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Hormones and depression in women

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ABSTRACT

The biological plausibility for the effect of sex hormones on the central nervous system is now supported by a considerable amount of clinical data. This critical review guides the reader through the plethora of data, from the earliest reports of menstrual madness in the nineteenth century to neurobiological work in the new millennium. It illustrates through the scientific evidence base that, although the effect of estrogen on the central nervous system, particularly on mood and depression, remains a controversial area, there is now considerable evidence for the psychotherapeutic benefits of estrogens in the triad of hormone-responsive depressive disorders: postnatal depression, premenstrual depression and perimenopausal depression. The article also reviews the compelling data that testosterone supplementation has positive effects for depression, libido and energy, particularly where patients have only partially responded to estrogen therapy.

INTRODUCTION

On Boxing Day 1851, Charles Dickens attended the patients' Christmas dance at St. Luke's Hospital for the insane. On describing his visit in an article for 'Household Words', he commented that the experience of the asylum proved that insanity was more prevalent amongst women than men. Of the 18 759 inmates over the century, 11 162 had been women. He adds, 'It is well known that female servants are more frequently affected by lunacy than any other class of persons.' Charles Dickens was as great an observer as any Nobel prize winner and, indeed, this passage is one of the very few references in Victorian literature that make the link between gender and depression, but there are none to our knowledge relating reproductive function to depression. Jane Eyre's red room and Berthe Mason's monthly madness may be coded examples of this from Charlotte Bronte's pen.

Modern epidemiology confirms that depression is more common in women than men, whether we look at hospital admissions, population studies, suicide attempts or the prescription of antidepressants[1]. The challenge remains to determine whether this increase in depression is environmental, reflecting women's perceived role in contemporary society, or whether it is due to hormonal changes.

It is clear that this excess of depression in women starts at puberty and is no longer present in the 6th and 7th decades. The peaks of depression occur at times of hormonal fluctuation in the premenstrual phase, the postpartum phase, and the climacteric perimenopausal phase, particularly in the 1 or 2 years before the periods cease. This triad of hormone-responsive mood disorders often occurs in the same vulnerable woman. The depression of these patients can usually be treated effectively by estrogens, preferably by the transdermal route and in a moderately high dose. In published placebo-controlled studies, the 200 μg transdermal estrogen patch has been used, but the 100 μg dose is frequently effective.

The 45-year-old depressed perimenopausal woman who is still menstruating will often give a history of worsening premenstrual depression and also have physical manifestations of hormonal fluctuations, such as menstrual migraine. She will have usually enjoyed very good mood during the latter half of pregnancy, when hormonal levels

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were stable. Such a woman will often say that *she last felt well during her last pregnancy*. She then developed postnatal depression for several months. When the periods returned, the depression became cyclical and, as she approached the menopause, the depression became more constant.

Reproductive events also affect the course of bipolar disorder in women; 67% of such women have a history of postpartum depression[2]. Of these, all will have had episodes of depression after subsequent pregnancies. Subsequently, women who were not using hormone replacement therapy (HRT) were significantly more likely than those who were using HRT to report worsening of depressive symptoms during the perimenopause.

In spite of this clear clinical history of a woman who will probably respond to estrogens, most psychiatrists believe that such patients are ideal for the use of antidepressants. This is because they identify that these women will have had a 'premorbid history of depression' and that they therefore must have a chronic relapsing depressive illness. The fact that this depression is postnatal or premenstrual in timing may escape them. It is sad that both gynecologists and psychiatrists are products of their own training, with too little overlap in knowledge. The patients thus become victims of this professional schism.

The clue to the use of estrogens came with the important and somewhat eccentric paper by Klaiber and colleagues[3] who performed a placebo-controlled study of very high-dose estrogens in patients with chronic relapsing depression. They had various diagnoses and were both premenopausal and postmenopausal. They were given Premarin 5 mg daily with an increase in dose of 5 mg each week until a maximum of 30 mg/day was used. There was a huge improvement in depression on these high doses, but this work has not been repeated because of anxiety over giving high-dose estrogens.

