Use of estrogens in the treatment of mental disorders

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El uso de los estrógenos en el tratamiento de los trastornos mentales

Summary

The relationship between female sex steroids and mental disorders was not thoroughly studied until the last decades. However, in recent years, many studies have appeared that evaluate the influence of estrogens on the onset, outcome and treatment of mental disorders.

Although the data are still preliminary, it could be concluded that the estrogens can be useful in the treatment of postpartum depression and menopause related depression, especially if surgically induced. There is still no support for the usefulness of estrogen treatment in non-reproductive related mood disorders. Regarding its utility in schizophrenia, several studies have considered the possibility of adding estrogen treatment in the cases in which patients with schizophrenia experience a worsening of their symptoms clearly related with the fluctuations of the hormonal levels during the menstrual cycle or in patients with resistant forms of the illness. Furthermore, hormone replacement therapy could be useful in some postmenopausal schizophrenic women.

Key words: *Estrogen treatment. Depression. Schizophrenia. Menopause. Postpartum depression.*

Resumen

La relación entre las hormonas sexuales femeninas y los diversos trastornos psiquiátricos ha sido poco estudiada hasta estas últimas décadas; sin embargo, en los últimos años han ido apareciendo numerosos trabajos que examinan la influencia de los estrógenos en la aparición, pronóstico y tratamiento de los trastornos mentales. Aunque los datos son todavía preliminares, se podría concluir que los estrógenos pueden ser útiles en el tratamiento de la depresión posparto y en la depresión relacionada con la menopausia, especialmente en la menopausia quirúrgica. En la actualidad no existen pruebas de la utilidad del tratamiento estrogénico en los trastornos depresivos no relacionados con el ciclo reproductivo. Respecto a su utilidad en la esquizofrenia, se podría considerar la posibilidad de añadir tratamiento estrogénico en los casos en que las pacientes con esquizofrenia experienten un empeoramiento de los síntomas, claramente relacionado con las fluctuaciones de los niveles hormonales a lo largo del ciclo menstrual, o en pacientes resistentes a la medicación neuroléptica. También podría ser útil el tratamiento hormonal sustitutivo en pacientes posmenopáusicas.

Palabras clave: *Tratamiento estrogénico. Depresión. Esquizofrenia. Menopausia. Depresión posparto.*

INTRODUCTION

The relationship between female sexual hormones and different psychiatric disorders was hardly studied until the last few decades. However, in order to treat mental disorders in women better, the need for knowledge about the hormonal cycle of the woman and the hormonal changes occurring during it seems to be increasing. In the last few year, many studies that examine the influence of estrogens on the onset, prognosis and treatment of different psychiatric disorders have been appearing. In a near future, collaboration between psychiatric and gynecology and obstetrics professionals could be considered; this would help to improve the approach to those patients who could benefit from the use of sexual hormones in the treatment of psychiatric disorders.

This article reviews the relationship between estrogens and different psychiatric disorders, placing special emphasis on the aspects related to the treatment.

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ESTROGENS AND NEUROTRANSMITTERS

Gonadal hormones determine the patterns of female and male development and influence physiology both genomically as well as through membrane mechanisms. Sexual hormones affect the neuronal functions, regula-

ting synthesis and the activity of enzymes, neurotransmitters, receptors and effectors.

