A guide to the treatment of depression in women by estrogens

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ABSTRACT

Premenstrual depression, postnatal depression and climacteric depression are related to changes in ovarian hormone levels and can be effectively treated by hormones. It is unfortunate that psychiatrists have not accepted this form of treatment and this paper is an attempt to simplify this treatment, which should include transdermal estrogens, possibly testosterone and, if the woman has a uterus, also progestogen. A balance is often necessary between these three hormones.

Transdermal estrogens in the appropriate dose will suppress ovulation and suppress the cyclical hormonal changes that produce premenstrual depression. Estrogens also have a mood-enhancing effect in postnatal depression and the depression in the transitional phase of the menopause. It is possible to add transdermal testosterone which will improve mood, energy and libido. The problem is the progestogen as these women are often progestogen-intolerant. Progestogen should be used in the lowest dose and for the shortest duration necessary to prevent endometrial hyperplasia or the return of premenstrual syndrome-type symptoms if the women are progestogen-intolerant. The use of estrogens for depression in these women does not exclude the use of antidepressants. Hormone-responsive depression cannot be diagnosed by measuring hormone levels but can only be diagnosed by a careful history relating depression to the menstrual cycle, pregnancies and the perimenopausal years. These appropriate questions should prevent the endocrine condition of premenstrual depression being misdiagnosed as bipolar disorder and the woman given inappropriate treatment.

INTRODUCTION

For those who believe that there is a hormonal cause for specific forms of depression in women, it is disappointing that so few women are treated with hormones. This may be because psychiatrists do not believe the literature or because they are not familiar with the subtleties or route, dose or combination of hormones[1]. By avoiding such treatment, they will be spared having to cope with the minor problems of hormone therapy, such as irregular bleeding or breast discomfort, which are easy enough to deal with but which will be outside the experience and training of psychiatrists. But their patients may suffer. The purpose of this paper is to outline the recognition of hormonal depression, the indications and the simple details of therapy, together with the minor complications of hormone treatment, thus making this therapy available as first choice for the depressed women who might benefit from it.

No doubt the more serious side-effects reported in the 2002 study from the Women's Health Initiative (WHI)[2] are reason enough for many psychiatrists not to attempt this course of therapy. But, in reality, these specialists have never been interested in hormone therapy. Subsequent reports from the same group have made it clear that these problems occurred in women who started a combined oral estrogen and progestogen preparation when 20 years past the menopause or over the age of 70 years[3]. Those women discussed in this paper are younger premenopausal women receiving transdermal estrogens, without the small risk of venous thrombosis or stroke found with the oral route of administration[4]; moreover, as little progestogen as possible is used because the major complications of hormone therapy seem to result from the progestogen component.

There are many types of depression which occur in women who experience depression at times of hormonal fluctuation

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OPINION

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that can be effectively treated by estrogens[5]. These are the monthly cyclical premenstrual depression of premenstrual syndrome (PMS) (or premenstrual dysphoric disorder (PMDD) to psychiatrists)[6,7], the postnatal depression that occurs several weeks or months after delivery[8,9], and also the depression in the months of hormonal fluctuations that occur in the transition phase of the climacteric before the periods stop[10–12]. It has been suggested that this group of estrogen-responsive mood disorders, premenstrual depression, postnatal depression and perimenopausal depression, should be known as 'reproductive depression' in order to stress the importance of gonadal hormones in the etiology and the possible effective treatment of these common conditions.

These conditions often occur in the same vulnerable woman who may be first seen by the general practitioner or psychiatrist as a depressed 45-year-old. This is a common event. She will usually have a history of premenstrual depression in her younger years and, typically when the cycles cease during pregnancy, she enjoys good mood throughout the pregnancy, in spite of possible problems of nausea and other obstetric complications. After delivery, the same woman will often experience postnatal depression that may last for many months or years. When the periods recur, the depression becomes cyclical as premenstrual depression again. This can last for many years, often becoming more severe and less cyclical as the menopause approaches. During all of this time, she may be treated with antidepressants or mood-stabilizing drugs or even electroconvulsive therapy for severe refractory depression when a range of selective serotonin receptor inhibitors (SSRIs) have failed to help[13].

