Reviews

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Depression and perimenopause: a review

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Depressive symptoms and disorders are highly prevalent throughout life, particularly in the middle-aged. From adolescence, women have a 1.5-3 times higher risk than men of suffering different depressive disorders. Traditionally, it has been assumed that transition to menopause, or perimenopause, is a period of higher depressive vulnerability, although there is some degree of controversy. This period seems to be associated with the appearance of both depressive symptoms and *de novo* depressive disorders, particularly if a background of depression exists. With regard to its etiopathogeny, genetic, hormonal, psychological and sociocultural factors have been suggested, but there are no solid data that support any of these explanations. Treatment basically depends on the severity of the disorder and includes antidepressants and/or psychotherapy. Maintained treatment with hormone replacement therapy (estrogens) is under discussion.

Key words:
Depression. Perimenopause. Estrogens.

Depresión y perimenopausia: una revisión

La prevalencia de los síntomas y trastornos depresivos a lo largo de la vida es elevada, particularmente en la edad media. A partir de la adolescencia, las mujeres presentan un riesgo 1,5-3 veces mayor que los hombres de padecer trastornos depresivos. Tradicionalmente, se asume que la transición a la menopausia o perimenopausia, es un período de mayor vulnerabilidad depresiva, aunque los datos no son del todo concluyentes. Este período parece asociarse a la aparición tanto de síntomas depresivos como de trastornos depresivos *de novo*, particularmente si existen antecedentes de depresión. Respecto a la etiopatogenia se han postulado mecanismos gené-

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ticos, hormonales, psicológicos y socioculturales, aunque no existen resultados definitivos que apoyen cualquiera de estas hipótesis. El abordaje terapéutico de la depresión en la perimenopausia está determinado principalmente por su gravedad, implicando el tratamiento con fármacos antidepresivos y/o psicoterapia. El tratamiento mantenido con terapia hormonal sustitutiva (estrógenos) está en discusión.

Palabras clave:
Depresión. Perimenopausia. Estrógenos.

INTRODUCTION

Depressive symptoms and disorders are very frequent over a lifetime, especially in the middle-aged. Major depression[1] and minor depression[2] are two very important sources of discapacity in developed countries. There is an 8% to 40% rate of depressive symptoms in middle-aged women.[3,4] Prevalence-life of major depression is 17%, women accounting for twice the amount than men.[5] In addition, it has been estimated that the prevalence of minor depression is twice that of major depression.[6]

Natural menopause *per se* has no negative consequences for most healthy women.[7] However, even though most women do not suffer clinical depression during transition to menopause or perimenopause, this seems to be a period of greater depressive vulnerability[8] as it is associated to the appearance of both depressive symptoms and *de novo* depressive disorders.[9,10] This is a period in which hormonal, cultural and sociofamilial factors can exert a «depressogenic» influence. Thus, women who have early menopause, defined as non-surgical menopause that occurs prior to 40 years of age, may experience a more noticeable decrease in ovarian function and estrogens than women with later menopause.[11] In the Liao et al. study,[12] 74% of the women with early menopause were classified as depressive, although this relationship may also be due to its negative cultural connotations, for example, infertility. On the other hand, post-menopause does not seem to be associated to an increased risk of depression.[3]

A background of depression, the presence of hot flushes and greater duration of perimenopause,[3] background of premenstrual depressive symptoms or post-partum depression,[13] and stressful life circumstances[14] have been indicated as depression risk factors in middle-aged women.[13] However, most of these risk factors are also risk factors during other life stages, that is, they are not specific to depression in the perimenopause period.[8]

Perimenopause *per se* seems to be an independent risk factor of depression in middle-aged women. The previously mentioned studies suggest that some women will have greater vulnerability for decreases and sudden changes in estrogen. Even though the different theories (domino effect theory, psychosocial theory, etc.) have attempted to find a causal connection between depression and perimenopause, no consistent findings supporting them have been found. Sufficient evidence is also lacking to state that perimenopausal depressive symptoms are qualitatively or quantitatively different from the depression symptoms found during another life period. Finally, the best treatment for perimenopausal depressive disorders has still not been clearly established.

Definitions

Lack of uniformity in the definition of perimenopause and of the measurement instruments of the different de-

pressive disorders makes it difficult to compare the different studies.[8] In the following, we present the definitions of the concepts used most in the studies on depression and perimenopause, definitions that are summarized in table 1.