BIOLOGICAL PLAUSIBILITY

It is generally accepted that endogenous estrogenic steroids have a pivotal influence on the development of the female central nervous system (CNS) through genomic organizational effects in fetal life. Recent work has shown that not only α but also β estrogen receptors are located in the hypothalamus and other parts of the CNS[4]. It is therefore not surprising that exogenous estrogens may have benefits in controlling mood, cognition and neuronal health.

It has long been recognized that non-genomic activational effects can also be produced by the activation of the CNS neuroreceptors to alter the concentration of neurotransmitter amines such as serotonin and noradrenaline[5]. Estrogen can increase the level of serotonin in a number of ways: it can enhance the degradation of monoamine oxidase (which catabolizes serotonin), it displaces tryptophan from its albumin binding sites, making more available for serotonin synthesis, and it also enhances the transport of serotonin[6]. This may, in part, explain how estrogen can improve mood, when used in ovarian cycle-stabilizing doses, as depression is largely due to falling levels of serotonin. However, the interaction is complex and may also involve up-regulation of receptors over a period of days to weeks[7].

PREMENSTRUAL SYNDROME

This condition is mentioned in the fourth century BC by Hippocrates, but became a medical epidemic in the nineteenth century. Victorian physicians were aware of menstrual madness, hysteria, chlorosis, ovarian mania, as well as the more commonplace neurasthenia. In the 1870s, Maudsley[8], the most distinguished psychiatrist of the time, wrote '...The monthly activity of the ovaries which marks the advent of puberty in women has a notable effect upon the mind and body; wherefore it may become an important cause of mental and physical derangement...'. This and other female maladies were recognized, rightly or wrongly, to be due to the ovaries. As a consequence, bilateral oophorectomy – Battey's operation[9] – became fashionable, being performed in approximately 150 000 women in North America and Northern Europe in the 30 years from 1870. Longo[10], in his brilliant historical essay on the decline of Battey's operation, posed the question whether it worked or not. Of course, they had no knowledge of osteoporosis and the devastation of long-term estrogen deficiency; therefore, in balance, the operation was not helpful as a long-term solution but it probably did, as was claimed, cure the 'menstrual/ovarian madness' which would be a quaint Victorian way of labelling severe premenstual syndrome (PMS). The essential logic of this operation was to remove cyclical ovarian function, but, happily, this can now effectively be achieved by simpler medical therapy.

Only in 1931 was the phrase 'premenstrual tension' introduced by Frank[11], who described 15 women with the typical symptoms of PMS as we

know it. Greene and Dalton extended the definition to 'premenstrual syndrome' in 1953[12], recognizing the wider range of symptoms.

Severe PMS is a poorly understood collection of cyclical symptoms, which cause considerable psychological and physical distress. The psychological symptoms of depression, loss of energy, irritability, loss of libido and abnormal behavior, as well as the physical symptoms of headaches, breast discomfort and abdominal bloating, may occur for up to 14 days each month. There may also be associated menstrual problems, pelvic pain and menstrual headaches, and the woman may only enjoy as few as 7 good days per month. It is obvious that the symptoms mentioned can have a significant impact on the day-to-day functioning of women. It is estimated that up to 95% of women have some form of PMS, but, in about 5% of women of reproductive age, they will be severely affected with disruption of their daily activities[13]. Considering these figures, it is disturbing that many of the consultations at our specialist PMS clinics start with women saying that, for many years, they have been told that there are no treatments available and that they should simply 'live with it'. In addition, many commonly used treatments of PMS, particularly progesterone or progestogens, have been shown by many placebo-controlled trials to be not only ineffective but they commonly make the symptoms worse as these women are progesterone- or progestogen-intolerant.