This history may take place over 20 years, with profoundly deleterious effects upon general health, employment, marriage and sexuality and without any apparent improvement in the depression. After this time, it is more difficult to help with estrogens because patients have become dependent upon their psychoactive drugs, their psychiatrist or their psychologist. It is easy to understand why the prescription of antidepressants has increased fourfold in the last 10 years[14] in spite of the reported side-effects of weight gain, mental confusion, loss of libido and the doubling of fatal stroke[15].

After the menopause, there is less excess of depression in women compared with men of similar age. Also, the evidence that estrogens help postmenopausal depression is less clear[16], although estrogens will help insomnia and tiredness due to vasomotor night sweats, with an improvement in mood. Similarly, estrogens for treatment of vaginal atrophy causing dyspareunia, marital problems and recurrent attacks of 'cystitis' can improve marriage and mood in the postmenopausal woman, but their beneficial effect on endogenous depression is unconvincing. It is tempting to be pedantic and state that estrogens should be used for specific symptoms of the menopause in postmenopausal women and not primarily as a treatment of depression, but, in the reality of clinical practice, estrogens often do help the depression of the postmenopausal years, with or without characteristic vasomotor symptoms or symptoms of pelvic atrophy[15].

DIAGNOSIS OF HORMONE-RESPONSIVE DEPRESSION

Fundamental to the treatment of depression by hormone therapy is the correct diagnosis of an estrogen-responsive type of depression. The most important fact to appreciate is that the measurement of hormone levels is not in any way helpful. All of the examples given are in premenopausal women who have normal levels of estradiol, follicle stimulating hormone and testosterone which, although they may not be optimal for the patient, will be within the normal wide range. It is common for patients, who believe their depression is 'hormonal' because the severity or even its occurrence changes with the menstrual cycle, to visit their general practitioner only to be told that the hormone levels are normal and therefore they should not have hormone therapy. Hormone levels will be normal because the patients are premenopausal and an opportunity for effective treatment has been lost.

It is their history that is the most important factor in differentiating this diagnosis from other causes of depression, particularly bipolar disorder. This is not an uncommon misdiagnosis of hormone-related depression. It is well recognized that the severity of bipolar and unipolar disorder frequently changes with the menstrual cycle, but the frequent diagnostic confusion between these psychiatric disorders and PMDD, which requires very different therapy, is not recognized[17]. **[AQ4]**

Perhaps the most important clue is the relationship to periods. These women may have troublesome PMS as teenagers and, although they may learn to cope with it in early adult life, it still affects their relationships and their work. It may be associated with heavy and painful periods, and patients should be asked how many good days a month they enjoy. It is important to realize that they almost invariably have runs of many good days (as much as 10–20 good days each month) when they have no depression. Apart from the relief of not having depression on these good days, women with PMDD do not experience the mania or the highs associated with bipolar disorder.

These women will have a history of having a good mood in pregnancy when all gonadal/placental hormone levels are elevated and constant. Many of these perimenopausal women with a long history of depression will say that they last felt well during their last pregnancy many years previously. This is an important clue to the diagnosis of a depression that will respond to estrogens. A history of postnatal depression in one or more of the previous pregnancies is also a strong marker for a depression that has a hormonal basis[1,18].

TREATMENT OF HORMONE-RESPONSIVE DEPRESSION

The first controlled trial of estrogens was in 1979 by Klaiber and colleagues[19], who treated a group of women who had been hospitalized with recurrent depression of many types and who were prescribed very large doses of oral estrogen. Doses of Premarin starting at 5 mg increasing to 25 mg daily were

used, with significant improvement in depression regardless of diagnosis. This study has not been repeated because of subsequent caution about dose. However, there have been positive results for the three hormone-related types of reproductive depression using physiological doses of estrogens given by a non-oral route[6–12].

Premenstrual depression

PMS has been renamed premenstrual dysphoric disorder (PMDD) by the American Association of Psychiatrists (AAP) in the DSM IV report. This has done nothing to clarify the condition but, by using the term 'dysphoric', it clearly promotes PMDD as a psychiatric condition rather than the more logical endocrine condition. The change of name by the AAP is about territory and reimbursement rather than a greater understanding. Perhaps ovarian cycle syndrome is a more useful label as it clearly emphasizes the role of the monthly endocrine cycles of the ovary.