The term climacteric, that comes from the Greek word *klimater* and which means rung of a ladder, refers to the loss of procreation capacity and is not equivalent to that of menopause.[15]

Menopause is clinically defined as when a woman has 12 or more months of amenorrhea without any justifying cause,[11] the mean age in the United States of America being 51 years.[16] From the hormonal point of view, it is characterized by a follicle-stimulating hormone (FSH) level greater than 40 IU/l and a estrogen one less than 25 pg/ml.[17]

Finally, perimenopause is defined from the endocrinological point of view by a FSH level > 25 IU/L and estradiol level < 40 pg/ml.[16] Three definitions are used most from the clinical point of view: the first, when the woman has irregular periods or prolonged amenorrhea of less than 12 months,[18] secondly, that time period with menstrual irregularities of more than seven days (regarding that which is common in the woman in question) with or without amenorrhea greater than three months[19] and, finally, an amen-

Table 1	Climacteric, perimenopause and menopause: clinical and endocrinological
Terms	**Clinical and endocrinological definition**
Climacteric	End of procreation capacity
	It is not equivalent to menopause
Perimenopause	Clinically: 3 definitions
	- Irregular menstrual period or prolonged amenorrhea of than 12 months
	- Menstrual irregularities of more than 7 days (regarding that normal in the woman in question) with or without amenorrhea greater than 3 months
	- Amenorrhea period between 3 and 11 months
	Endocrinologically:
	- Level of FSH > 25 IU/l
	- Level of estradiol < 40 pg/ml
Menopause	Clinically:
	- Amenorrhea of 12 or more months duration with or without a justifying cause
	Endocrinologically:
	- Follicle-stimulating hormone level (FSH) > 40 IU/l
	- Level of estrogens < 25 pg/ml

orrhea period of between 3 and 11 months.[20] The practical utility of establishing a separation between early and late premenopause is less. In a longitudinal study of 2,569 women between 45 and 55 years, it was found that the two symptoms that best defined onset of perimenopause was amenorrhea of 3-11 months and greater menstrual irregularity.[21]

Regarding the definition of the term depression, it must be taken into account that investigators have used different definitions and instruments for their evaluation-diagnosis. Thus, although most of the studies have focused on major depressive disorder, the subsyndromic depressive symptoms could have a significant impact on (peri)menopause.[22] Structured diagnostic interviews are the most reliable method to diagnose depressive disorders.[8] One of the instruments used the most to evaluate depressive symptoms in general population studies is that of the Center for Epidemiologic Studies-Depression (CES-D) questionnaire, which as been validated in many countries.[23]

Another limitation in the study on depression in perimenopause is that few studies have used reliable endocrinological measurements of ovarian aging and standard instruments for the diagnosis of depression.[18]

EPIDEMIOLOGY

The greater prevalence of depression in women than in men worldwide is one the best documented findings of psychiatric epidemiology, it being 1.5 to 3 times greater in women than in men for major depression, dysthymia, recurrent brief depression and minor depression.[24] However, a study conducted in the USA found that this difference in gender was not constant and that it depended on the racial-ethnic group[25] since the increase of post-pubertal depressive symptoms only occurred in Caucasian girls and not in those of Hispanic or Afro-American origin.

The difference of gender begins to appear after adolescent age.[26] This suggests the involvement of sex hormones, since mood changes are found in situations in which there are changes of the sex hormones, as in the case of menopause,[27] hormone replacement therapy (HPT)[28] or the use of oral contraceptives.[29] However, in the case of major depression, more studies are required to be able to establish a solid causal connection between hormone alterations associated to these situations and to it since other factors may be involved.[25] Post-partum is the only situation in where there is a solid causal connection between hormone change and major depression.[30] This seems to be related with the presence of a family background of depression.[24]

Although the importance of affective symptoms during the climacteric period may have been over-evaluated, de-

pression rates of up to 44% have been reported in menopause-specialized clinics.[31] On the other hand, in a preliminary study it was found that 68% of the women with bipolar disorder would have at least one depression episode during perimenopause.[32] In the same study, no increase in the risk of relapse in manic phases was found.

SYMPTOMS

Post-menopause does not seem to be associated with an increased risk of depression.[3] However, transition to menopause or perimenopause seems to be a period with greater depressive vulnerability.[8] This period is associated with the appearance of both depressive symptoms[33] as well as de novo depressive disorders,[9,34,10] especially when there is a background of depression.[18] Even so, some authors have suggested that perimenopause is not an important risk factor for the development of major depression.[18,35] In the latter study,[18] 29 asymptomatic premenopausal women were followed-up for up to 6-12 months after their last menstrual period. Risk of depression was 14 times greater in the 12 months prior to and after the date of the their last menstrual period. However, most of the women did not suffer depression during the study period. A recent study also did not find any evidence in this sense.[36] The authors suggested that those women who have a familial vulnerability and who are faced with a greater and more serious number of stressful life events would be those having the most likelihood of suffering depression.