The exact cause is uncertain, but fundamentally it is due to hormonal fluctuations during the menstrual cycle and the resulting complex interaction between ovarian steroid hormones, e.g. progesterone or allopregnenalone, and central nervous system neurotransmitters, such as GABA and serotonin. These cyclical neuroendocrine changes produce the varied premenstrual symptoms in women who are genetically predisposed to the changes in their normal reproductive hormone levels.

ESTROGENS

PMS does not occur if there is no ovarian function[14]. Obviously, it does not occur before puberty, after the menopause or after oophorectomy. It also does not occur during pregnancy. It is therefore not surprising that hysterectomy with conservation of the ovaries does not cure PMS[15], as patients are left with the usual cyclical symptoms and cyclical headaches in spite of the absence of menstruation. This condition, best called 'the ovarian cycle syndrome'[16], is usually not recognized to be hormonal in etiology, as there is no reference point of menstruation. The failure to make this diagnosis is regrettable because these monthly symptoms of depression, irritability, mood change, bloating and headaches, which might affect women for most days in the month, with only perhaps a good week each month, can easily be treated with transdermal estrogens, which suppress ovarian function and thus remove the symptoms.

A medical Battey's operation can be achieved by the use of gonadotropin releasing hormone (GnRH) analogs. Leather and colleagues[17] have demonstrated that 3 months of goserelin therapy cures all of the symptom groups of PMS. The long-term risk of goserelin therapy is bone demineralization, but the same group showed that add-back with a product containing 2 mg of estradiol valerate and cyclical levonorgestrel (Nuvelle®, Schering Healthcare, UK) maintains bone density at the spine and the hip, as well as alleviating vasomotor side-effects[18]. Most PMS symptoms remain improved with this 'add-back', but bloating, tension and irritability can recur due to the cyclical progestogen. The tissue-selective agent tibolone and low-dose continuous combined HRT are therefore better add-back preparations, as these do not regenerate the hormonal fluctuations of the ovarian cycle[19].

In a Scandinavian study, Sundstrom and colleagues used low-dose GnRH analogs (100 μg buserelin) with good results on the symptoms of PMS, but the treatment still caused anovulation in as many as 56% of patients[20]. Danazol is another method to treat PMS by inhibiting pituitary gonadotropins, but it has side-effects, including androgenic and virilizing effects. When used in the luteal phase only[21], it only relieved mastalgia but not the general symptoms of PMS, even though side-effects were minimal.

Greenblatt and colleagues showed the effects of an anovulatory dose of estrogen implants for the use of contraception[22] and the first study for its use in PMS was by Magos and colleagues[23], using 100 mg estradiol implants, the dose that had been shown to inhibit ovulation by using ultrasound and day 21 progesterone measurements in earlier studies by the same group. There was a large (84%) improvement with placebo implants but, despite this, the improvements of every symptom cluster were greater in the active estradiol group. In addition, the placebo effect waned after a few months compared with a continued response to estradiol. These patients were also given 12 days

of oral progestogen per month to prevent endometrial hyperplasia and irregular bleeding[24]. It was clear that the addition of progestogen attenuated the beneficial effect of estrogen. Subsequently, a placebo-controlled trial of cyclical norethisterone in well-estrogenized, hysterectomized women reproduced the typical symptoms of PMS[25]. This study of cyclical oral progestogen in the estrogen-primed woman was described as the model for PMS. It is also significant that progestogen intolerance is one of the principal reasons why older, postmenopausal women stop taking HRT[26], particularly if they have a past history of PMS or progesterone intolerance. It is common for progestogens to cause PMS-like symptoms in these women in the same way as endogenous cyclical progesterone secretion is the probable fundamental cause of premenstrual syndrome.

Although our group still uses estradiol implants, often with the addition of testosterone for loss of energy and loss of libido, we have reduced the estradiol dose, never starting with 100 mg because of concerns about tachyphylaxis. We will now insert pellets of estradiol 50 mg or 75 mg with 100 mg of testosterone. These women must have endometrial protection by either oral progestogen or a levonorgestrel-releasing intrauterine system (LNG-IUS, Mirena®, Schering Healthcare, UK)[27]. As women with PMS respond well to estrogens, but are often intolerant to progestogens, it is commonplace for us to reduce the orthodox 13-day course of progestogen to 10 or 7 days, starting, for convenience, on the first day of every calendar month. Thus, the menstrual cycle is reset.

