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Reappraisal

Should psychiatrists be prescribing oestrogen therapy to their female patients?

Michael C. Craig

Summary
Some studies have indicated that oestrogen therapy may be beneficial in the treatment of a number of neuropsychiatric disorders. However, it has been suggested that psychiatrists fail to prescribe oestrogen therapy to their patients, as they are 'not aware of' or 'do not believe' studies supporting their use. This paper reappraises the putative role of hormone treatments, particularly oestrogen therapy, in psychiatry.

Declaration of interest
M.C.C. is the clinical lead of the Female Hormone Clinic, Maudsley Hospital, London. This is part of the NHS National Services Directory that accepts NHS and private referrals for the assessment and treatment of women with mental health problems at times of hormonal fluctuation.

Types of oestrogen

In women there are three major naturally occurring oestrogens: oestrone (E₁), oestradiol (E₂ or 17β-oestradiol) and oestriol (E₃). Oestrogen therapy prescribed to postmenopausal women provides low dosages of one or more oestrogens. In the past, the most commonly prescribed form of oral oestrogen therapy was a compound containing conjugated equine oestrogens, predominantly E₁. Prior to being absorbed, oral oestrogens pass through the liver where, in addition to a large proportion being metabolised, it activates blood coagulation and increases the risk of venous thromboembolism. This can be avoided by prescribing oestrogen via methods of administration that enter the bloodstream directly (e.g. implants, patches, creams, vaginal rings, gels). Currently, the most common method is via transdermal E₂/17β-oestradiol skin patches. High-dose E₂/17β-oestradiol is also used in the combined oral contraceptive pill. However, in order to make it more resistant to de-activation in the liver, an ethinyl group is substituted at C₁₇β, leading to the production of ethinylestradiol.

There are gender differences in the incidence of a variety of neuropsychiatric disorders. For example, males are at increased risk of neurodevelopmental disorders (e.g. autism, attention-deficit hyperactivity disorder) and alcohol dependence, whereas females are at increased risk for developing Alzheimer’s disease, anxiety disorder and depression. The biological basis for these gender differences is still poorly understood but probably involves a complex interaction between genes, the environment and sex hormones on the brain. It has been reported that a subgroup of women are at especially high risk for developing depressive symptoms at times of sex hormone fluctuation. Some clinicians have proposed that individuals in this group have a discreet nosological entity, sometimes referred to as reproductive depression. It has also been suggested that these women are particularly responsive to oestrogen therapy and that it should be offered as a first-line treatment in this group. Further, other neuropsychiatric disorders, including Alzheimer’s disease and schizophrenia, have also been reported to be responsive to oestrogen therapy. It has recently been suggested that psychiatrists fail to prescribe oestrogen therapy to these women as they are 'not aware of' or 'do not believe' studies supporting their use. This paper therefore reappraises the putative role of hormone treatments, particularly oestrogen therapy, in psychiatry, focusing on women with reproductive depression.

Importantly, these mood changes were not found in women without a history of postnatal depression, suggesting that acute hormonal fluctuation may only trigger depressive symptoms in a specific subgroup of women. This study was, however, small and needs to be replicated. Despite the purported risk of depression in some women, early controlled studies reported that the incidence of depression did not increase in the postpartum period. Also, many studies included women that did not have postpartum onset of depression. However, after controlling for relevant risk factors and comparing with appropriate control groups, the incidence for unipolar depressive episodes has been reported to double and the rate of in-patient admissions to triple. Further support for the concept of reproductive depression is derived from the observation in some studies that women with vulnerability to depressed mood associated with one period of hormonal fluctuation (e.g. PMDD) are particularly vulnerable to depression at other times of hormonal fluctuation (e.g. postnatal and perimenopausal depression). Also, two of these studies suggest that it is the same women that experience all three conditions, but these findings need to be confirmed by larger studies.

Does reproductive depression exist?

Family and twin studies have reported that the heritability of premenstrual dysphoric disorder (PMDD) is over 50%, and that PMDD is associated with significant differences in single nucleotide polymorphisms modulating the alpha oestrogen receptor. Likewise, unipolar, non-psychotic depression has a heritability of 40% and a significant familial aggregation (especially when narrowly defined as developing within 6–8 weeks postpartum). Iatrogenic induction of acute hormonal fluctuation has also been reported to trigger a recurrence of symptoms in vulnerable women. For example, following ovarian suppression (i.e. with a gonadotropin-releasing hormone analogue) and subsequent treatment with high doses of oestrogen and progesterone, women with a history of postnatal depression had a recurrence of depressive symptoms post acute sex hormone withdrawal (i.e. modelling postnatal hormonal changes).
Should oestrogen therapy be prescribed in women with reproductive depression?

