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REVIEW ARTICLE

Reproductive depression

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Reproductive depression is the depression in women that is related to the hormonal changes of the menstrual cycle, pregnancy and the menopause and is manifested clinically as premenstrual depression, postnatal depression and climacteric depression. These three components occur in the same vulnerable women in that a woman with depression in the menopausal transition will usually have a history of premenstrual syndrome (PMS; premenstrual dysphoric disorder [PMDD]), would have been in a good mood during pregnancy and then develop postnatal depression. When the periods return the depression becomes cyclical as PMS. These three conditions are effectively treated with transdermal estrogens which should be the first-choice therapy rather than antidepressants. Estrogens can be used together with antidepressants. The critical time to prevent long-term mood problems is the correct treatment of postnatal depression. In women with low energy and libido, often a side effect of antidepressants, the addition of transdermal testosterone is useful. These women with reproductive depression are often progesterone/progestogen intolerant and a smaller dose or duration of progestogen is a necessary compromise. Alternatively a Mirena IUS or rarely a hysterectomy is required.

Keywords: Depression, estrogens, hysterectomy, menopausal transition, PMDD, postnatal depression, progestogen intolerance, testosterone

Introduction

It is probable that the first quantitative account of the incidence of depression in women and men came from Charles Dickens [1] who went through the books of St Luke's hospital for the insane reporting in his journal Household Words the increase of admission for depression in women. He claimed that this increase in depression occurred particularly in "women of the servant class" thus indicating the effect of both gender and social deprivation on mental illness. The excess of depression in women compared with men can be the result of social and environmental factors but most convincingly it occurs at times of hormonal fluctuation and is a result of these endocrine changes.

Reproductive depression and ovarian hormones

Depression in women commonly occurs at times of hormonal changes [2], most commonly seen with depression in the premenstrual days. There is also a peak of depression in the postnatal months, often following a pregnancy characterized by a good mood with less depression. Later in life depression occurs at its most severe in the 2 or 3 years before the periods cease in the menopausal transition. Together these three components of premenstrual depression, postnatal depression and climacteric depression with its probable endocrine etiology mostly influenced by changes in ovarian hormones are best termed "reproductive depression" as originally suggested by Nappi et al. [3]. This name gives emphasis to the fact that it is a hormone-mediated mood change, which may well be most effectively treated by correction of these hormonal changes.

The ability of sex hormones fluctuations to inflect neuroendocrine circuitries in the female brain is an elegant mechanism to adjust homeostasis in line with the demands of reproductive function. Neuroanatomical and functional peculiarities of the female gender predispose women to specific conditions when the brain is challenged by internal or external stimuli and these physiological changes allow estrogens to have a psychotherapeutic effect on women [4]. Adaptive responses at molecular, cellular and system levels depend on the individual threshold of vulnerability, which is modulated by a complex array of determinants from genetic disposition to environmental factors [5]. Stages of transition, such as menarche and menopause, and marked hormonal fluctuations, such as the premenstrual phase or the postpartum, exert a profound effect on brain regions directly associated with reproduction and on brain areas relevant for mood, memory, sensory-motor control, behavioral and cognitive responses [6].

It is vitally important for the management of neurologic and psychiatric disorders in women to understand how sex hormones, mainly estradiol but also progesterone, influence neurotransmission, neuromodulation, synaptic plasticity, neurodegeneration and other brain functions. Virtually every neural pathway (serotonergic, dopaminergic [DA], noradrenergic, cholinergic, GABAergic, etc.) responds to estrogens [7]. Estrogen signaling is implicated in this higher prevalence for depression in females compared to males. When estrogen concentrations are low, i.e. postpartum and menopause, or when progesterone concentrations are high, i.e. premenstrually, is when depression occurs in women vulnerable to hormonal fluctuation [8]. Indeed, progesterone and its neuroactive metabolites are also active at certain neural pathways, especially the γ-aminobutyric acid A (GABAA) receptor, to modulate mood changes [9].

Thus, sex hormones may exert both organizational and activational effects at multiple levels of the nervous system, and their actions are mediated by nongenomic as well as direct and indirect genomic pathways. It is our aim in this review to underline the role of estradiol, produced by the ovaries or converted from androgenic precursors due to aromatase activity, at the level of brain circuitries involved in symptoms of reproductive depression.

