

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 hormones¹. 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 years³. 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 administration⁴; 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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1 that can be effectively treated by estrogens⁵. These are the
 2 monthly cyclical premenstrual depression or premenstrual
 3 syndrome (PMS) (or premenstrual dysphoric disorder
 4 (PMDD) to psychiatrists)^{6,7}, the postnatal depression that
 5 occurs several weeks or months after delivery^{8,9}, and also the
 6 depression in the months of hormonal fluctuations that occur
 7 in the transition phase of the climacteric before the periods
 8 stop¹⁰⁻¹². It has been suggested that this group of estrogen-
 9 responsive mood disorders, premenstrual depression, postna-
 10 tal depression and perimenopausal depression, should be
 11 known as ‘reproductive depression’ in order to stress the
 12 importance of gonadal hormones in the etiology and the pos-
 13 sible effective treatment of these common conditions.

14 These conditions often occur in the same vulnerable woman
 15 who may be first seen by the general practitioner or psychia-
 16 trist as a depressed 45-year-old. This is a common event. She
 17 will usually have a history of premenstrual depression in her
 18 younger years and, typically when the cycles cease during
 19 pregnancy, she enjoys good mood throughout the pregnancy,
 20 in spite of possible problems of nausea and other obstetric
 21 complications. After delivery, the same woman will often
 22 experience postnatal depression that may last for many
 23 months or years. When the periods recur, the depression
 24 becomes cyclical as premenstrual depression again. This can
 25 last for many years, often becoming more severe and less
 26 cyclical as the menopause approaches. During all of this time,
 27 she may be treated with antidepressants or mood-stabilizing
 28 drugs or even electroconvulsive therapy for severe refractory
 29 depression when a range of selective serotonin receptor inhib-
 30 itors (SSRIs) have failed to help¹³.

31 This history may take place over 20 years, with profoundly
 32 deleterious effects upon general health, employment, marriage
 33 and sexuality and without any apparent improvement in the
 34 depression. After this time, it is more difficult to help with
 35 estrogens because patients have become dependent upon their
 36 psychoactive drugs, their psychiatrist or their psychologist. It
 37 is easy to understand why the prescription of antidepressants
 38 has increased fourfold in the last 10 years¹⁴ in spite of the
 39 reported side-effects of weight gain, mental confusion, loss of
 40 libido and the doubling of fatal stroke¹⁵.

41 After the menopause, there is less excess of depression in
 42 women compared with men of similar age. Also, the evi-
 43 dence that estrogens help postmenopausal depression is less
 44 clear¹⁶, although estrogens will help insomnia and tiredness
 45 due to vasomotor night sweats, with an improvement in
 46 mood. Similarly, estrogens for treatment of vaginal atrophy
 47 causing dyspareunia, marital problems and recurrent
 48 attacks of ‘cystitis’ can improve marriage and mood in the
 49 postmenopausal woman, but their beneficial effect on
 50 endogenous depression is unconvincing. It is tempting to
 51 be pedantic and state that estrogens should be used for
 52 specific symptoms of the menopause in postmenopausal
 53 women and not primarily as a treatment of depression, but,
 54 in the reality of clinical practice, estrogens often do help
 55 the depression of the postmenopausal years, with or with-
 56 out characteristic vasomotor symptoms or symptoms of
 57 pelvic atrophy¹⁵.

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 com-
 mon 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 oppor-
 tunity for effective treatment has been lost.

It is their history that is the most important factor in dif-
 ferentiating this diagnosis from other causes of depression,
 particularly bipolar disorder. This is not an uncommon mis-
 diagnosis 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 recognized¹⁷.

[AQ4]

Perhaps the most important clue is the relationship to peri-
 ods. 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 bipo-
 lar 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 colleagues¹⁹, 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}.

9 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 progesterone-intolerant to any progestogens administered²⁰, and these progestogenic side-effects are both dose- and duration-dependent²¹. 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 progesterone 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 progesterone component remains a problem and the PMS-type symptoms become continuous rather than cyclical. The progesterone drospirenone is an antiandrogenic progesterone contained in the oral contraceptives Yasmin and Yaz (Bayer Pharma, Berlin, Germany). These have been claimed to be effective for the treatment of PMS²² and have been recommended by some to be suitable as first-line therapy²³.

An effective hormone therapy for severe PMS is the use of transdermal estrogens for suppression of ovulation²⁴. 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 therapy²⁵. 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 progesterone to prevent endometrial hyperplasia and irregular bleeding but, because of the progesterone 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 problem²⁹. 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 progesterone³⁰. Once again, although the progesterone is necessary to protect the endometrium, it may produce progesterone PMS-type side-effects. One way to avoid the use of progesterone is to use tibolone, which does not produce a withdrawal bleed³¹.