**Postnatal unipolar depression**

Research into the effects of oestrogen therapy in postpartum unipolar depression remains limited. An open-label study of 17β-oestradiol treatment in women with postnatal depression reported a significant sustained reduction in depressive symptoms, measured using the Montgomery–Asberg Rating Scale, over an 8-week period.²³ Furthermore, a randomised controlled trial (RCT) of 61 women with postpartum depression reported a significantly larger reduction in Edinburgh Postnatal Depression Scale scores when randomised to oestrogen therapy compared with placebo, at 3 and 6 months.²⁴ Women allocated to oestrogen therapy received 17β-oestradiol skin patches for 6 months (plus additional dydrogesterone tablets for 12 days each month) and those in the placebo group received non-hormonal patches and tablets.

In summary, there is preliminary support for the use of oestrogen therapy to treat postpartum depression but there is still insufficient evidence available to justify the widespread use of hormone treatment for postnatal depression in clinical practice.²⁵ More definitive recommendations may, however, be available following analysis of a phase II RCT of 17β-oestradiol treatment (v. sertraline and placebo) at the National Institute of Mental Health, USA (trial registration: NCT00059228).

**Peri- and postmenopausal depression**

Oestrogen therapy has been reported to be associated with improvement in psychological ‘well-being’ in postmenopausal women without depression.²⁶,²⁷ However, this improvement has been reported to be no greater than placebo after 4 months.²⁷,²⁸ In women with clear depressive symptoms, studies have reported mixed results. Several studies of oestrogen therapy have failed to demonstrate superiority over placebo in menopausal women with depression.²⁹–³² However, these studies included longer-term postmenopausal women and the benefits of oestrogen therapy may be limited to perimenopausal women. This is supported by a 4-week pilot study of 22 menopausal women with depression, which reported improvement in mood in 6/10 perimenopausal but only 2/12 postmenopausal women with 17β-oestradiol (100 µg/day) therapy.³³ Also, a 6-week RCT of 34 women with perimenopausal depression (major and minor) reported that 17β-oestradiol (50 µg) was associated with a significant improvement in mood compared with placebo.³⁴ These findings were replicated in a 12-week double-blind RCT of 17β-oestradiol (100 µg) in 50 women with perimenopausal depression (major/ minor) or dysthymic disorder.³⁵ These results were still significant at the 4-week follow-up, but it remains unclear whether improvements extended beyond this time. Larger clinical trials, with longer treatment follow-up, are still needed before recommending widespread clinical use of oestrogen therapy in this patient population.

**What about premenstrual syndrome/dysphoric disorder?**

Premenstrual syndrome (PMS) has been defined as:

> ‘a condition which manifests with distressing physical, behavioural and psychological symptoms, in the absence of organic or underlying psychiatric disease, which regularly recurs during the luteal phase of each menstrual (ovarian) cycle and which disappears or significantly regresses by the end of menstruation’.³⁶

In DSM-IV, women with severe dysphoric symptoms may also fulfil criteria for PMDD, where it is classified as a ‘depressive disorder not otherwise specified’.³⁷ The main difference between PMDD and major depressive disorder is that the affective symptoms associated with PMDD are cyclical and subside with onset of menses.

Until relatively recently the predominant theory to explain the biological basis for dysphoric symptoms associated with PMS was the ‘ovarian hormone hypothesis’.³⁸ This proposed that the symptoms of premenstrual dysphoria were caused by an imbalance in the ratio of oestrogen to progesterone, with a relative deficiency in progesterone.³⁹,⁴⁰ Despite an absence of evidence to support this theory, it became widely accepted and led to progestogens and progesterone becoming the most commonly prescribed treatment for PMS from 1993 to 1998 in the UK.⁴¹ However, a meta-analysis of all RCTs from 1966 to 2000⁴² reported that, although there was a statistically significant improvement for women taking progesterone or progestogens compared with placebo, this was clinically insignificant. This publication contributed to the more recent decline in prescription of progestogens and progesterone in the UK and the Royal College of Obstetricians and Gynaecologists have confirmed that there is ‘insufficient evidence to recommend the routine use of progesterone or progestogens for women with PMS’.⁴³ Although the Royal College of Obstetricians and Gynaecologists still supports the use of hormonal treatments for PMS/PMDD, these treatments are based on the simple principle that premenstrual symptoms may be eliminated by ovulation suppression.⁴⁴ This principle was, perhaps surprisingly, poorly supported by early RCTs using the combined oral contraceptive pill. However, this may have been due to intolerance to the type of progesterone (i.e. levonorgestrel or norethisterone) contained in second-generation contraceptive pills studied.⁴⁵ More recent observational and small randomised trials have suggested that a third-generation contraceptive pill may be effective in some women with PMS⁴⁶ (particularly when prescribed continuously, with fewer pill-free breaks)⁴⁷. This pill contains a progestrone with anti-mineralocorticoid and low androgenic properties (i.e. drospirenone). Further, a lower-dose version may be even more effective,⁴⁸ but it is still not licensed for use in the UK.