Some of the risk factors that have been related with the presence of depressive symptoms or depression in perimenopause are having a background of affective instability or depressive symptoms,[37,38] background of premenstrual syndrome (BPS),[39,40] lower educational and economic level,[41] surgical menopause,[38] and a longer duration of the perimenopause - which could be secondary to a prolonged exposure to hormone fluctuations.[3,38] They have also been related with the present of typical symptoms of perimenopause, such as hot flushes, insomnia, anxiety, sexual problems, including vaginal dryness, and urogenital problems, etc. Thus, in a study with women of 40 to 60 years of age, those who had vasomotor symptoms had a greater likelihood of suffering depressive symptoms than those who had no vasomotor symptoms, even after controlling for a background of depression.[42] The months immediately before or after the their last menstrual period, which would be those having the greatest depressive risk, are characterized by a significant decrease in estrogen.[43] This suggests that the endocrine factors related with perimenopause could be directly related with the presentation of depressive symptoms.[8] In any event, it still cannot be established that depressive symptoms are secondary to hormone changes of menopause.[14,44]

Regarding the question of whether perimenopausal depressive symptoms are quantitatively or qualitatively dif-

ferent from the depressive symptoms during another life period, some authors suggest that this is true.[45] However, a case-control study did not find any differences between perimenopausal depression and pre-perimenopausal depression, except that the pre-perimenopausal depressive group scored significantly higher on «emotional withdrawal» evaluated with the Montgomery Asberg Depression Rating Scale (MADRS). This could indicate the presence of a higher level of anhedonía.[36]

ETIOPATHOGENIC MECHANISMS

Many hypotheses have been proposed, the main ones being the presence of stressors in middle age, hormone alterations, perimenopausal vasomotor symptoms, body image and self-esteem as well as the genetic factors[22] (table 2).

Genetic factors

It is very likely that the genetic factors interact with the environment so that perimenopausal depression occurs in some women and not in others. It has been discovered that women who have a short allele (SS) of the cytosine-adenine repeat polymorphism of the estrogen receptor-beta gene have a seven times greater risk of vasomotor symptoms and 13 times greater one of psychological symptoms than those women who have the long allele.[46]

In an interesting case-control study, it was found that 15.1% of non-depressive perimenopausal women compared to 44% of perimenopausal depressive women (p = 0.009) had a familial background of depression.[36] In the same study, it was also found that the incidence of familial background of depression in the group of perimenopausal depressive women was greater than in that of depressive pre-perimenopausal women. However, the former did not have a greater incidence of personal background of depression than the latter. This suggests that the hormonal changes and stressful life events in the

middle-aged could induce a first depressive episode in vulnerable women. It is possible that this vulnerability is genetic, but more studies must be performed in this regards.

Hormonal factors

In an interesting letter to the editor of the *British Medical Journal* in 1990, a group of London gynecologists bitterly complained about the generalized psychiatric opinion that estrogens were irrelevant both for the explanation of the etiology and for the treatment of depression in women as well as their tendency to attribute it to environmental causes[47]. The authors mentioned the excess of depression in the female gender from puberty and the limited frequency of depression in the first quarter of pregnancy, characterized by an elevated and stable level of estrogens. The development of the neurosciences in the last two decades has allowed for some shift in this position.

Estrogens increase the serotonin levels and norepinephrine activity in the central nervous system (SNS). The estrogen receptors are distributed throughout the brain and it has been suggested that estrogens have a mood regulating role[22]. Some authors have reported that the fluctuations of the estradiol levels in the transition to menopause and their influence on serotonin could mediate the presence of depressive mood.[48,49]

One study found that the decrease of depressive symptoms followed a parallel course to the decrease of FSH. Thus, the authors suggested that perimenopausal depression could reflect episodic alterations of the ovarian function, limiting the utility of cross-sectional studies.[50] In another study, women in whom the FSH levels rapidly increased –a sign of ovarian aging– had a greater likelihood of depression and depressive symptoms similar to the Premenstrual Syndrome (PMS) were more frequent as the estradiol levels increased.[35] Alterations of the estradiol level, especially sudden falls, have also been related with perimenopausal psychological symptoms.[51] It has also been found that depressed perimenopausal