1. The brain dopaminergic systems are sexually dimorphic. In some dopamine rich areas, there are receptors for progesterone and estrogen. Estrogens seem to have short term rapid membrane effects through the alteration of the function in the dopaminergic synapsis and also some longer term genomic effects, modifying the synthesis of the dopamine receptors[1]. Studies in animals have shown that estrogens have antidopaminergic properties since they reduce dopamine concentrations and sensitivity of the dopamine D_2 receptors[2,3].
2. There is abundant evidence in basic research studies that show that estrogens modulate serotonin neurotransmission in many aspects. Estrogens down-regulate the 5-HT_2 receptors, increase the release of endogeneous catecholamines from the hypothalamus and inhibit monoamine-oxidase. In studies with animals, it has been found that the 5-HT levels increase due to displacement of trypotphan (precursor of 5-HT) from albumin and the estrogens increase the number of sites available for active transportation of 5-HT towards the brain cells[4].
3. Steroids are also potent bimodal modulators of the GABA-A receptor. Given that this receptor controls neuronal excitability, its regulation has important physiological and pharmacological consequences. Certain metabolites of the progesterone (3α-5α tetrahydroprogesterone THP, and 3α-5α tetrahydrodeoxycorticosterone) are agonists of the GABA-A receptor, while pregnenolone sulfate (PS) and dihydroepinandrosterone sulfate (DHEAS) are antagonists of this receptor. The brain distribution of gabaergic steroids is sexually dimorphic. During the luteal phase and in pregnancy, the THP levels in plasma and brain are increased and exert a sedative and anxiolytic action. It is possible that its premenstrual or postpartum decrease can explain a worsening of anxiety similar to that observed due to abstinence of benzodiazepines[5]. The estrogens also seem to have an up-regulation of the GABA-A receptor. Thus, the fluctuations of progesterone, THP and estrogens during the menstrual cycle may contribute to the changes that are produced in mood in some women[6].

TREATMENT WITH ESTROGENS OF DEPRESSIVE DISORDERS

Depression is more prevalent in women than in men (2:1 ratio) and, furthermore, has some different clinical and prognostic characteristics. Several longitudinal studies performed in patients with depression have shown that the women more frequently present a more chronic course with more frequent and prolonged recurrences than men. Greater comorbidity with other psychiatric disorders in women has also been found. The differences in the response to treatment are still not very conclusive; in general, women may have more frequent side effects to the usual doses and the need to adjust the medication in the premenstrual period and if sexual hormones are taken should be taken into account[7].

Estrogens in the treatment of postpartum depression

In the postpartum period, incidence of psychiatric admissions increases significantly in the first six months regarding other periods of the life of the woman[8].

Postpartum depression generally occurs between 2-4 weeks after delivery and the potential negative consequences for the cognitive emotional development of the newborn are added to the negative consequences for the mother that arise from the seriousness itself of depression. Prevalence rates for post-partum depression seem to range from 12-15 %. Appearance of the first depressive episode coinciding with puerperium is frequent and women with a previous depressive disorder have an increased risk of developing depression during postpartum. A history of previous post-partum depression significantly increases the risk of other puerperal depressive episodes[10].

Several studies have found a positive response to the administration of estrogens in post-partum depression[11], and in puerperal psychosis[12]. In a recent study[13], 23 patients who suffered post-partum depression were treated with sublingual 17β−estradiol for eight weeks. The estradiol concentrations were measured in baseline blood and weekly. It was found that in the baseline evaluation, the patients had low levels of estradiol. The patients improved significantly after the first week and the estradiol levels increased. At the end of the second week, 19 of the patients showed clinical recovery of the depression (according to the score on the Montgomery-Asberg Depression Rating Scale [MADRS]).

It also seems that the administration of estrogens prophylactically after delivery in women having a high risk of developing an affective disease during postpartum significantly reduces the risk of relapses. Sichel et al.[14] treated 11 women with a background of severe affective disorder prophylactically with high dose estrogens immediately after the delivery and reduced the hormone doses in 4 weeks. The patients remained asymptomatic during the year of the follow-up.

Estrogens in the treatment of premenstrual dysphoric disorder

Premenstrual dysphoric disorder can be considered a more serious subtype than the premenstrual syndrome. In this disorder, affective and anxiety symptoms predominate and interfere in the social functioning of the patients.

The treatments that have shown a clear effectivity in the premenstrual dysphoric disorder are selective serotonin reuptake inhibitor antidepressants and treatments that inhibit ovulation, such as GnRh analogues, estradiol and danazol patches[15]. Estrogens have been used in the treatment of premenstrual dysphoric disorder with unequal results. Two studies[16,17] that compared 17β-estradiol and norethisterone with placebo found that the hormonal treatment was more effective. Another study that used conjugated estrogens[18], however, did not find that these were more effective than the placebo.

Although treatment with contraceptives has been used, it does not seem that they improve the depressive symptoms and, in some patients, they can worsen them[19].