Other methods for ovulation suppression recommended for women with severe PMS/PMDD include the use of percutaneous oestradiol, either as an implant or as a patch. This requires the addition of cyclical progestogen (10–12 days) or a levonorgestrel intrauterine system, to avoid endometrial hyperplasia in women who have a uterus. Ovulation suppression can be achieved by the unlicensed use of gonadotropin-releasing analogues (with oestrogen add-back) or, as a last resort, hysterectomy with bilateral salpingo-oophorectomy.

The clear association between PMS and the cyclical fluctuation in ovarian sex hormones has contributed to the virtual absence of mental health professionals being involved in treating the depressive symptoms associated with this disorder in the UK. Instead, patients are predominantly managed by their general practitioner or, in more severe cases, by a gynaecologist. However, mental health professionals should perhaps be taking a more active role in treating women with PMS/PMDD in the UK. This argument is supported by the robust finding that selective serotonin (and noradrenaline) reuptake inhibitors (SSRIs/SNRIs) significantly improve symptoms in 60–90%⁴⁹ of women with PMS/PMDD. Also, a recent RCT reported that although SSRIs significantly improved PMDD symptoms, 10 sessions of cognitive–behavioural therapy (CBT) was associated with an even better outcome at 1-year follow-up.⁵⁰ However, the study needs replicating as the sample size was small and the drop-out rate was high. Although mental health professionals are more likely to be able to identify women with the capacity to engage and
benefit from CBT, they are still rarely involved in guiding such decisions or providing treatment to this group of women in the UK.

Should oestrogen therapy be used in women with postnatal bipolar episodes/psychosis?

It has been estimated that women with bipolar disorder have a greater than one in four risk of relapse during the postpartum period,50 with most episodes occurring within the first 2 weeks.51 This risk doubles in women with a history of severe postpartum psychosis or in women with bipolar disorder and a family history of postpartum psychosis.50,52 Familial (probably genetic) factors have been implicated in this postpartum susceptibility50 and linkage studies have reported the location of possible susceptibility genes.53

To date there have been three open-label pilot studies into the efficacy of oestrogen therapy in the prevention or treatment of postpartum psychosis. In the first preventive study, only one out of seven women with histories of puerperal psychosis experienced a postpartum psychotic episode after treatment with a reducing regime of oestrogen following a subsequent birth (intravenous oestradiol for 2 days, then oral premarin 5 mg twice daily to 0.625 mg daily over 26 days).54 Further, partial non-adherence was reported in one woman who had a relapse. In a subsequent treatment study of ten women with postpartum psychosis, a significant reduction of symptoms was reported following sublingual oestrogen therapy (1 mg three to six times daily).55 Also, psychiatric symptoms resumed within 1 week in one patient who discontinued the treatment. However, the largest preventive study to date reported no significant reduction in the postpartum relapse rate in an open trial of transdermal 17β-oestradiol in 29 women with a history of postpartum affective psychotic episodes. Although women who had been prescribed the highest dose of oestradiol (800 µg/day) required less antipsychotic medication, and were discharged sooner than women prescribed lower doses, it was concluded that the use of prophylactic oestrogen therapy in such circumstances is ‘highly questionable’.56 In summary, wider prescribing of oestrogen therapy to women with postpartum psychosis cannot be supported at the present time.

Is there a role for oestrogen therapy in the treatment of schizophrenia?

Women with schizophrenia have been reported to have a later onset and require less antipsychotic medication than men. However, they also have an increased vulnerability to relapse around the time of menopause and postpartum.57 It has been suggested that these factors are modulated by oestrogen and that women may have a neutral or negative effect, particularly if it is associated with antipsychotic medication alone.58 Although it was concluded that these results were ‘promising’, the absence of follow-up beyond 28 days prohibits support for wider change in current prescribing practice in this patient population.