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Estrogen receptors (ERs) signaling and expression, as well as aromatase expression, in the brain may be age dependent [10]. Both ERα and ERβ receptor subtypes are located in brain regions associated with cognitive function and emotion [11]. ERα is more predominantly expressed in brain areas that mediate affective, motivational and cognitive processing, including the cerebral cortex, the hippocampus, the amygdala and the hypothalamus, while ERβ is highly expressed in the hypothalamus, in the hippocampus and in serotonin (5-HT) neurons of the dorsal raphe, which are key targets for antidepressant drugs [12].

In these regions estrogen regulates gene products such as brain-derived neurotrophic factor, neurotransmitter-synthesizing enzymes, neurotransmitter-metabolizing enzymes and neurotransmitter receptors [13]. In addition, in hypothalamic and hippocampal neurons estrogen, by reducing GABA inhibition and by stimulating glutamate release, regulates dendritic spine formation and synaptogenesis in a cyclical pattern with a peak when estradiol is high and a downregulation when estradiol begins to fall and progesterone remains high [14].

Estrogen may be considered as a neuroprotective agent at multiple levels of the nervous system [15]. Estrogen exerts generally positive effects on serotonergic raphe neurons and on their cortical postsynaptic targets. In castrated animals, estrogen treatment increases protein levels of tryptophan hydroxylase, the key synthetic enzyme for 5-HT [16], and also increases the 5-HT content and activity in raphe neurons [17]. In postmenopausal women, RMN (NMR) findings showed that a short-period estrogen treatment increased 5-HT_{2A} receptors in the right prefrontal cortex improving verbal fluency and cognition [18]. Estrogen positively modulates also the noradrenergic (NE) network and its hypothalamic targets by increasing α_{1B} NE receptors [19,20]. Similarly, the DA system is positively affected by estrogen, being DA release and reuptake facilitated in several brain areas, including the nucleus accumbens [21]. Another neuroprotective activity of estrogen is the increase of glucose uptake and utilization by enhancing the expression of glucose transporter at the blood-brain barrier and on the membranes of neurons [22,23].

It is important to underline that estrogen strongly modulates other endocrine functions, such as the activity of the adrenal and thyroid glands, and circadian rhythmicity that are relevant in reproductive depression [24,25]. Although it is clear that endogenous estrogen and progesterone have a profound effect on neurophysiology and mood, the tragedy for women is that this endocrine association is not recognized by psychiatrists who will treat depression with antidepressants [26]. As these are inappropriate for hormone-responsive depression they often do not work so the dose is increased, a second or third antidepressant is used and even mood stabilizing and antiepileptic drugs are used with the diagnosis when the condition is now dangerously diagnosed as bipolar disorder [2].

These peaks of depression often occur in the same woman. The typical story is one who has mild to moderate premenstrual syndrome (PMS) as a teenager which may become worse with age with fewer good days per month. When pregnancy occurs they are normally in a good mood throughout pregnancy in spite of possible common problems such as nausea, preeclampsia or other obstetric complications. After delivery they develop postnatal depression for many months and it is at this point that women often have their first "nervous breakdown". They are treated with various antidepressants that are barely effective. When the periods return, the depression becomes cyclical and more severe but improves with subsequent pregnancies. They still have cyclical depression in their forties and the depression becomes worse in the 2 or 3 years of the menopause transition [27]. If they develop vasomotor symptoms of flushes and sweats they may be given oestrogens which will cure these symptoms and usually often helps the depression.

With this history in mind it is important to realize that hormone-responsive depression cannot be diagnosed by any blood test. Too frequently women who believe that their depression is related to her hormone visit their family doctor, their gynecologist or psychiatrist who measures their hormone levels which are normal and the association with hormonal changes is dismissed. These are all premenopausal women who will have normal follicle stimulating hormone (FSH) and estradiol levels which may not be optimal for the individual but they are normal. It is a huge mistake to exclude hormone-responsive depression because of normal blood levels [2]. The clue to the diagnosis is in the history and even then psychiatrists will often regard the association of depression with periods and postpartum changes as irrelevant.