The LNG-IUS also plays a vital role in preventing PMS-like symptoms, as it performs its role of protecting the endometrium without significant systemic absorption. A recent study has shown a 50% decrease in hysterectomies in our practice since the introduction of the LNG-IUS in 1995[24]. With its profound effect on menorrhagia and the possibility of less progestogenic side-effects, the LNG-IUS looks a very promising component of PMS treatment in the future.

Hormone implants are not licensed in all countries and are unsuitable for women who may wish to easily discontinue treatment in order to become pregnant. Estradiol patches are an alternative and our original double-blind, crossover study used the 200 μg estradiol patch twice weekly[28]. This produced plasma estradiol levels of 800 pmol/l and suppressed luteal-phase progesterone and ovulation. Once again, this treatment was better than placebo in every symptom cluster of PMS. This is now our treatment of choice in severe PMS.

Subsequently, a randomized but uncontrolled observational study from our PMS clinic indicated that PMS sufferers could have the same beneficial response to 100 μg patches as they do with the 200 μg dose. They also have fewer symptoms of breast discomfort and bloating and there is less anxiety from the patient or general practitioner about high-dose estrogen therapy[29]. A 21-day assay of progesterone in the patients receiving 100 μg showed low anovulatory levels, prompting the intriguing question that even this moderate dose might reliably suppress ovulation and be contraceptive. Clearly, a great deal of work must be done before we can suggest that this treatment is an effective birth control, but it is of great importance because many young women on this therapy for PMS will be pleased if it was also an effective contraceptive. This is a study which needs to be conducted.

The original studies outlined in this paper are all scientifically valid, placebo-controlled trials showing a considerable improvement in PMS symptoms with estrogens. Although this treatment is used by most gynecologists in the UK, its value has not been exploited by psychiatrists anywhere in the world. We believe that the benefit of this therapy in severe PMS is due to the inhibition of ovulation, but there is probably also a central mental tonic effect. Klaiber and colleagues[3], in their study of high-dose Premarin, showed this, and our other psycho-endocrine studies of climacteric depression[30] and postnatal depression[31] have shown the benefit of high-dose transdermal estrogens for these conditions that are not related to or dependent upon suppression of ovulation.

Ultimately, there are some women who, after treatment with estrogens and the LNG-IUS, will prefer to have a hysterectomy in order to remove all cycles, with a virtual guarantee of improvement of symptoms. This should not be seen as a failure or even treatment of last resort, as it does carry many other advantages[32]. It is important that these women who have had a hysterectomy and bilateral salpingo-oophorectomy have effective replacement therapy, ideally with replacement of the ovarian androgens. Implants of estradiol 50 mg and testosterone 100 mg are an ideal route, and the combination of hormones for this long-term therapy post-hysterectomy have a continuation rate of 90% at 10 years[24]. We have data of 47 such patients who have had a hysterectomy, bilateral salpingo-oophorectomy and implants of estradiol and testosterone for severe PMS. They

have gone through many years of treatment with transdermal estrogens and cyclic progestogens or the LNG-IUS. The symptoms are removed in all patients and all but one was 'very satisfied' with the outcome[33].

POSTNATAL DEPRESSION

Postnatal depression is another example of depression being caused by fluctuations of sex hormones and having the potential to be effectively treated by hormones. It is a common condition which affects 10–15% of women following childbirth and may persist for over 1 year in 40% of those affected. There does seem to be a lack of any overall influence of psychosocial background factors in determining vulnerability to this postpartum disorder, although it can be recurrent.