Early studies reported that oestrogen therapy improved cognitive function in postmenopausal women with Alzheimer’s disease. However, interpretation of these findings was limited by the absence of standardised diagnostic criteria for Alzheimer’s disease, small sample size, brief follow-up and poor study design. A meta-analysis of seven double-blind RCTs (n=351) reported that, although oestrogen therapy was associated with a statistically significant improvement in verbal episodic memory and Mini-Mental State Examination scores at 2 months, these effects were not evident at 3 months (or longer) and are probably not clinically significant.59 Therefore, current evidence suggests that oestrogen therapy does not have a significant beneficial effect in treating Alzheimer’s disease.

Our current understanding of the role of oestrogen therapy in preventing Alzheimer’s disease remains less clear but can be summarised as follows: oestrogen therapy prescribed to older women may have a neutral or negative effect, particularly if it is combined with a progestagen.60 However, oestrogen therapy prescribed at a ‘critical period’ around the time of menopause (particularly postsurgical menopause in younger premenopausal women) may reduce the risk of Alzheimer’s disease in later life.7 However, further studies are currently needed to test the ‘critical period’ hypothesis further and widespread prescription of oestrogen therapy cannot be supported based on current evidence.

Conclusions

Studies to date suggest that:

(a) PMDD responds positively to the prescription of certain agents that suppress ovulation (e.g. oestrogen therapy);
(b) there is preliminary support for the use of oestrogen therapy to treat postpartum and peri- (not post-) menopausal depression, but the definitive work has not yet been completed and oestrogen therapy cannot be recommended as a first-line treatment;
(c) there is limited support for the prescription of E₂, in conjunction with antipsychotic medication, to treat women with postnatal psychosis or schizophrenia, but the current evidence does not support a wider change in current prescribing practice;
(d) oestrogen therapy prescribed at a ‘critical period’ around the time of menopause (particularly postsurgical menopause in younger premenopausal women) may reduce the risk of Alzheimer’s disease in later life but current evidence suggests that oestrogen therapy does not have a significant beneficial effect in treating Alzheimer’s disease.

In those situations where it is considered appropriate to prescribe oestrogen therapy, it is important for physicians to be familiar with specific side-effects and risks associated with this form of therapy in different patient populations.61 It has been suggested that ‘coping’ with the minor problems of hormone therapy, such as irregular bleeding or breast discomfort, ‘will be outside the experience and training of psychiatrists’.5 Although this may be accurate in many cases, this could be overcome locally via liaison with gynaecology colleagues or, in more complex
cases, by referral to a tertiary referral service (e.g. www.national.
slam.nhs.uk/services/adult-services/femalehormonelclinic/).

In addition to the need for larger RCTs, further research is also
required to help understand the biological basis of oestrogen
therapy in neuropsychiatric disorders in women. Preliminary
brain imaging studies in women with a vulnerability to repro-
ductive depression have, for example, reported differences in
limbic brain function (e.g. within the amygdala and orbitofrontal
cortex). However, it is unknown whether these findings are
specific to women vulnerable to reproductive depression (i.e. as
opposed to other forms of depression), and/or how sex hormones
differentially modulate brain function (e.g. whether this involves
differential modulation of neurochemical systems).62)

Despite the significant health burden there remains a paucity of
institutional or government support for psychiatric research into
women’s mental health. It is hoped that this reappraisal will
contribute to a renewed interest in this area and stimulate further
research.

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Dino Campana

Here we are alone before the nocturnal mystery. The moon May shine over mankind's sad loves, She's veiled with mist and tears like Venus rising From the sea on the first morning of the world The world still smoking in primal chaos as she laughs With so much tender sorrow Since then much time has flown, and still that sorrow is weighing on the tender breast of Venus Yet it is infinitely sweet to feel the tiredness Of our hearts exhausted but still burning Through immemorial time Towards the soul of the world that none can slake.

This poem is from Dino Campana's (1885–1932) Selected Works, translated by Cristina Viti and published by Survivors' Poetry in 2006. Dino Campana was admitted to San Salvi, an asylum in Florence at the age of 32 years and transferred to Castel Pulci, a place designated for those regarded as incurable in April 1918 where he remained until his death. Another of his poems, Easy Listening, was published in the Journal in August 2012.

Chosen by Femi Oyebode.