Premenstrual depression

Most women will be aware of physical and mood changes a day or two before the periods, which indicates that they are premenstrual but this is not a severe abnormality. Perhaps 10% of women suffer severe premenstrual syndrome for 10–14 days a month with severe depression, behavioral changes, anxiety, aggression, loss of energy, loss of libido and somatic symptoms of headaches, abdominal bloating and mastalgia.

The American Association of Psychiatrists in their DSM IV publication has termed this premenstrual dysphoric disorder (PMDD). The word dysphoric strongly indicates a psychiatric origin of a condition we can now view as incorrect. The motive behind this renaming by psychiatrists is one done for a reason of territory and of course reimbursement in the American system. "Ovarian cycle syndrome" would be a better name as it clearly establishes the cyclical and hormonal etiology of the condition and the fact that the ovary being the architect of these changes [28], but this has not found favour with psychiatrists involved in the treatment of "PMDD".

This most common component of reproductive depression is an endocrine problem due to the hormonal changes that occur following ovulation, and it is logical that effective treatment should be one which suppresses ovulation and suppresses the ovarian hormonal changes (whatever they are) that produce the cyclical symptoms of the premenstrual syndrome. The most logical and easiest way to suppress ovulation is the birth control pill [29] but these women are usually progesterone/progestogen intolerant [30] and hence the birth control pill even when taken "back to back" will suppress cycles and even suppress bleeding if taken back to back but they may have depressive and somatic symptoms most of the time without having the usual 10 to 14 good days a month that even the most severe cases enjoy.

Suppression of ovulation by transdermal estradiol in the form of estradiol patch 200 μg twice weekly has been shown to be effective [31] and transdermal estrogen in the form of estradiol gels, oestrogel 2 measures daily or Sandrena 2 g per day, will also be effective. It is necessary to give cyclical progestogen by some route to prevent endometrial hyperplasia but it is common for the PMS symptoms to reoccur during these days, hence a minimum duration of progestogen is recommended for the first 7 days of each calendar month with a withdrawal bleeding occurring on about day 10 of each calendar month. Alternatively, a Mirena IUS is usually very effective although perhaps 10% of women do have absorption of the d-norgestrol and suffer almost continuous PMS symptoms [32]. These symptoms disappear within 24 hours of the removal of the Mirena IUS.

Alternatively, ablation of ovulation by the use of gonadotropin releasing hormone (GnRH) analogues is most effective [33] and indeed is a useful diagnostic tool if a hysterectomy and bilateral salpingo oophorectomy is contemplated [34]. There is a risk of distressing menopausal symptoms and even osteopenia so add-back hormone replacement therapy (HRT) is essential if prolonged treatment is required. This will usually be in the form of transdermal oestradiol and cyclical oral progestogen [35] which may produce a return of PMS symptoms or the insertion of a Mirena IUS. Using Livial as add-back is an effective way of avoiding bleeding and progestogenic side effects [36].

Women with severe PMS who respond partially to treatment because of progestogenic side effects or bleeding problems should be offered a hysterectomy and bilateral salpingo oophorectomy. A hysterectomy alone is not effective because the ovaries will still produce the cyclical hormonal changes and the cyclical symptoms, although menstruation has been abolished the cyclical symptoms have not.

There are now many studies showing the very beneficial effect of surgery and long-term replacement therapy for the most severe PMS [37,38]. This is a further example to indicate that the condition is endocrine and not psychiatric.

The great danger to women with severe PMS who do not respond to antidepressants is that they are given a higher dose then a second or third antidepressant which also do not work. By then they can be labeled as bipolar disorder and the scene is set for mood stabilizing drugs, antiepileptics and even electroconvulsive therapy. After ten or more years of this therapy, it is difficult but not impossible to wean them off these psychotropic drugs by transdermal estradiol that they should have had in the first place. The clues of course are in the history.

There are eight vital questions to diagnose PMS and to exclude bipolar disorder [39]:

1. Relating earlier depressive episodes to the menstrual cycle.
2. The relief of depressive symptoms during pregnancy.
3. The recurrence of depression postpartum.
4. Premenstrual depression on menstruation recurs after delivery.
5. The premenstrual depression becoming worse with age blending into the menopausal transition.
6. Often the coexistence of somatic symptoms such as menstrual migraine, abdominal bloating or cyclical mastalgia.
7. These patients usually have 7 to 10 good days per month.
8. Although depression can be cyclical they rarely have highs.

