at-risk women, reproductive history clearly have an important role to play. Women obviously do not arrive at menopause with equal risk of psychiatric disorder or equal susceptibility to the effects of HT, although this point has not been taken into account in the major RCTs conducted to date such as the HERS or WHI study [90,96]. Why some women seem more vulnerable to neuropsychiatric disorder remains poorly understood; however, certain implications of this observation may nonetheless be incorporated into clinical practice. The description of reproductive life events, evaluation of past history of psychiatric disorders and their timing in relation to reproductive stages should be a routine part of the mental status examination of women and should be taken into account in formulating a treatment strategy. This could help in predicting whether a patient is vulnerable to depressive episodes as a function of changes in hormonal levels. In 2001, the Treatment of Depression in Women Expert Consensus Guidelines were published to provide recommendations for management and treatment of four depressive conditions specific to women (PMDD, depression in pregnancy, PPD and depression related to perimenopause) [50]. HT was recommended as first-line therapy by 69% of experts for first episodes of mild and moderate depression occurring at perimenopause, antidepressants being recommended as the second option.

HT is still the first line treatment for the 75% of women who experience menopausal symptoms at the perimenopausal stage. Although no trials have focused specifically on women in this age group most likely to require menopausal symptom relief, it is increasingly acknowledged that the risks are probably negligible (see Refs. [165,166] for recent reviews), for women with menopausal symptoms who typically do not require ongoing use of estrogen therapy beyond the 5 year-period after which the cumulative risk of breast cancer and cardiovascular disease may become significant. The use of HT appears to be most appropriate for depressive perimenopausal women with a history of mood disorders associated with reproductive fluctuations or if vasomotor symptoms are present. In women whose depression or hot flushes are not responsive to antidepressants, HT may be

considered as adjunctive treatment. Obviously recognized contraindications and health risks of HT (*e.g.* hormone-dependent cancer, (cardio)vascular disease [167]) have to be taken into account [168]. Natural formulations (micronized progesterone, transdermal 17- β -estradiol) are preferable given their probable lower side effects notably in relation to breast cancer [169] and greater impact on mood disorders. Hormonal treatment may also prove valuable in the treatment of the 30% of patients who are resistant to conventional anti-depressant therapy. Selection for hormonal treatment in the postgenomic era may eventually be based on genetic markers identifying populations responsive to antidepressants, to estrogen, or to combinations of antidepressants and estrogens. This type of individually-tailored clinical strategy appears on present evidence to provide a more rational and personalized approach to the hormonal treatment of depression in women [170].

Declaration of interest: None.

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Table 2: Clinical trials investigating the effect of HT in women with clinically diagnosed depression

Study	Subjects	HT type and duration	Instrument	Clinical outcomes
[61] RCT	34 perimenopausal women [24%, major depression; 76%, minor depression (<i>DSM III-R</i>)]	Transdermal estradiol (50 µg/day), 3 or 6 weeks	Standardized mood rating scale scores and visual analog scale symptom scores	Full or partial therapeutic response in 80% of ET users vs. 22% in the placebo group ($p < 0.01$)
[62] RCT	50 perimenopausal women [52%, major depression; 22%, dysthymia; 26%, minor depression (<i>DSM IV</i>)]	Transdermal estradiol (100 µg/day), 12 weeks	Montgomery-Asberg Depression Rating Scale	Complete remission in 68% of ET users, regardless of depression type (and even after a 4-week washout period) vs. 20% in the placebo group ($p = .001$)
[63] Open-label treatment	9 perimenopausal and 11 postmenopausal women [54%, major depression; 14%, dysthymia; 32%, minor depression (<i>DSM IV</i>)]	Transdermal estradiol (100 µg/day), 4 weeks	Montgomery-Asberg Depression Rating Scale, Beck Depression Inventory and Clinical Global Impression	Remission in 67% of perimenopausal and 18% of postmenopausal women, irrespective of the severity or subtypes of depression
[98] RCT	57 postmenopausal women [54%, major depression; 24%, dysthymia; 28%, minor depression (<i>DSM IV</i>)]	Transdermal estradiol (100 µg/day), 8 weeks followed by oral MPA (10 mg), 2 weeks	Depressive symptomatology: CES-D and Hamilton Depression scales	No improvement in ET users and placebo group

CES-D, Center for Epidemiologic Studies Depression Scale