Although common, the disease is often not reported to the health-care professional, particularly the general practitioner or the visiting midwife, as the exhaustion and depression are regarded as normal. Indeed, the symptoms of postnatal depression may be confused with the normal sequelae of childbirth. The symptoms can consist of depressed mood with lack of pleasure with the baby or any interest in her surroundings. There may be sleep disturbance, either insomnia or hypersomnia. There may be loss of weight, loss of energy and certainly loss of libido, together with agitation, retardation and feelings of worthlessness or guilt. Frequent thoughts of death and suicide are common.

Postnatal depression is not more common after a long labor, difficult labor, Cesarean section, or separation from the baby after birth, nor is it determined by education or socioeconomic group. The only environmental factor that seems to be important is the perceived amount of support given by the partner. There is no doubt that the first 6 or more months after delivery can be an exhausting time, full of anxiety and insecurity in mothers with the new responsibility of the baby. Even allowing for that, there does seem to be a clear hormonal aspect to this condition.

Postnatal depression is severe and more prolonged in women who are lactating, and lower estradiol levels are found in depressed women following delivery than with controls. It is probable that the low estradiol levels with breast-feeding and the higher incidence of depression are related in a causative way.

We studied the effect of high-dose transdermal estrogens in this condition, in an attempt to close the circle of studies treating this triad of hormone-responsive depressions – premenstrual depression, climacteric depression and postnatal depression. This was a double-blind, placebo-controlled trial of 60 women with major depression that began within 3 months of childbirth and persisted for up to 18 months postnatally[31]. They had all been resistant to antidepressants and the diagnosis of postnatal depression was made by two psychiatrists who are expert in the field. We excluded breast-feeding women from the study. They were given either placebo patches or transdermal estradiol patches 200 μg daily for 3 months without any added progestogen. After 3 months, cyclical Duphaston 10 mg daily was added for 12 days each month. The women were assessed monthly by a self-rating of depressive symptoms on the Edinburgh postnatal depression score (EPDS) and by clinical psychiatric interview. Both groups were severely depressed, with a mean EPDS score of 21.8 before treatment. During the first month of therapy, the women who received estrogen improved rapidly and to a greater extent than controls. None of the other factors, age, psychiatric, obstetric or gynecological history, severity and duration of current episode of depression and concurrent antidepressant medication, influenced the response to treatment.

The study showed that the mean EPDS score was less with the active group at 1 month and was then maintained for 8 months and that the percentage with EPDS scores over 14 (diagnostic of postnatal depression) was reduced by 50% at 1 month and 90% at 5 months. This was better than the placebo response.

Not only did this study show that transdermal estrogens were effective for the treatment of postnatal depression, but a subsequent study by Lawrie and colleagues[34] showed that depot-progestogen was worse than placebo, causing deterioration in the severity of postnatal depression. Thus, we have again the picture of the mood-elevating effect of estrogens and the depressing effect of progestogen.

An uncontrolled study showed similar improvements using sublingual estradiol in 23 women with major postnatal depression[35]. These women had plasma levels of 79.0 pmol/l before the treatment with sublingual estradiol. The estradiol levels were 342 pmol/l at 1 week and 480 pmol/l at 8 weeks. There was improvement in 12 out of the 23 patients at 1 week, and after 2 weeks there was recovery in 19 of the 23 patients. The mean Montgomery Asberg depression rating scale (MADRS) was 40.7 before treatment, 11 at 1

week and 2 at 8 weeks. At the end of the second week of treatment, the MADRS scores were compatible with clinical recovery in 19 out of the 23 patients. This study stressed the rapidity of response to the estradiol therapy and this was our observation also. However, it must be stressed that this is an uncontrolled study in women with a very low, almost postmenopausal level of estradiol. Another placebo-controlled study is required, together with information about bleeding patterns, to support or refute our original paper[31].

It would support the hormonal pathogenesis of this condition if we could mimic postnatal depression by hormonal manipulation. This was done in a study by Bloch and colleagues[36], who studied 16 women, eight with a history of postnatal depression. They induced hypogonadism with leuprolide acetate and stimulated pregnancy by 'add back' supraphysiological doses of estradiol and progesterone for 8 weeks and then withdrew both steroids. Five of the eight women (62.5%) with a history of postnatal depression and none of the women without a prior history developed significant mood symptoms during the withdrawal period.