Postnatal depression

The seriousness of this condition cannot be overstated as both the mother and the child can be in great danger. It occurs in 10% of healthy women and can last for months or years. It is not the "baby blues" occurring in the week after delivery. It is usually treated with varying success with antidepressant drugs, psychotherapy or admission to mother and baby units, but once again the association with profound, abrupt hormone changes after childbirth should point to a hormonal etiology. Prolonged breast feeding that is associated with lower oestradiol levels often produces more severe and prolonged depression.

Depression has been reproduced experimentally in women with a history of postnatal depression by creating a pseudopregnancy with excess doses of oestradiol and progesterone which is then suddenly discontinued [40]. Depression occurred in women with a history of postnatal depression but not in the women in the study without a previous history of postnatal problems. Transdermal oestradiol is effective in the treatment of postnatal depression even in those women who have inadequately responded to antidepressants [41]. Unfortunately, psychiatrists rarely use this therapy preferring antidepressants, psychotherapy or admission to mother and baby units. Formerly progesterone and progestogen have been recommended but there is no evidence that they are effective. On the contrary, studies have shown them to be ineffective, and the Cochrane report has agreed that oestrogen improves mood and postnatal depression and norethisterone makes depression worse [42].

Climacteric depression

There are many reasons why women become depressed around the time of menopause. Hot flushes and sweats produce insomnia and social embarrassment, headaches are troublesome and the vaginal atrophy producing dyspareunia, recurrent cystitis together with loss of libido are enough to cause some depression. These typical symptoms of oestrogen deficiency can easily be treated with routine HRT and the low mood associated with these problems of sexuality and sleep is improved [2]. However, there is another type of depression not associated with characteristic menopausal symptoms in the 3 or 4 years before the periods cease, in the so called menopausal transition [43]. This is the depression that occurs usually in the absence of vasomotor symptoms or vaginal dryness and has been shown in many studies to be responsive to oestrogens, both oral oestrogens and transdermal oestrogens [44,45]. In fact, the evidence for the benefit of oestrogens on perimenopausal depression is more convincing than the beneficial effects in the depression of the postmenopausal woman [46]. This treatment is best done by transdermal oestrogens in the form of gels or patches continuously with cyclical progestogen if the woman has a uterus [2]. Gynecologists are aware that depression occurring in *most* perimenopausal women respond well to oestrogens given for the depression or associated symptoms although most psychiatrists are unaware of this because they do not use oestrogens. Antidepressants would be their first choice therapy.

General principles of hormone therapy for reproductive depression

The use of transdermal oestrogens is recommended to suppress ovulation in women with premenstrual syndrome, or in correcting the profound oestrogen decrease with postpartum depression. It should be the first choice therapy in perimenopausal women with depression whether they have associated vasomotor symptoms or not. But such therapy does not exclude the combined therapy with antidepressants [47]. Most studies looking at hormone-responsive depression have used transdermal patches or implants but there is no reason why oral oestrogen should not be effective although the appropriate studies have yet to be published. However, transdermal oestrogens are preferable because they do not invoke hepatic coagulation factors and are not associated with the higher rates of venous thromboembolism of oral estrogens.

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References

1. Dickens C. Household words. 1852;95:385–389.
2. Studd J. A guide to hormone therapy for the treatment of depression in women. Climacteric 2011;14:637–642.
3. Nappi RE, Tonani S, Santamaria V, Ornati A, Albani F, Pisani C, Polatti F. Luteal phase dysphoric disorder and premenstrual syndrome. It J Psych 2009;28:27–33.