As premenstrual depression and other cyclical disorders of this syndrome are related to ovulation, it is logical that the mainstay of treatment should be the suppression of ovulation and the removal of the cyclical hormonal changes (whatever they are) which produce the cyclical symptoms of this condition. It is likely that the essential cause of premenstrual depression is the intolerance to endogenous progesterone following ovulation, and it is regrettable that such patients are also progestogen-intolerant to any progestogens administered[20], and these progestogenic side-effects are both dose- and duration-dependent[21]. Any progestogen used for endometrial protection in these patients should be one that produces the least symptoms given in the lowest effective dose and for the least number of days.

It is for this reason that the birth control pill, although suppressing ovulation and cycles, is not so effective because of the daily progestogen for 21 days a month. Even taking the birth control pill back-to-back without a break removes all fluctuations but, in some patients, the progestogen component remains a problem and the PMS-type symptoms become continuous rather than cyclical. The progestogen drospirenone is an antiandrogenic progestogen contained in the oral contraceptives Yasmin and Yaz (Bayer Pharma, Berlin, Germany). These have been claimed to be effective for the treatment of PMS[22] and have been recommended by some to be suitable as first-line therapy[23].

An effective hormone therapy for severe PMS is the use of transdermal estrogens for suppression of ovulation[24]. This can be given by gel (2.5–5.0 g daily), patch (200 μg twice weekly) or – in those patients who have already responded well to transdermal estrogens – an estradiol implant of 50 mg every 6 months, which gives long-term therapy[25]. The women should be warned that they may feel less well in the first 2 weeks – rather like the mood changes seen in early pregnancy – and that the treatment may not work for the 1st month until ovulation has been suppressed. Oral estrogens may also be effective, but there are no published studies to support this.

The patients will need progestogen to prevent endometrial hyperplasia and irregular bleeding but, because of the progestogen intolerance found in these women, a smaller dose for shorter duration is recommended, usually in the form of 2.5 mg of norethisterone or 100 mg of Utrogestan for the first 7 days of each calendar month; this will produce a regular withdrawal bleed on about day 10 of each calendar month. Re-setting the periods in this way prevents abnormal bleeding; instead, normal, usually scanty, bleeding occurs at a predictable time of the month. Another minor advantage of this regimen is that periods now occur 12 times a year rather than 13.

Suppression of ovulation and ovarian function by gonadotropin releasing hormone (GnRH) analogs is a most useful treatment[26–28] as well as a diagnostic and therapeutic test for women who may wish to have a hysterectomy and bilateral oophorectomy to solve this problem[29]. Such treatment is not inexpensive. Moreover, as the monthly injections produce menopausal symptoms of hot flushes and sweats and loss of bone density, GnRH analogs are usually accompanied by 'add back' of standard HT preparations of estrogen and progestogen[30]. Once again, although the progestogen is necessary to protect the endometrium, it may produce progestogen PMS-type side-effects. One way to avoid the use of progestogen is to use tibolone, which does not produce a withdrawal bleed[31].

If symptoms of progestogen intolerance cannot be ameliorated by a change of progestogen or a lower dose, then the insertion of a Mirena intrauterine system (IUS) is recommended. This should be replaced every 5 years, but it does allow the woman to have effective abolition of the cycles and avoid troublesome irregular bleeding[20]. The Mirena IUS is a very effective treatment. However, systemic absorption does occur, producing continuous symptoms of depression, tiredness and bloating[32] in about 10% of women with progestogen intolerance. These disappear within 24 h of removal of the IUS.

These patients often experience loss of energy and libido, particularly if they have been taking antidepressants for some time. This can have a very distressing effect upon their sexual relationships and self-esteem but can be corrected by the use of transdermal testosterone[33]. The testosterone patch can be used in the dose of 100 μg twice weekly[34], or testosterone gel can be given in the appropriate dose, which would be approximately one-tenth of the daily male dose. After improvement is well established and if implants are being used, a 100-mg pellet of testosterone can be added to the 50-mg estradiol implant. For long-term therapy, an implant every 6 months and a Mirena IUS every 4 years is a simple uncomplicated treatment which can even be continued for many years past the menopause[35]. If this dose or lesser doses and the interval between implants are maintained over the years, tachyphylaxis will be avoided.