Estrogens in the treatment of depression associated to menopause

Menopause and depression

Perimenopause is defined as the period in which the menstrual cycle duration varies due to frequent anovulatory periods with an important fluctuation of the circulating gonadal hormones and it is the interval between regular ovulatory menstrual cycles and the complete cessation of the ovarian function. Menopause is the permanent cessation of menstruation as a result of the loss of ovarian follicular activity and it is considered to be established after twelve months of spontaneous amenorrhea.

The possible relationship between perimenopause, menopause and appearance of affective disorders is a controversial subject. In general, the longitudinal studies in general population have not found that there is an increase in the risk of depression in most of the women during perimenopause[20-22]. The studies in women who come to gynecology visits, on the contrary, find a higher prevalence of depressive symptoms in women during perimenopause. It has also been found that there is more risk of depression in surgical menopause than in the natural one[21]. Finally, it seems that women with a background of affective syndromes related with hormonal changes, as those related with the taking of hormonal contraceptives, premenstrual dysphoric disorder or postpartum depression, can have a higher risk of presenting depression coinciding with perimenopause[23]. In general, it can be concluded that although some studies have found that the appearance of major depression is slightly associated with perimenopause, however, after menopause, the risk of depression not only does not increase but decreases[24].

Estrogenic treatment of depression associated with menopause

The efficacy of hormone replacement therapy in the improvement of mood status is still a subject of debate. The fact that many of the studies performed do not clearly distinguish between peri- or post-menopausal women makes it difficult to interpret the results. A qualitative meta-analysis study[25] found that estrogens seem to be effective in the treatment of depressive symptoms associated both to peri- as well as post-menopause, however the most consistent results are found in the treatment of depression in women with surgical menopause and in the cases of mild depression.

A double blind placebo controlled study that used scales to measure depression found that the administration of estrogens was useful to improve mood status in women with natural menopause who presented depression symptoms, but who did not fulfill the criteria of major depression[26]. Other studies that have found that estrogen replacement therapy can be useful in depressive disorders are:

1. Schmidt et al.[27] evaluated the efficacy of estradiol in the treatment of major and minor depression in perimenopausal women in a double blind study. After three weeks of treatment with HRT, a significant difference was found in the improvement of the depressive symptoms among women treated with HRT and those treated with placebo.
2. In another more recent study, by Rasgon et al.[28], 16 patients who fulfilled criteria of major depression received treatment with HRT (10 received it in single drug therapy and 6 patients as treatment associated to fluoxetine due to lack of response). All the patients improved their depression (measured with the Hamilton depression rating scale) after the first week of treatment. Of the patients who received HRT as single drug therapy, 6 were in remission of the depressive episode, 3 responded partially and one patient did not respond at 8 weeks. Of the 6 patients who received fluoxetine and HRT, 1 patient experienced remission and 5 patients a partial response.
3. In a double blind study[29], Soares et al. compared the effect of transdermal 17β-estradiol and placebo for 12 weeks in 50 patients in perimenopause with depression (major, minor and dysthmic depression). The patients showed a good response to hormonal treatment, regardless of the diagnosis.

These studies seem to also suggest that the antidepressant effect of HRT is independent of its effects on the physical manifestations of perimenopause such as hot flushes.

The fact that estrogens can induce the appearance of rapid cycles or, at least predispose to the appearance of tricyclic induced rapid cycles, seems to also indicate an antidepressant effect of them. On the other hand, progesterone can suppress rapid cycles[30]. Furthermore, the addition of progesterone can decrease the beneficial effect of the estrogens on mood[25].

There have also been studies that assess the efficacy of the utilization of estrogen therapy as a treatment that potentiates the medication with antidepressants in postmenopausal women and the results have been contro-

versial. While a study with elderly women with depression who received fluoxetine found a positive interaction between the addition of estrogens to the treatment and the therapeutic response[31], another study did not confirm these results[32].

A promising treatment in the field of estrogen therapy is selective estrogen receptor modulators (SERMs) that are estrogenic compounds that do not affect the mammary or uterine tissue. Raloxifene is a first generation SERM and seems to act on dopamine and serotonin in a similar way as to the conjugated estrogens[33]. There are still no studies on its usefulness in psychiatric disorders. An interesting study is that performed by Jarkova et al.[34] who, in a double blind study to assess the action of raloxifene in prevention of osteoporosis, also studied its effect in the mood status in a subgroup of women who did not present depression. They assessed the depressive symptoms with the Hamilton scale and found that the scores on the scale decreased in the women under treatment with raloxifene while this was not so in those treated with placebo.