4. Panay N, Studd JW. The psychotherapeutic effects of estrogens. Gynecol Endocrinol 1998;12:353–365.
5. Stahl SM. Basic psychopharmacology of antidepressants, part 2: Estrogen as an adjunct to antidepressant treatment. J Clin Psychiatry 1998;59 Suppl 4:15–24.
6. Wise PM, Dubal DB, Wilson ME, Rau SW, Liu Y. Estrogens: trophic and protective factors in the adult brain. Front Neuroendocrinol 2001;22:33–66.
7. McEwen BS, Alves SE. Estrogen actions in the central nervous system. Endocr Rev 1999;20:279–307.
8. Studd J, Panay N. Hormones and depression in women. Climacteric 2004;7:338–346.
9. Genazzani AR, Stomati M, Morittu A, Bernardi F, Monteleone P, Casarosa E, Gallo R, et al. Progesterone, progestagens and the central nervous system. Hum Reprod 2000;15 Suppl 1:14–27.
10. McCarthy MM. Estradiol and the developing brain. Physiol Rev 2008;88:91–124.
11. Laflamme N, Nappi RE, Drolet G, Labrie C, Rivest S. Expression and neuropeptidergic characterization of estrogen receptors (ERalpha and ERbeta) throughout the rat brain: anatomical evidence of distinct roles of each subtype. J Neurobiol 1998;36:357–378.
12. Weiser MJ, Foradori CD, Handa RJ. Estrogen receptor beta in the brain: from form to function. Brain Res Rev 2008;57:309–320.
13. Wise DD, Felker A, Stahl SM. Tailoring treatment of depression for women across the reproductive lifecycle: the importance of pregnancy, vasomotor symptoms, and other estrogen-related events in psychopharmacology. CNS Spectr 2008;13:647–662.
14. McEwen BS, Alves SE, Bulloch K, Weiland NG. Ovarian steroids and the brain: implications for cognition and aging. Neurology 1997;48:S8–15.
15. Stahl SM. Natural estrogen as an antidepressant for women. J Clin Psychiatry 2001;62:404–405.
16. Smith LJ, Henderson JA, Abell CW, Bethea CL. Effects of ovarian steroids and raloxifene on proteins that synthesize, transport, and degrade serotonin in the raphe region of macaques. Neuropsychopharmacology 2004;29:2035–2045.
17. Di Paolo T, Diagle M, Picard V, Barden N. Effect of acute and chronic 17 beta-estradiol treatment on serotonin and 5-hydroxyindole acetic acid content of discrete brain nuclei of ovariectomized rat. Exp Brain Res 1983;51:73–76.
18. Kugaya A, Epperson CN, Zoghbi S, van Dyck CH, Hou Y, Fujita M, Staley JK, et al. Increase in prefrontal cortex serotonin 2A receptors following estrogen treatment in postmenopausal women. Am J Psychiatry 2003;160:1522–1524.
19. Pau KY, Hess DL, Kohama S, Bao J, Pau CY, Spies HG. Oestrogen upregulates noradrenaline release in the mediobasal hypothalamus and tyrosine hydroxylase gene expression in the brainstem of ovariectomized rhesus macaques. J Neuroendocrinol 2000;12:899–909.
20. Vetrivelan R, Mallick HN, Kumar VM. Tonic activity of alpha1 adrenergic receptors of the medial preoptic area contributes towards increased sleep in rats. Neuroscience 2006;139:1141–1151.
21. Thompson TL, Moss RL. Modulation of mesolimbic dopaminergic activity over the rat estrous cycle. Neurosci Lett 1997;229:145–148.
22. Cheng CM, Cohen M, Wang J, Bondy CA. Estrogen augments glucose transporter and IGF1 expression in primate cerebral cortex. FASEB J 2001;15:907–915.
23. Shi J, Simpkins JW. 17 beta-Estradiol modulation of glucose transporter 1 expression in blood-brain barrier. Am J Physiol 1997;272:E1016–E1022.
24. Nappi RE, Rivest S. Ovulatory cycle influences the stimulatory effect of stress on the expression of corticotropin-releasing factor receptor messenger ribonucleic acid in the paraventricular nucleus of the female rat hypothalamus. Endocrinology 1995;136:4073–4083.
25. Tahboub R, Arafah BM. Sex steroids and the thyroid. Best Pract Res Clin Endocrinol Metab 2009;23:769–780.
