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.


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, background of premenstrual depressive symptoms or post-partum depression, and stressful life circumstances have been indicated as depression risk factors in middle-aged women. 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.

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 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 depressive disorders makes it difficult to compare the different studies. 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 menopause.

Menopause is clinically defined as when a woman has 12 or more months of amenorrhea without any justifying cause, the mean age in the United States of America being 51 years. 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.

Finally, perimenopause is defined from the endocrinological point of view by a FSH level > 25 IU/L and estradiol level < 40 pg/ml. 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, secondly, that time period with menstrual irregularities of more than seven days (regarding that which is normal in the woman in question) with or without amenorrhea greater than three months and, finally, an amen-

Table 1 Climacteric, perimenopause and menopause: clinical and endocrinological

<table>
<thead>
<tr>
<th>Terms</th>
<th>Clinical and endocrinological definition</th>
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<tr>
<td>Climacteric</td>
<td>End of procreation capacity</td>
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<td>It is not equivalent to menopause</td>
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<td>Perimenopause</td>
<td>Clinically: 3 definitions</td>
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<tr>
<td></td>
<td>- Irregular menstrual period or prolonged amenorrhea of than 12 months</td>
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<td>- Menstrual irregularities of more than 7 days (regarding that normal in the woman in question)</td>
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<td>with or without amenorrhea greater than 3 months</td>
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<td>- Amenorrhea period between 3 and 11 months</td>
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<td>Endocrinologically:</td>
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<td></td>
<td>- Level of FSH &gt; 25 IU/l</td>
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<td></td>
<td>- Level of estradiol &lt; 40 pg/ml</td>
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<td>Menopause</td>
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<td></td>
<td>- Amenorrhea of 12 or more months duration with or without a justifying cause</td>
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<td>- Follicle-stimulating hormone level (FSH) &gt; 40 IU/l</td>
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<td>- Level of estrogens &lt; 25 pg/ml</td>
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orrhea period of between 3 and 11 months. 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. 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. Structured diagnostic interviews are the most reliable method to diagnose depressive disorders. One of the instruments used to evaluate depressive symptoms in general population studies is that of the Center for Epidemiologic Studies-Depression (CES-D) questionnaire, as which been validated in many countries.

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.

**EPIDEMIOLOGY**

The greater prevalence of depression in women than in men worldwide is one of 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. 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 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 adolescence. 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, hormone replacement therapy (HPT) or the use of oral contraceptives. 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. Post-partum is the only situation in where there is a solid causal connection between hormone change and major depression. This seems to be related with the presence of a family background of depression.

Although the importance of affective symptoms during the climacteric period may have been over-evaluated, depression rates of up to 44% have been reported in menopause-specialized clinics. 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. 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. However, transition to menopause or perimenopause seems to be a period with greater depressive vulnerability. This period is associated with the appearance of both depressive symptoms as well as de novo depressive disorders, especially when there is a background of 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, background of premenstrual syndrome (BPS), lower educational and economic level, surgical menopause, and a longer duration of the perimenopause - which could be secondary to a prolonged exposure to hormone fluctuations. 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. The months immediately before or after the last menstrual period, which would be those having the greatest depressive risk, are characterized by a significant decrease in estrogen.

This suggests that the endocrine factors related with perimenopause could be directly related with the presentation of depressive symptoms. In any event, it still cannot be established that depressive symptoms are secondary to hormone changes of menopause.

Regarding the question of whether perimenopausal depressive symptoms are quantitatively or qualitatively differ-
different from the depressive symptoms during another life period, some authors suggest that this is true. 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 anhedonia.

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 (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.

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. 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. 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. 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.

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. 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. Alterations of the estradiol level, especially sudden falls, have also been related with perimenopausal psychological symptoms. It has also been found that depressed perimenopausal

<table>
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<th>Table 2</th>
<th>Etiopathogenic factors involved in the depression in the perimenopause</th>
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<tr>
<td>Genetic factors</td>
<td>Hormone factors</td>
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<td>Short allele (SS) of the cytosine-adenine repeat polymorphism of the estrogen receptor-beta gene</td>
<td>Estradiol</td>
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<td>Follicle-stimulating hormone (FSH)</td>
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<td></td>
<td>Luteinizing hormone (LH)</td>
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<td>Dehydroepiandrosterone (DHEA)</td>
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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.52 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.51,52 We have just indicated that women with PMS also have a greater risk of depression. In a prospective study,20 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.44

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.23,29 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.58 However, in a case-control study in which a group of depressive perimenopausal women (n = 48) was compared with a control group of non-depressed 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.52 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.39

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 hopeless?» and «During the past two weeks, have you lacked interest or desire to do things?» had the same predictive value as the CES-D.

regarding dual action antidepressants, norepinephrine and dopamine reuptake inhibitors, or selective 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. Convention- al 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 better clinical outcome, impact on disease in terms of functioning and better quality of life or cost.

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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,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

32. Marsh WK, Templeton A, Ketter TA, Rasgon NL. Increased frequency of depressive episodes during the menopausal transition.