Table 2	Etiopathogenic factors involved in the depression in the perimenopause	
Genetic factors	**Hormone factors**	**Psychosocial and cultural factors**
- Short allele (SS) of the cytosine-adenine repeat polymorphism of the estrogen receptor-beta gene	- Estradiol - Follicle-stimulating hormone (FSH) - Luteinizing hormone (LH) - Dehydroepiandrosterone (DHEA)	- Previous personality - Cultural connotations of menopause - Presence of negative life events

women have a lower concentration of morning dehydroepiandrosterone (DHEA).[52]

Many studies support the hypothesis that some women would have special vulnerability to depressive symptoms during perimenopause.[22] It has been hypothesized that some women would be more vulnerable to depressive symptoms in periods of hormonal change such as premenstrual period, pregnancy or perimenopause.[51,53] We have just indicated that women with PMS also have a greater risk of depression. In a prospective study,[39] they were twice as likely to suffer depressive mood, menopausal symptoms and problems sleeping. On the other hand, in a follow-up study, it was found that women who had a background of depression during their lifetime had higher levels of FSH and LH, and lower ones of estradiol. This suggests that they would have an earlier initiation of ovarian function decline.[34]

There is little information on the relationship of the menopause symptoms with hormonal disorders that occur in transition to it.[54] However, even in studies in which no relationship had been found with depressive symptoms and with perimenopause, an association was found between the presence of perimenopausal symptoms such as hot flushes and depressive symptoms.[3,14,55] This suggests that the hormonal alteration could mediate in both types of symptoms. In another study, even though no significant association was found between estradiol levels during menopause and depressive symptoms measured with the Epidemiologic Studies Depression Scale (CES-D), a significant relationship was found between depression and hot-flushes, nighttime sweating and problems sleeping.[44] These authors suggested a «domino effect/theory» according to which depression or some depressive symptoms, such as insomnia, dysphoria or concentration problems, would be secondary to hormonal vasomotor symptoms, such as hot flushes or nighttime sweating. Other authors have also suggested that the depressive symptoms could be due to dysphoria secondary to vasomotor symptoms and to the increase of stressful psychosocial factors during this period.[56] However, in a case-control study in which a group of depressive perimenopausal women (n = 48) was compared with a control group of non-depressive perimenopausal women (n = 53), no statistically significant association was found between the nighttime sweating (considered as the main cause of depressive symptoms, acting through the loss of quality of nighttime rest) and the severity of the depressive symptoms.[36] The authors criticized the previous assumption that perimenopausal depression could be due to nighttime sweating and hot flushes since the presence of vasomotor symptoms in their study did not predict the presence and severity of the depression.

One factor to keep in mind is that in all of these studies, women who smoked could have menopause up to one year earlier due to the antiestrogen effect of the smoking habit.[11]

Psychosocial and cultural factors

Menopause occurs in a period of life that entails a series of cultural, social and personal connotations that could influence the mood status of the woman. The psychosocial theory defends the idea that the presence of affective symptoms during perimenopause may be explained by marital problems, physical diseases and financial problems.[57] However, in a case-control study, no differences were found regarding education level, marital problems or economic level when a group of depressive perimenopausal women were compared with another non-depressive one.[36]

On the other hand, this is a period in which there are a series of stressful factors, such as the empty nest syndrome, the need to care for elderly parents or cope with their death, etc., that may influence mood and depressive conditions. Schmidt et al. found that the empty nest syndrome was not related with the presence of perimenopausal depression. However, they did find that regardless of the presence of hot flushes, depressed perimenopausal women reported the presence of negative life events and lower self-esteem with significantly greater frequency when they were compared with a group of non-depressed perimenopausal women.[58] On the other hand, good sociofamilial support could serve as a protection factor, especially in vulnerable women.

A critical factor and one that has probably been studied insufficiently is the previous personality and adaptive styles of perimenopausal women. One study found that women who considered menopause as a stressful event were characterized by greater neuroticism, by greater social support seeking, and by greater avoidance and lower tendency to aggregation.[59]

Finally, the woman's cultural setting must also be kept in mind. It can be hypothesized that the depressive symptoms would be more frequent in cultures where menopause has negative connotations and vice versa. There are cultures where menopause carries greater respect and authority while it has a negative connotation in others.[22] One study found that women from India, Singapore and China had a lower rate of vasomotor and urogenital symptoms but greater psychological symptoms during menopause than Caucasian women.[60] Another study found that depressive symptoms were related with a negative attitude towards menopause, but also with low levels of education, perception of economic status, health condition and social support.[41]

THERAPEUTIC APPROACH

In regards to the therapeutic approach of depression during perimenopause, the main challenges are the capacity of identifying women at risk of having depressive symptoms and the choice of the treatment that offers the best

therapeutic results with the least side effects.[61] Regarding the first question, although it would be very interesting to systematically use screening instruments to detect women at risk, Whooley et al. found that the affirmative answer to one of the following questions «During the past two weeks, have you felt down, depressed or hopelessness?» and «During the past two weeks, have you lacked interest or desire to do things?» had the same predictive value as the CES-D, with the consequent savings in time and money.[62] Those women considered to be «at risk» would then be clinically interviewed in order to establish or rule out a solid diagnosis of major depression.