If symptoms of progesterone intolerance cannot be ameliorated by a change of progesterone 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 bleeding²⁰. The Mirena IUS is a very effective treatment. However, systemic absorption does occur, producing continuous symptoms of depression, tiredness and bloating³² in about 10% of women with progesterone 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 testosterone³³. The testosterone patch can be used in the dose of 100 µg twice weekly³⁴, 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 menopause³⁵. 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 progesterone 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.

1 These regimes of therapy do presuppose that the condition
 2 is an endocrine one and not psychiatric. Apart from depression
 3 and loss of energy, PMS is often associated with cyclical somatic
 4 symptoms such as mastalgia, bloating and headaches that
 5 would also be removed when the cycles are abolished by any
 6 of the regimens described. The most important advice to women
 7 with severe PMS is to avoid any psychiatrist or general practi-
 8 tioner who does not offer this hormone therapy as an option.
 9

11 **POSTNATAL DEPRESSION**

13 Nobody would understate the seriousness of this condition,
 14 which may occur in up to 10% of healthy women weeks or
 15 months after delivery and last for several years. It is not the
 16 ‘baby blues’ occurring in the week after delivery. It is usually
 17 treated with varying success by antidepressant drugs, psycho-
 18 therapy or admission to a mother-and-baby unit, but, once
 19 again, the association with profound abrupt hormonal changes
 20 after childbirth should point to a hormonal etiology. Depres-
 21 sion has been reproduced experimentally in women with a his-
 22 tory of postnatal depression by creating a pseudo-pregnancy by
 23 hormonal manipulation, which is then suddenly discontinued³⁶.
 24 Although estradiol has been shown to be effective in the treat-
 25 ment of postnatal depression, even in those who have inade-
 26 quately responded to antidepressants^{8,37}, psychiatrists rarely
 27 use this therapy, although obstetricians are increasingly using
 28 it. Progesterone and progestogen have been recommended, but
 29 there is no evidence that they work. On the contrary, studies
 30 have shown them to be ineffective³⁸ and a Cochrane report has
 31 agreed that estrogen improves mood in postnatal depression
 32 and norethisterone makes depression worse³⁹.

33 The recommended hormonal treatment is with transdermal
 34 estrogens. The original study used 200-µg patches twice
 35 weekly with clear benefit but larger doses may be used. Once
 36 again, the equivalent dose of estradiol gel such as 2.5–5.0 g
 37 EstroGel (Ascend Therapeutics) twice daily is an alternative.
 38 Although the original study investigated women who were not
 39 breastfeeding, there is no objection to the use in such patients
 40 as estrogens will not suppress breast-feeding once it is estab-
 41 lished and, although present in the breast milk, estrogens will
 42 have no adverse effect on the neonate regardless of gender. As
 43 a transdermal preparation, it is not associated with venous
 44 thrombosis in the puerperium⁴.

45 This treatment can continue for as long as necessary; this may
 46 be for more than a year and will no doubt be required when
 47 the periods return and cyclical PMDD-type symptoms occur. It
 48 is unlikely that estrogens will replace antidepressants as first-line
 49 therapy even if they are a more effective and logical treatment.
 50 The advice that a combination of both estrogens and antidepres-
 51 sants should be used is sound and should be considered¹⁵.

52 It should be recognized that postnatal depression may be
 53 the turning point in the mental health of a woman who later
 54 consults her medical practitioner with a long history of depression,
 55 which started years after a pregnancy associated with good
 56 mood and a complete absence of the depression which started
 57 after delivery. This is followed by a downward spiral of

depression and drugs which could have been avoided if estro- 58
 gens had been the initial therapy for this hormone-related 59
 mental problem. These middle-aged women will report that 60
 they were last well when they were last pregnant, and that 61
 depression occurred in the postnatal months, later becoming 62
 cyclical again as periods reappear. 63
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66 **PERIMENOPAUSAL DEPRESSION**

68 Perimenopausal depression is due to a mixture of many problems,
 69 which may dependent on the hormonal status. The simplest and
 70 most predictable result of estrogen therapy is the relief of vaso-
 71 motor symptoms such as hot flushes and night sweats, which
 72 produce insomnia, tiredness, inefficiency and depression. Nev-
 73 ertheless, there is currently a move to use SSRI drugs for this
 74 indication. Veloflaxine is recommended⁴⁰, although its with-
 75 drawal is difficult and it is not as effective as estrogens. Pelvic
 76 atrophy following a decrease in estrogens results in vaginal dry-
 77 ness and discharge, painful intercourse, loss of libido and cystitis 77 [AQ5]
 following dry uncomfortable intercourse. These problems can
 78 be removed by any of the standard HT preparations, either oral
 79 or transdermal, using low doses with cyclical or continuous
 80 progestogen. There are many such preparations. 81