26. Studd J. Why are estrogens rarely used for the treatment of depression in women? Gynecol Endocrinol 2007;23:63–64.
27. Burger HG, Hale GE, Robertson DM, Dennerstein L. A review of hormonal changes during the menopausal transition: focus on findings from the Melbourne Women's Midlife Health Project. Hum Reprod Update 2007;13:559–565.
28. Studd J. Ovarian cycle syndrome. Gynecol Endocrinol 2009;25:74.
29. Rapkin AJ. YAZ in the treatment of premenstrual dysphoric disorder. J Reprod Med 2008;53:729–741.
30. Panay N, Studd J. Progestogen intolerance and compliance with hormone replacement therapy in menopausal women. Hum Reprod Update 1997;3:159–171.
31. Watson NR, Studd JW, Savvas M, Garnett T, Baber RJ. Treatment of severe premenstrual syndrome with oestradiol patches and cyclical oral norethisterone. Lancet 1989;2:730–732.
32. Elovainio M, Teperi J, Aalto AM, Grenman S, Kivelä A, Kujansuu E, Vuorma S, et al. Depressive symptoms as predictors of discontinuation of treatment of menorrhagia by levonorgestrel-releasing intrauterine system. Int J Behav Med 2007;14:70–75.
33. Leather AT, Studd JW, Watson NR, Holland EF. The prevention of bone loss in young women treated with GnRH analogues with "add-back" estrogen therapy. Obstet Gynecol 1993;81:104–107.
34. Wyatt KM, Dimmock PW, Ismail KM, Jones PW, O'Brien PM. The effectiveness of GnRHa with and without 'add-back' therapy in treating premenstrual syndrome: a meta analysis. BJOG 2004;111:585–593.
35. Leather AT, Studd JW, Watson NR, Holland EF. The treatment of severe premenstrual syndrome with goserelin with and without 'add-back' estrogen therapy: a placebo-controlled study. Gynecol Endocrinol 1999;13:48–55.
36. Di Carlo C, Palomba S, Tommaselli GA, et al. Use of leuprolide acetate plus tibolone in the treatment of severe premenstrual syndrome. Fertil Steril 2001;76:850–852.
37. Casson P, Hahn PM, Van Vugt DA, Reid RL. Lasting response to ovariectomy in severe intractable premenstrual syndrome. Am J Obstet Gynecol 1990;162:99–105.
38. Cronje WH, Vashisht A, Studd JW. Hysterectomy and bilateral oophorectomy for severe premenstrual syndrome. Hum Reprod 2004;19:2152–2155.
39. Studd J. Spotlight on severe premenstrual syndrome and bipolar disorder: a frequent tragic confusion. Climacteric 2011;14:602.
40. Bloch M, Schmidt PJ, Danaceau M, Murphy J, Nieman L, Rubinow DR. Effects of gonadal steroids in women with a history of postpartum depression. Am J Psychiatry 2000;157:924–930.
41. Gregoire AJ, Kumar R, Everitt B, Henderson AF, Studd JW. Transdermal oestrogen for treatment of severe postnatal depression. Lancet 1996;347:930–933.
42. Dennis CL, Ross LE, Herxheimer A. Oestrogens and progestins for preventing and treating postpartum depression. Cochrane Database Syst Rev 2008;4:CD001690.
43. Dennerstein L, Lehert P, Burger H, Dudley E. Mood and the menopausal transition. J Nerv Ment Dis 1999;187:685–691.
44. Brincat M, Magos A, Studd JW, Cardozo LD, O'Dowd T, Wardle PJ, Cooper D. Subcutaneous hormone implants for the control of climacteric symptoms. A prospective study. Lancet 1984;1:16–18.
45. Soares CN, Almeida OP, Joffe H, Cohen LS. Efficacy of estradiol for the treatment of depressive disorders in perimenopausal women: a double-blind, randomized, placebo-controlled trial. Arch Gen Psychiatry 2001;58:529–534.
46. Montgomery JC, Appleby L, Brincat M, Versi E, Tapp A, Fenwick PB, Studd JW. Effect of oestrogen and testosterone implants on psychological disorders in the climacteric. Lancet 1987;1:297–299.
47. Graziottin A, Serafini A. Depression and the menopause: why antidepressants are not enough? Menopause Int 2009;15:76–81.