Regarding the decision on what the best treatment would be, many factors must be taken into account, such as severity of the disorder, the patient's own opinion, or the presence of somatic disease or risk factors that contraindicates the use of some drugs.

Psychotherapy

There are practically no studies that evaluate the efficacy of psychotherapy in the treatment of depressive symptoms or major depression in perimenopause.[61] In one study that was not limited to the study of perimenopause that asked the experts for their opinion on the best antidepressant treatment in women, psychotherapy was considered as coadjuvant to drug treatment when the symptoms were severe; there was a greater balance between those who considered that drugs, psychotherapy and other strategy should be the treatment of choice in the case of moderate symptoms; and finally it was suggested that psychotherapy should be treatment of first choice for less severe cases.[63]

Antidepressive drugs

There is still no clear recommendation regarding the type of antidepressant, these including tricyclics or heterocyclics, selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine receptor inhibitor, alpha 2-antagonists, norepinephrine and dopamine reuptake inhibitors, or serotonin-norepinephrine reuptake inhibitors, that offers a better clinical outcome, impact on disease in terms of functioning and better quality of life or cost.

Most cases of depression (basically mild and moderate ones) are adequately treated in primary care. Conventional antidepressants have been shown to be efficient at six weeks in peri- or post-menopausal women, and a maintenance period of 6-12 weeks after clinical improvement is recommended.[61] It has been reported that SSRIs would be effective when the depressive symptom is primary and not accompanied by vasomotor symptoms or other menopausal symptoms.[22] Regarding dual action antidepressants (SNRI), data from an observational study with venlafaxine suggest that this antidepressant improves the general condition, reduces depressive symptoms and can reduce vasomotor symptoms in perimenopausal depressive patients.[64]

In those cases in which there is little or no clinical response after six weeks of treatment at adequate doses, the treatment dose could be increased two to four weeks more (above all if there has been some response).[22] However, if after 8-12 weeks of treatment at maximum doses, no adequate response is found, the antidepressant drug should be changed for another one of the same class or a different one or the patient could be referred to psychiatry. It has been calculated that only 50% of the patients with major depression who are treated in primary care respond to the first antidepressant drugs, 20% stop taking it due to side effects and 30% abandon it due to lack of response.

Hormone replacement therapy

The role of hormone replacement therapy (HRT) has not been clearly established in perimenopausal mood disorders.[65] It has been suggested that a short-duration HRT (3-6 weeks) could relieve the depressive symptoms associated to vasomotor symptoms during perimenopause.[53,66,67]

In a longitudinal study (8 years) with 231 perimenopausal women with no previous background of depression, it was found that the transition to menopause was associated to an increased risk of depressive symptoms and depressive disorders, related with the «intra-subject» increase of follicle-stimulating hormone (FSH) and luteinizing hormone (LH), lower levels of inhibin B and greater variability of FSH levels and estradiol. The authors suggested that the depressive symptoms could be due to destabilization of the typical fluctuations of estradiol related with aging. This is interesting since it supports the hypothesis that the perimenopausal depressive conditions could be treated with estrogens,[68,69] even though perimenopausal depression does not seem to be secondary to an estrogen level,[9,70] but rather to its variability. In a study conducted in women who had had their menopause 5-10 years earlier, no improvement was observed in the depressive symptoms using estadiol treatment.[71] As indicated,[8] it seems that antidepressive efficacy of the estrogens in perimenopause and their ineffectiveness in menopause suggests that perimenopausal depressive disorders are due to hormone changes (sudden decline or fluctuations) rather than to an estrogen deficit itself.

CONCLUSIONS

1. Most authors consider perimenopause as a period of greater depressive vulnerability of both depressive symptoms and *de novo* depression disorders.

2. Some studies suggest that depression in perimenopause would have specific clinical characteristics, especially greater emotional withdrawal.

3. From the etiopathogenic point of view, both genetic factors and hormonal, psychosocial and cultural ones would be involved.

4. The therapeutic approach of depression in perimenopause involves pharmacological and/or psychotherapeutic strategies based on the severity level. In spite of the generalized acceptance of the role of hormone fluctuations in perimenopausal depression, currently there are no conclusive data on the role or hormone replacement therapy in its treatment.