Estrogens in the treatment of depressive disorders not related with menopause

There are few studies that have evaluated the usefulness of estrogen therapy in single drug therapy as treatment of depression not related with menopause and none of them found that it was useful. A double blind study with placebo that used high doses of conjugated estrogens in 40 pre and postmenopause patients with serious depression[35] found that although the patients improved more with the estrogen treatment than with the placebo, they did not totally recover from the depression. Regarding the use of estrogens as a potentiating treatment in resistant depression, the few studies done that added estrogens to patients who did not respond to treatment with tricyclic antidepressants found negative results[25].

As conclusions and although the results are preliminary, it seems that estrogens, either alone or associated to antidepressants, could be useful in the treatment of postpartum depression and in depression related with menopause, especially in surgical menopause. At present, there is no proof of the usefulness of estrogen treatment in depressive disorders not related with the reproductive cycle.

TREATMENT OF SCHIZOPHRENIA WITH ESTROGENS

The evidence that schizophrenia in women is less frequent, has a later onset and generally has a less serious course[36] has led several authors to propose the «estrogen hypothesis» of schizophrenia. This hypothesis proposes the existence of an estrogen protector effect in women with a vulnerability to present the disease.

This hypothesis has been contrasted in several studies. Several studies have found that the levels of estrogen in schizophrenic women are significantly lower than in healthy women[37], and that the onset of the disease or relapses appear more frequently coinciding with the menstrual cycle phases with low levels of estrogens38. Riecher-Rösler et al.[37] studied 32 patients with schizophrenia admitted for an acute episode who had a history of regular menstrual cycles. The results were that most of the patients had lower levels of estradiol and progesterone compared with healthy women. In addition, on studying the correlation between the different phases of the menstrual cycle and symptoms, they found that the symptoms worsened during the phase of the cycle with low levels of estrogens and improved during the phase with high levels (except for the symptoms of anxiety and depression). Other authors have found similar results[39,40]. In a more recent study, however, Choi et al.[41], who also investigated the evolution of the symptoms during the menstrual cycle in 30 hospitalized patients with schizophrenia, found that the most affective and somatic symptoms worsened in the premenstrual period while no significant differences were found in the psychotic symptoms.

An interesting study is that of Hoff et al.[42] who studied the association between the estrogen and progesterone levels and different cognitive functions in a sample of 22 patients with schizophrenia. The results indicated that the highest levels of estrogens were associated to better performance in several cognitive areas, especially those related with memory. However, they did not find any correlation between estrogen levels and psychotic symptoms.

The modulator effect of estrogens on the dopaminergic system has led to the study of the possibility of their therapeutic use in patients with schizophrenia.

In an open study performed by Kulkarni et al.[43], estradiol was added in 11 premenopausal women with acute psychotic symptoms and a faster improvement of the psychotic symptoms was obtained. These differences, however, lessened at 15 days of treatment and the final recovery was equal in one group and the other. In a more recent study of Kulkarni et al.[44], the usefulness of adding estrogen treatment in the form of transdermal estradiol to a standard neuroleptic treatment was investigated in a double blind study and it was compared with adding placebo to the neuroleptic treatment and they found that the response to adding estrogens was significantly better. A study of Lindamer et al.[45] examined the psychopathology of patients with post-menopausal schizophrenia and found that the patients who were under hormone replacement treatment took lower doses of antipsychotic treatment and presented fewer negative symptoms while no differences were found in the positive ones.

Some open studies have demonstrated that estrogen treatment can be useful in the treatment of tardive dyskinesia[46].

As conclusions, and although the data are still very preliminary, some studies indicate that the estrogens associated to neuroleptic treatment could be useful in the cases in which the patients with schizophrenia experience a worsening of the symptoms clearly related with the fluctuations of the hormonal levels during the mens-

trual cycle or in patients resistant to antipsychotic medication.

Hormone replacement treatment could also be useful in postmenopausal patients.

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