This study supported the view that there was an involvement of the reproductive hormones, estradiol and progesterone, in the development of postpartum depression in a specific group of women. Furthermore, the study showed that women with a history of postpartum depression are differentially sensitive to the mood-destabilizing effects of gonadal steroids.

CLIMACTERIC DEPRESSION

Like many aspects of depression in women, the diagnosis of climacteric depression and its treatment remain controversial. Whereas gynecologists who deal with the menopause have no difficulty in accepting the role of estrogens in the causation and the treatment of this common disorder, psychiatrists seem to be implacably opposed to it. This may be because there is no real evidence of an excess of depression occurring *after* the menopause, nor any evidence that estrogens help *post*menopausal depression or what used to be called 'involutional melancholia'. This is quite true and, indeed, many women with long-standing depression improve considerably when the periods stop. This is because the depression created by premenstrual syndrome, heavy painful periods, menstrual headaches and the exhaustion that attends excess blood loss disappears. Therefore, the longitudinal studies of depression carried out by many psychologists, particularly those as notable as Hunter[37], have shown no peak of depression in a large population of menopausal women. Randomized studies have also shown no significant improvement in depressed postmenopausal women[38].

The depression that occurs in women around the time of the menopause is at its worst in the 2 or 3 years before the periods stop. This, of course, is perimenopausal depression and is no doubt related to premenstrual depression, as it becomes worse with age and with falling estrogen levels.

The earliest placebo-controlled study that defined the precise menopausal syndrome showed that estrogens helped hot flushes, night sweats and vaginal dryness. They also had a mood-elevating effect[39]. This work was further supported by the work of Campbell and Whitehead[40], who used Premarin, and by the study of Montgomery and colleagues[30] using higher-dose estradiol implants. This study of 90 peri- and postmenopausal women with depression showed considerable improvement in the treatment group compared with placebo but only in the perimenopausal women. There is no improvement in the depression in the postmenopausal women with this treatment when compared with placebo. This effect is not transient and we have shown that the improvement in depression is maintained even at 23 months. By this stage, the placebo patients had dropped out and there was no placebo group in the study. It was therefore decided not to publish this uncontrolled, observational study.

After more than 15 years, psychiatrists, particularly in the USA, are coming round to the view that transdermal estrogens are effective in the treatment of depressed perimenopausal women. Soares and colleagues[41] in 2001 studied 50 such women, 26 with major depressive disorder, 11 with dysthymic depression and 30 with minor depressive illness. They treated them with 100 μg estradiol patches in a 12-week placebo-controlled study. There was a remission of depression in 17 out of 25 of the treatment patients (68%) and only five out of the 25 placebo patients (20%). This improvement occurred regardless of the precise DSM-IV diagnosis, which seemed to be in question in some patients due to an element of self-selection from specialist clinics.

Rasgon and colleagues[42] studied 16 perimenopausal women with unipolar major depressive disorder for an 8-week period in an open protocol trial comparing low-dose 0.3 mg Premarin to fluoxetine daily. There was a greater response

with estrogen alone. All but two of the total patients responded, but the response was greater in the estrogen therapy patients and it was significant that the reduction of depression scores began rapidly after the first week of treatment.

More recently, Harlow and colleagues[43] studied a large number (976) of perimenopausal women with a history of major depression and those without. The patients with the history of depression had higher follicle stimulating hormone levels and lower estradiol levels at enrolment to the study and those women with a history of antidepressant medication had three times the rate of early menopause. A similar excess rate was found in perimenopausal women who had had a history of severe depression.