REFERENCES

1. López AD, Murray, CC. The global burden of disease, 1990-2020. Nat Med 1998;4:1241-43.
2. Judd LL, Rapaport MH, Paulus MP, Brown JL. Subsyndromal symptomatic depression: a new mood disorder? J Clin Psychiatry 1994;55 (Suppl.):18-28.
3. Avis NE, Brambilla D, McKinlay SM, Vass K. A longitudinal analysis of the association between menopause and depression. Results from the Massachusetts Women's Health Study. Ann Epidemiol 1994;4:214-20.
4. Avis NE, Stellato R, Crawford S, Bromberger J, Ganz P, Cain, V, et al. Is there a menopausal syndrome? Menopausal status and symptoms across racial/ethnic groups. Soc Sci Med 2001; 52(3):345-56.
5. Kessler RC, McGonagle KA, Zhao S, Nelson CB, Hughes M, Eshleman S, et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. Arch Gen Psychiatry 1994;51:8-19.
6. Kessler RC, Zhao S, Blazer DG, Swartz M. Prevalence, correlates, and course of minor depression and major depression in the National Comorbidity Survey. J Affect Disord 1997;45:19-30.
7. Matthews KA, Wing RR, Kuller LH, Meilahn EN, Kelsey SF, Costello EJ, et al. Influences of natural menopause on psychological characteristics and symptoms of middle-aged healthy women. J Consult Clin Psicol 1990;58:345-51.
8. Schmidt PJ. Mood, depression, and reproductive hormones in the menopausal transition. Am J Med 2005;118 (Suppl. 12B):54-8.
9. Freeman EW, Samuel MD, Lin H, Nelson DB.Associations of hormones and menopausal status with depressed mood in women with no history of depression. Arch Gen Psychiatry 2006;63:375-82.
10. Woods NF, Mariella A, Mitchell ES. Patterns of depressed mood across the menopausal transition: approaches to studying patterns in longitudinal data. Acta Obstet Gynecol Scand 2002;81:623-32.
11. Harlow BL, Signorello LB. Factors associated with early menopause. Maturitas 2000;35:3-9.
12. Liao KL, Wood N, Conway GS. Premature menopause and psychological well-being. J Psychosom Obstet Gynaecol 2000;21: 167-74.
13. Stewart DE, Boydell KM. Psychologic distress during menopause: associations across the reproductive life cycle. Int J Psychiatry Med 1993;23:157-62.
14. Dennerstein L, Lehert P, Burger H, Dudley E. Mood and the menopausal transition. J Nerv Ment Dis 1999;187:685-91.
15. Torres Hernández P, Gutiérrez Rojas L, Robles Rodríguez I. Trastornos afectivos en los ciclos hormonales de la mujer. Salud Mental. Aten Primaria 2005;6:1-8.
16. Rasgon N, Shelton S, Halbreich U. Perimenopausal mental disorders: epidemiology and phenomenology. CNS Spectr 2005;10:471-78.
17. Gracia CR, Samuel MD, Freeman EW, Lin H, Langan E, Kapoor S, Nelson DB. Defining menopause status: creation of a new definition to identify the early changes of the Monopausal transition. Monopause 2005;12:128-35.
18. Schmidt PJ, Haq N, Rubinow DR. A longitudinal evaluation of the relationship between reproductive status and mood in perimenopausal women. Am J Psychiatry 2004;161(12):2238-44.
19. Binfa L, Castelo-Branco C, Blumel JE, Cancelo MJ, Bonilla H, Munoz I, et al. Influence of psycho-social factors on climacteric symptoms. Maturitas 2004;48(4):425-31.
20. Owens JF, Matthews KA. Sleep disturbance in healthy middle-aged women. Maturitas 1998; 30(1):41-50.
21. Brambilla DJ, McKinlay SM, Johannes CB. Defining the perimenopause for application in epidemiologic investigations. Am J Epidemiol 1994;140:1091-95.
22. Gyllstrom ME, Schreiner PJ, Harlow BL. Perimenopause and depression: strength of association, causal mechanisms and treatment recommendations. Best Pract Res Clin Obstet Gynaecol 2007;21:275-92.
23. Knight RG, Williams S, McGee R, Olaman S. Psychometric properties of the Centre for Epidemiologic Studies Depression Scale (CES-D) in a sample of women in middle life. Behav Res Ther 1997;35:373-80.
24. Kessler RC. Epidemiology of women and depression. J Affect Disord 2003;74:5-13.
25. Hayward C, Gotlib IH, Schraedley PK, Litt IF. Ethnic differences in the association between pubertal status and symptoms of depression in adolescent girls. J Adolesc Health 1999;25:143-49.
26. Angold A, Costello EJ, Worthman CM. Puberty and depression: the roles of age, pubertal status and pubertal timing. Psychol Med 1998;28:51-61.
27. Hunter M, Battersby R, Whitehead M. Relationships between psychological symptoms, somatic complaints and menopausal status. Maturitas 1986;8:217-28.
28. Zweifel JE, O'Brien WH. A meta-analysis of the effect of hormone replacement therapy upon depressed mood. Psychoneuroendocrinology 1997;22(3):189-212.
29. Cullberg J. Mood changes and menstrual symptoms with different gestagen/estrogen combinations. A double blind comparison with a placebo. Acta Psychiatr Scand 1972; 236 (Suppl.):1-86.
30. Wisner KL, Peindl K, Hanusa BH.Relationship of psychiatric illness to childbearing status: a hospital-based epidemiologic study. J Affect Disord 1993;28:39-50.
31. Hay AG, Bancroft J, Johnstone EC. Affective symptoms in women attending a menopause clinic. Br J Psychiatry 1994;164:513-16.
32. Marsh WK, Templeton A, Ketter TA, Rasgon NL. Increased frequency of depressive episodes during the menopausal transition