82 There is also depression in the transitional phase, before
 83 cessation of periods not associated with vasomotor or atrophy
 84 symptoms that respond to estrogens⁴¹. This perimenopausal
 85 depression begins many years before the periods cease and is
 86 responsive to estrogens^{10,42}, more responsive than the depres-
 87 sion which occurs in the older postmenopausal woman^{10,16}. 87

88 Once again, transdermal hormones are to be preferred –
 89 either by patch¹¹, gel³⁶ or implant¹¹ – in the same doses used
 90 as above for premenstrual depression. It has been suggested
 91 that depressed women in the climacteric taking antidepressants
 92 should also receive estrogens to improve the response⁴³. 92

93 Women who still have a uterus need cyclical progestogens
 94 or a Mirena IUS. However, if the patient has had a hysterecto-
 95 my, progestogens are not required but, if she has also had a
 96 bilateral oophorectomy and lost her ovarian androgens, she
 97 will benefit from additional testosterone for correction of
 98 libido and energy problems as well as improvement of mood
 99 and headaches⁴⁴. 99

100 **THE ROLE OF SURGERY**

101 Women with PMS or perimenopausal depression often have
 102 progestogen intolerance and suffer a recurrence of PMS-type
 103 symptoms with the 7 or more days of progestogen therapy. 104
 105 The response to this is to use another less androgenic proges-
 106 togen at a lower dose or for an even shorter duration. Trans-
 107 dermal progesterone gels are not useful since little if any is
 108 absorbed and they do not give endometrial protection⁴⁵. A
 109 natural progesterone such as Utrogestan or Mirena IUS can
 110 be used. If this fails, there is a choice between stopping all
 111 hormone therapy or agreeing to a hysterectomy and bilateral
 112 oophorectomy. 113
 114

1 There is not much to choose between these alternatives, as
 2 progestogens are still required after endometrial ablation and
 3 embolization is inappropriate. These procedures are men-
 4 tioned in order to stress the lengths to which patients and
 5 doctors will go in order to avoid the more logical and effective
 6 treatment of these persistent problems. Successful surgical
 7 treatment of severe PMDD has been reported in many studies³⁵,
 8 and, in more general terms, hysterectomy has been shown to
 9 have a beneficial effect on mood⁴⁶, no doubt because of the
 10 combined effect of the removal of PMDD and other cyclical
 11 symptoms³⁵. The fact that 4% of women die of uterine, cervi-
 12 cal or ovarian cancer should not be forgotten when this deci-
 13 sion is being contemplated⁴⁷.

14 With the correct selection, this surgery is associated with a
 15 virtually 100% total permanent cure of PMS and other cyclical
 16 symptoms of heavy painful periods, mastalgia, menstrual
 17 migraine and monthly abdominal bloating. It should not be
 18 regarded as a radical treatment of last resort as the health
 19 benefits are enormous. The full operation is required because
 20 conservation of the ovaries will not abolish the cyclical symp-
 21 toms⁴⁸; moreover, the hormone therapy already in place will
 22 prevent postoperative menopausal symptoms³⁹ and should be
 23 continued. To remove the ovaries without a hysterectomy,
 24 although a shorter procedure, is not sensible as estrogens and
 25 progestogens will be necessary for relief of estrogen deficiency
 26 in women who are both premenopausal and progestogen-intol-
 27 erant. Also, the use of estrogens and progestogens will
 28 reproduce the PMDD symptoms and periods, and these may
 29 be as bad as the patient's usual premenstrual and menstrual
 30 symptoms. The surgery can be performed laparoscopically
 31 with a 1- or 2-day hospital stay.

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CONCLUSION

This paper is an attempt to encourage psychiatrists, general
 practitioners and gynecologists to consider the use of estro-
 gens in certain forms of depression in women. This is not
 proposed as a treatment for all types of depression but specifi-
 cally for those showing a temporal relationship between hor-
 monal 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 condi-
 tions 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 psy-
 chiatrists. No doubt, professional reasons based upon training
 and unfamiliarity with hormone therapy explain this. This
 treatment is reliant upon a balance between three major hor-
 mones. In general terms, estrogen improves mood^{46,49} and
 testosterone improves mood, energy and libido^{31,32}. The prob-
 lem is progestogen, or even the natural progesterone, which
 may produce depression, loss of energy and recurrence of
 PMS-type symptoms²¹. The use of 7 days of progestogen is a
 compromise from the 12-day orthodoxy but has been shown to
 offer adequate endometrial protection⁵⁰. 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.

[AQ3]

[AQ4]

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