Another method of suppressing ovulation and preventing progestogen intolerance is to use the antiandrogen cyproterone acetate, 25 mg daily. It is also a contraceptive, being very effective in women with acne or with excess hair and aggression. It will remove severe cyclical PMS symptoms but is totally unproven as a trial has not been attempted – no doubt because it is a cheap, out-of-patent, low-profit drug. But it does work.

These regimes of therapy do presuppose that the condition is an endocrine one and not psychiatric. Apart from depression and loss of energy, PMS is often associated with cyclical somatic symptoms such as mastalgia, bloating and headaches that would also be removed when the cycles are abolished by any of the regimens described. The most important advice to women with severe PMS is to avoid any psychiatrist or general practitioner who does not offer this hormone therapy as an option.

POSTNATAL DEPRESSION

Nobody would understate the seriousness of this condition, which may occur in up to 10% of healthy women weeks or months after delivery and last for several years. It is not the 'baby blues' occurring in the week after delivery. It is usually treated with varying success by antidepressant drugs, psychotherapy or admission to a mother-and-baby unit, but, once again, the association with profound abrupt hormonal changes after childbirth should point to a hormonal etiology. Depression has been reproduced experimentally in women with a history of postnatal depression by creating a pseudo-pregnancy by hormonal manipulation, which is then suddenly discontinued[36]. Although estradiol has been shown to be effective in the treatment of postnatal depression, even in those who have inadequately responded to antidepressants[8,37], psychiatrists rarely use this therapy, although obstetricians are increasingly using it. Progesterone and progestogen have been recommended, but there is no evidence that they work. On the contrary, studies have shown them to be ineffective[38] and a Cochrane report has agreed that estrogen improves mood in postnatal depression and norethisterone makes depression worse[39].

The recommended hormonal treatment is with transdermal estrogens. The original study used 200-μg patches twice weekly with clear benefit but larger doses may be used. Once again, the equivalent dose of estradiol gel such as 2.5–5.0 g EstroGel (Ascend Therapeutics) twice daily is an alternative. Although the original study investigated women who were not breastfeeding, there is no objection to the use in such patients as estrogens will not suppress breast-feeding once it is established and, although present in the breast milk, estrogens will have no adverse effect on the neonate regardless of gender. As a transdermal preparation, it is not associated with venous thrombosis in the puerperium[4].

This treatment can continue for as long as necessary; this may be for more than a year and will no doubt be required when the periods return and cyclical PMDD-type symptoms occur. It is unlikely that estrogens will replace antidepressants as first-line therapy even if they are a more effective and logical treatment. The advice that a combination of both estrogens and antidepressants should be used is sound and should be considered[15].

It should be recognized that postnatal depression may be the turning point in the mental health of a woman who later consults her medical practitioner with a long history of depression, which started years after a pregnancy associated with good mood and a complete absence of the depression which started after delivery. This is followed by a downward spiral of depression and drugs which could have been avoided if estrogens had been the initial therapy for this hormone-related mental problem. These middle-aged women will report that they were last well when they were last pregnant, and that depression occurred in the postnatal months, later becoming cyclical again as periods reappear.

PERIMENOPAUSAL DEPRESSION

Perimenopusal depression is due to a mixture of many problems, which may dependent on the hormonal status. The simplest and most predictable result of estrogen therapy is the relief of vasomotor symptoms such as hot flushes and night sweats, which produce insomnia, tiredness, inefficiency and depression. Nevertheless, there is currently a move to use SSRI drugs for this indication. Veloflaxine is recommended[40], although its withdrawal is difficult and it is not as effective as estrogens. Pelvic atrophy following a decrease in estrogens results in vaginal dryness and discharge, painful intercourse, loss of libido and cystitis following dry uncomfortable intercourse. These problems can be removed by any of the standard HT preparations, either oral or transdermal, using low doses with cyclical or continuous progestogen. There are many such preparations. [AQ5]

There is also depression in the transitional phase, before cessation of periods not associated with vasomotor or atrophy symptoms that respond to estrogens[41]. This perimenopausal depression begins many years before the periods cease and is responsive to estrogens[10,42], more responsive than the depression which occurs in the older postmenopausal woman[10,16].