in women with bipolar disorder: Preliminary report. J Psychiatr Res 2008;42(3):247-51.

33. Bromberger JT, Assmann SF, Avis NE, Schocken M, Kravitz HM, Cordal A. Persistent mood symptoms in a multiethnic community cohort of pre- and perimenopausal women. Am J Epidemiol 2003;158:347-56.

34. Harlow BL, Wise LA, Otto MW, Soares CN, Cohen LS. Depression and its influence on reproductive endocrine and menstrual cycle markers associated with perimenopause: the Harvard Study of Moods and Cycles. Arch Gen Psychiatry 2003;60:29-36.

35. Freeman EW, Sammel MD, Liu L, Gracia CR, Nelson DB, Hollander L. Hormones and menopausal status as predictors of depression in women in transition to menopause. Arch Gen Psychiatry 2004;61(1):62-70.

36. Ozturk O, Eraslan D, Mete HE, Ozsener S. The risk factors and symptomatology of perimenopausal depression. Maturitas 2006;55(2):180-6.

37. Amore M, Di DP, Papalini A, Berti A, Palareti A, Ferrari G, Chirico C, De AD. Psychological status at the menopausal transition: an Italian epidemiological study. Maturitas 2004;48:115-24.

38. Dennerstein L, Guthrie JR, Clark M, Lehert P, Henderson VW. A population-based study of depressed mood in middle-aged, Australian-born women. Menopause 2004;11:563-68.

39. Freeman EW, Sammel MD, Rinaudo PJ, Sheng L. Premenstrual syndrome as a predictor of menopausal symptoms. Obstet Gynecol 2004;103:960-66.

40. Novaes C, Almeida OP. Premenstrual syndrome and psychiatric morbidity at the menopause. J Psychosom Obstet Gynaecol 1999;20:56-7.

41. Choi H, Lee D, Lee K, Kim H, Ham E. A structural model of menopausal depression in Korean women. Arch Psychiatr Nurs 2004;18:235-42.

42. Joffe H, Hall JE, Soares CN, Hennen J, Reilly CJ, Carlson K, et al. Vasomotor symptoms are associated with depression in perimenopausal women seeking primary care. Menopause 2002; 9:392-98.

43. Santoro N, Brown JR, Adel T, Skurnick JH. Characterization of reproductive hormonal dynamics in the perimenopause. J Clin Endocrinol Metab 1996;81:1495-501.

44. Avis NE, Crawford S, Stellato R, Longcope C. Longitudinal study of hormone levels and depression among women transitioning through menopause. Climacteric 2001;4:243-49.

45. Schmidt PJ, Roca CA, Bloch M, Rubinow DR. The perimenopause and affective disorders. Semin Reprod Endocrinol 1997;15:91-100.

46. Takeo C, Negishi E, Nakajima A, Ueno K, Tatsuno I, Saito Y, et al. Association of cytosine-adenine repeat polymorphism of the estrogen receptor-beta gene with menopausal symptoms. Gend Med 2005;2:96-105.

47. Studd JW, Watson NR, Montgomery J. Depression and the menopause. BMJ 1990;300:1653.

48. Joffe H, Cohen LS. Estrogen, serotonin, and mood disturbance: where is the therapeutic bridge? Biol Psychiatry 1998;44:798-811.

