Understanding Climacteric Depression and Depression in Other Phases of Women’s Life

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ABSTRACT

Neuroanatomical and hormonal peculiarities of women are cause of higher prevalence of depression in females compared to males. Endogenous estrogen and progesterone have a profound effect on neurophysiology and neural pathways, this is the reason why depression is more common at the time of hormonal fluctuations, such as premenstrual, postpartum, premenopausal. Unique differences in life experiences, temperament and biology suggests no single treatment is effective for everyone, combination of psychotherapy and medications should be used.

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REPRODUCTIVE DEPRESSION AND OVARIAN HORMONES

Depressions in women commonly occur at times of hormonal changes, most commonly seen as 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. Depression is seen at its most severe form in perimenopausal age group, i.e. 2 to 3 years prior to cessation of menstrual cycle. Together these three components, premenstrual depression, postnatal depression and climacteric depression with their probable endocrine etiology mostly influenced by changes in ovarian hormones are best termed ‘Reproductive Depression’ as originally suggested by Nappi et al.

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.

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.

Virtually every neural pathway (serotonergic, dopaminergic, noradrenergic, cholinergic, GABAergic, etc.) responds to estrogens. 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, it is then that depression occurs in vulnerable women.

Progesterone and its neuroactive metabolities are also active at certain neural pathways, especially the gamma-aminobutyric acid A (GABA) receptor to modulate mood changes.

Both ERα and ERβ receptor subtypes are located in brain regions associated with cognitive function and emotion. ERα is 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.

Estrogen regulates gene products, such as brain-derived neurotrophic factor, neurotransmitter synthesizing enzymes, neurotransmitter metabolizing enzymes and neurotransmitter receptors. 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.\textsuperscript{11}

Estrogen may be considered a neuroprotective agent at multiple levels of the nervous system.\textsuperscript{12} 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, and also increases the 5-HT content and activity in raphe neurons.\textsuperscript{13} In postmenopausal women, reproductive medicine network (RMN) findings showed that a short period estrogen treatment increased 5-HT2A receptors in the right prefrontal cortex improving verbal fluency and cognition.\textsuperscript{14} Estrogen also positively modulates the noradrenergic network and its hypothalamic targets by increasing \(\alpha_{1B}\) noradrenergic receptors.\textsuperscript{15} Similarly, the dopaminergic system is positively affected by estrogen, DA release and reuptake in several brain area, including the nucleus accumbens. Another neuroprotective activity of estrogen is enhancing the expression of glucose transporter therapy increasing glucose uptake and utilization at the blood-brain barrier and on the membranes of neurons.\textsuperscript{16}

Estrogen strongly modulates other endocrine functions, such as the activity of the adrenal and thyroid glands and circadian rhythmicity.

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.

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.

The typical story is of the 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, pre-eclampsia or other obstetric complications. After delivery, they develop postnatal depression for many months.

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. If they develop vasomotor symptoms, such as flushes and sweats, they may be prescribed estrogens which will cure these symptoms and usually also help the depression.

**PREMENSTRUAL DEPRESSION**

There are eight vital questions to diagnose PMS and to exclude bipolar disorder as follows:

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

The American Association of Psychiatrists in their DSM IV publication has termed this premenstrual dysphoric disorder. 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,\textsuperscript{17} but this has not found favor with psychiatrists involved in the treatment of ‘premenstrual dysphoric disorder’ (PMDD).

The most logical and easiest way to suppress ovulation is the birth control pill but these women are usually progesterone/progestogen intolerant.

- 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.
- Alternatively, a Mirena IUS (Bayer), a levonorgestrel-releasing intrauterine system, is usually very effective, although perhaps 10% of women do have absorption of the D-norgestrel and suffer almost continuous PMS symptoms. These symptoms disappear within 24 hours of removal of the Mirena IUS.
- Ablation of ovulation by the use of GnRH analogues is most effective and indeed is a useful diagnostic tool if a hysterectomy and bilateral salpingo-oophorectomy is contemplated. 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.
Using livial (tibolone) as add-back is an effective way of avoiding bleeding and progestogenic side effects.