It is reassuring for those 'menopausologists' who have been trying to persuade the world of psychiatry that estrogens have a place in the treatment of depressed women and pleasing to read at last the view that 'Periods of intense hormonal fluctuations have been associated with the heightened prevalence and exacerbation of underlying psychiatric illness, particularly the occurrence of premenstrual dysphoria, puerperal depression and depressive treatment during the perimenopause. Although a certain degree of mood alleviation in the perimenopause is probably due to relief of climacteric symptoms, it is speculated that sex steroids such as estrogens, progestogens (sic), testosterone and DHEA exert a significant modulation of brain functioning. There are preliminary, although promising, data on the use of estradiol, (particularly transdermal estradiol) to alleviate depression during the menopause'[42]. Neuropsychiatrists have also conceded that 'there is a clear need to examine the necessary duration of HRT for neuroprotection to decrease a woman's risk for depression, cognitive dysfunction and development of Alzheimer's disease'[44].

PROGESTOGEN INTOLERANCE

Those women having moderately high-dose estrogen therapy must of course have cyclical progestogen if they still have a uterus in order to prevent irregular bleeding and endometrial hyperplasia. The problem is that women with hormone-responsive depression enjoy a mood-elevating effect with estrogens, but this is attenuated by the necessary progestogen[45]. This hormone can produce depression, tiredness, loss of libido, irritability, breast discomfort and, in fact, all of the symptoms of premenstrual syndrome, particularly in women with a history or previous history of PMS. A randomized trial of norethisterone against placebo in estrogenized hysterectomized women, previously referred to, clearly shows this and, in fact, the paper was subtitled a 'A model for the causation of PMS'[23].

If women become depressed with 10–12 days of progestogen, it may be necessary to halve the dose, decrease the duration or change the progestogen used[46]. It is our policy to routinely shorten the duration of progestogen in women with hormone-responsive depression because adverse side-effects with any gestogen are almost invariable. We would therefore use transdermal estrogens, either 100 μg or 200 μg of an estradiol patch or a 50 mg estradiol implant, and then reset menstrual bleeding by prescribing norethisterone 5 mg for the first 7 days of each calendar month. This will produce a regular bleed on about day 10 or 11 of each calendar month.

Should heavy withdrawal bleeds occur, the duration of progestogen can be extended to the more orthodox 12 days. At this stage, many women would prefer to have an LNG-IUS inserted, so there will be reduced bleeding (and eventual amenorrhea in 40–50%), and no need to take oral progestogen with its side-effects. An alternative to the LNG-IUS would be vaginal progesterone pessaries or gel to minimize systemic progestogenic side-effects. It is not unusual for women at this stage, who are aware of the benefits of estrogens and the problems of their menstrual cycles, to request hysterectomy and bilateral salpingo-oophorectomy with the use of unopposed estradiol and often testosterone[33,47].

CONCLUSIONS

The effect of estrogen on the central nervous system, particularly mood and depression, remains a controversial area. However, there are now considerable data for the psychotherapeutic benefits of estrogens in the triad of hormone-responsive depressive disorders. Estrogen therapy is effective for the treatment of postnatal depression, premenstrual depression and perimenopausal depression, the triad of hormone-responsive mood disorders. Transdermal estradiol with 100 μg or 200 μg patches, producing plasma levels of 300 pmol/l and 600 pmol/l, respectively, is the optimum therapy. These patients often require plasma levels of more than 600 pmol/l for efficacy, as there does appear to be a dose–response effect. In non-hysterectomized women, cyclical progestogen is usually added for endometrial protection. The most effective long-term medical therapy is

estradiol patches or an implant of estradiol with the lenonorgestrel-releasing intrauterine system. This intrauterine system minimizes systemic PMS-like side-effects, thus maximizing efficacy. Consideration should also be given to the addition of testosterone for depression, libido and energy, particularly where patients have only partially responded to estrogen therapy alone. Ultimately, a hysterectomy plus bilateral salpingo-oophorectomy and implants with estradiol and testosterone may be requested.

Conflict of interest Both authors have acted in an advisory capacity and lectured for various pharmaceutical companies, including those manufacturing products mentioned in this review.

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