49. Rubinow DR, Schmidt PJ, Roca CA. Estrogen-serotonin interactions: implications for affective regulation. Biol Psychiatry 1998;44:839-50.

50. Daly RC, Danaceau MA, Rubinow DR, Schmidt PJ. Concordant restoration of ovarian function and mood in perimenopausal depression. Am J Psychiatry 2003;160:1842-46.

51. Steiner M, Dunn E, Born L. Hormones and mood: from menarche to menopause and beyond. J Affect Disord 2003;74:67-83.

52. Schmidt PJ, Murphy JH, Haq N, Danaceau MA, St CL. Basal plasma hormone levels in depressed perimenopausal women. Psychoneuroendocrinology 2002;27:907-20.

53. Boyd RC, Amsterdam JD. Mood disorders in women from adolescence to late life: an overview. Clin Obstet Gynecol 2004;47:515-26.

54. Freeman EW, Samuel MD, Lin H, Gracia CR, Pien GW, Nelson DB, et al. Symptoms associated with menopausal transition and reproductive hormones in midlife women. Obstet Gynecol 2007;110:230-40.

55. Bosworth HB, Bastian LA, Kuchibhatla MN, Steffens DC, McBride CM, Skinner CS, et al. Depressive symptoms, menopausal status, and climacteric symptoms in women at midlife. Psychosom Med 2001;63:603-8.

56. Burt VK, AltshulerLL, Rasgon N. Depressive symptoms in the perimenopause: prevalence, assessment, and guidelines for treatment. Harv Rev Psychiatry 1998;6:121-32.

57. Ballinger CB. Psychiatric aspects of the menopause. Br J Psychiatry 1990;156:773-87.

58. Schmidt PJ, Murphy JH, Haq N, Rubinow DR, Danaceau MA. Stressful life events, personal losses, and perimenopause-related depression. Arch Womens Ment Health 2004;7:19-26.

59. Bosworth HB, Bastian LA, Rimer BK, Siegler IC. Coping styles and personality domains related to menopausal stress. Womens Health Issues 2003;13:32-8.

60. Chim H, Tan BH, Ang CC, Chew, EM, Chong YS, Saw SM. The prevalence of menopausal symptoms in a community in Singapore. Maturitas 2002;41:275-82.

61. Cohen LS, Soares CN, Joffe H. Diagnosis and management of mood disorders during the menopausal transition. Am J Med 2005;118 (Suppl. 12B):93-7.

62. Whooley MA, Avins AL, Miranda J, Browner WS. Case-finding instruments for depression. Two questions are as good as many. J Gen Intern Med 1997;12:439-45.

63. Altshuler LL, Cohen LS, Moline ML, Kahn DA, Carpenter D, Docherty JP, Ross RW. Treatment of depression in women: a summary of the expert consensus guidelines. J Psychiatr Pract 2001;7:185-208.

64. Ladd CO, Newport DJ, Ragan KA, Loughhead A, Stowe ZN. Venlafaxine in the treatment of depressive and vasomotor symptoms in women with perimenopausal depression. Depress Anxiety 2005;22(2):94-7.

65. Pearlstein T, Rosen K, Stone AB. Mood disorders and menopause. Endocrinol Metab Clin North Am 1997;26:279-94.

66. Cohen LS, Soares CN, Poitras JR, Prouty J, Alexander AB, Shifren JL. Short-term use of estradiol for depression in perimenopausal and postmenopausal women: a preliminary report. Am J Psychiatry 2003;160:1519-22.

67. Schmidt PJ. Depression, the perimenopause, and estrogen therapy. Ann NY Acad Sci 2005; 1052:27-40.

68. Rasgon NL, Altshuler LL, Fairbanks LA, Dunkin JJ, Davtyan C, Elman S, Rapkin AJ. Estrogen replacement therapy in the treatment of major depressive disorder in perimenopausal women. J Clin Psychiatry 2002; 63 (Suppl. 7):45-8.

69. Soares CN, Almeida OP, Joffe H, Cohen LS. Efficacy of estradiol for the treatment of depressive disorders in perimenopausal women: a double-blind, randomized, placebo-controlled trial. Arch Gen Psychiatry 2001;58:529-34.
70. Schmidt PJ, Nieman L, Danaceau MA, Tobin MB, Roca CA, Murphy JH, et al. Estrogen replacement in perimenopause-related depression: a preliminary report. Am J Obstet Gynecol 2000;183:414-20.
71. Morrison MF, Kallan MJ, Ten HT, Katz I, Tweedy K, Battistini M. Lack of efficacy of estradiol for depression in postmenopausal women: a randomized, controlled trial. Biol Psychiatry 2004;55:406-12.