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.

Mood stabilizing drugs, antiepileptics and even electroconvulsive therapy after 10 or more years of this therapy, it is difficult but not impossible to wean them off these psychotropic drugs by transdermal estradiol which they should have had in the first place.

**POSTNATAL DEPRESSION**

National Institute of Health and Care Excellence (NICE) have recommended that for women with a new onset of mild to moderate depression in the postnatal period, self-help strategies, nondirective counseling and brief courses of cognitive-behavioral therapy or interpersonal psychotherapy should be offered first, with antidepressant medication reserved for those who are resistant to the above, those with a history of severe depression and those who decline psychological treatment. For those with moderate depression with a history of a depressive episode or those with severe depression during the postnatal period, treatment should be structured psychological treatment or, if the patient has a preference for them, with antidepressants. If either of these treatments fail, a combination of the two treatments should be considered.18

Treatment with high doses of estrogen did appear to reduce the depression scores of women with severe postnatal depression, but the potential side effects of thromboembolic disease, endometrial hyperplasia and inhibition of lactation make this an unattractive therapy for women to take. Progesterone therapy was associated with a higher incidence of postnatal depression than placebo. This could be because the mood elevation seen with natural progesterone is not an effect of synthetic progestogens. Therefore, these medication cannot be recommended for women with postnatal depression. Modern therapy, therefore, revolves around supportive therapy and pharmacological treatments.

Transdermal estradiol is effective in the treatment of postnatal depression even in those women who have inadequately responded to antidepressants. Unfortunately, psychiatrists rarely use this therapy preferring antidepressants, psychotherapy or admission to mother and baby units.

Cochrane report has agreed that estrogen improves mood and postnatal depression and norethisterone makes depression worse.19

**CLIMACTERIC DEPRESSION**

Hot flushes and sweats produce insomnia and social embarrassment, headaches are troublesome and their vaginal atrophy producing dyspareunia, recurrent cystitis together with loss of libido are enough to cause some depression.

However, there is another type of depression not associated with characteristic menopausal symptoms it usually occurs in perimenopausal age group, i.e. 2 to 3 years prior to cessation of menstrual cycle; in the so-called menopausal transition. This is the depression that occurs usually in the absence of VMS or vaginal dryness and has been shown in many studies to be responsive to estrogens, both oral and transdermal estrogens. In fact, the evidence for the benefit of estrogens on perimenopausal depression is more convincing than the beneficial effects in the depression of the postmenopausal women.

**Puerperal Psychosis**

This is a psychiatric emergency and its treatment requires hospitalization. As it is preferable to avoid separation of the mother from her infant, admission to a specialized mother and baby unit should be arranged, where antidepressant and neuroleptic medications can be initiated and supervised by psychiatrists (C). Failure to treat the condition aggressively is associated with rates of infanticide as high as 4%.19 This aggressive treatment may include electroconvulsive therapy.

**Hysterectomy**

The belief that hysterectomy causes profound depression, loss of sexuality and marital breakup the reverse is true. In younger women having persistent cyclical depression as well as other cyclical problems of bleeding, pain and cyclical headaches, hysterectomy with bilateral oophorectomy will usually cure these problems. In the specific case of premenstrual depression in those women with progestogen intolerance, hysterectomy with bilateral oophorectomy and replacement of estradiol and testosterone have been shown in all studies to be beneficial.

**GENERAL PRINCIPLES OF HORMONE THERAPY FOR REPRODUCTIVE DEPRESSION**

For the women with libido and energy problems, which often coexist with depression and treatment by antidepressants, testosterone can be added in the form of testosterone gel in the appropriate dose. This would be approximately 10% of the average make dose which in practical terms would be one quarter of a sachet of testogel (testosterone) on alternative days or a quarter
of a tube of testim (testosterone gel) on alternate days. 100 mg testosterone pellets would be ideal but, at the time of writing, they are no longer available.

REFERENCES