Once again, transdermal hormones are to be preferred – either by patch[11], gel[36] or implant[11] – in the same doses used as above for premenstrual depression. It has been suggested that depressed women in the climacteric taking antidepressants should also receive estrogens to improve the response[43].

Women who still have a uterus need cyclical progestogens or a Mirena IUS. However, if the patient has had a hysterectomy, progestogens are not required but, if she has also had a bilateral oophorectomy and lost her ovarian androgens, she will benefit from additional testosterone for correction of libido and energy problems as well as improvement of mood and headaches[44].

THE ROLE OF SURGERY

Women with PMS or perimenopausal depression often have progestogen intolerance and suffer a recurrence of PMS-type symptoms with the 7 or more days of progestogen therapy. The response to this is to use another less androgenic progestogen at a lower dose or for an even shorter duration. Transdermal progesterone gels are not useful since little if any is absorbed and they do not give endometrial protection[45]. A natural progesterone such as Utrogestan or Mirena IUS can be used. If this fails, there is a choice between stopping all hormone therapy or agreeing to a hysterectomy and bilateral oophorectomy.

There is not much to choose between these alternatives, as progestogens are still required after endometrial ablation and embolization is inappropriate. These procedures are mentioned in order to stress the lengths to which patients and doctors will go in order to avoid the more logical and effective treatment of these persistent problems. Successful surgical treatment of severe PMDD has been reported in many studies[35], and, in more general terms, hysterectomy has been shown to have a beneficial effect on mood[46], no doubt because of the combined effect of the removal of PMDD and other cyclical symptoms[35]. The fact that 4% of women die of uterine, cervical or ovarian cancer should not be forgotten when this decision is being contemplated[47].

With the correct selection, this surgery is associated with a virtually 100% total permanent cure of PMS and other cyclical symptoms of heavy painful periods, mastalgia, menstrual migraine and monthly abdominal bloating. It should not be regarded as a radical treatment of last resort as the health benefits are enormous. The full operation is required because conservation of the ovaries will not abolish the cyclical symptoms[48]; moreover, the hormone therapy already in place will prevent postoperative menopausal symptoms[39] and should be continued. To remove the ovaries without a hysterectomy, although a shorter procedure, is not sensible as estrogens and progestogens will be necessary for relief of estrogen deficiency in women who are both premenopausal and progestogen-intolerant. Also, the use of estrogens and progestogens will reproduce the PMDD symptoms and periods, and these may be as bad as the patient's usual premenstrual and menstrual symptoms. The surgery can be performed laparoscopically with a 1- or 2-day hospital stay.

CONCLUSION

This paper is an attempt to encourage psychiatrists, general practitioners and gynecologists to consider the use of estrogens in certain forms of depression in women. This is not proposed as a treatment for all types of depression but specifically for those showing a temporal relationship between hormonal changes and the occurrence of depression. These would include premenstrual depression, postnatal depression and climacteric depression, particularly in those women in the menopausal transition before the periods cease. These conditions have all been shown to be responsive to estrogens in randomized, double-blind trials over the last 20 years but, nevertheless, this modality of treatment is rarely used by psychiatrists. No doubt, professional reasons based upon training and unfamiliarity with hormone therapy explain this. This treatment is reliant upon a balance between three major hormones. In general terms, estrogen improves mood[46,49] and testosterone improves mood, energy and libido[31,32]. The problem is progestogen, or even the natural progesterone, which may produce depression, loss of energy and recurrence of PMS-type symptoms[21]. The use of 7 days of progestogen is a compromise from the 12-day orthodoxy but has been shown to offer adequate endometrial protection[50]. The challenge is correctly to diagnose hormone-responsive depression in women and apply the correct proportion of these hormones, depending upon their needs and response to therapy.

Conflict of interest The author was previously involved in this study as an external medical expert and has no conflicts of interest to report.

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