Reproductive hormones as psychotropic agents?

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Abstract
The female preponderance in unipolar mood and anxiety disorders is well documented, with a double to triple lifetime prevalence compared to males. Much of this increased vulnerability is in the childbearing years. Hormones are a tempting explanation, although other biochemical factors such as cytokines may also be important. Psychosocial factors are clearly involved, including role issues.

Introduction

Primary care physicians and women's health specialists prescribe most psychotropic agents. Practitioners increasingly need to understand the role of reproductive hormones in psychiatric disorders. There is much research on the interaction between mood and endocrine factors that is impacting on the practice of women's health.

Hormone fluctuations are linked to behavioural changes as well as the onset and recurrence of mood disorders. Reproductive hormones can be both exacerbators and mitigators of psychiatric disorders. The role of reproductive hormones in management of mood disorders is increasingly coming under scrutiny

Neurochemistry of hormones

Oestrogen has a rich neurochemistry. Oestrogen interacts with neurotransmitters, including serotonin, acetylcholine and noradrenaline; these are key in both mood regulation and the mode of action on antidepressants. Oestrogens actions on neurotransmitters may explain their effect on behaviour and therapeutic mechanism

Oestrogen increases serotonin transporters, decreases mono amine oxidase (MAO) activity, and is permissive for serotonin receptor ($5HT_2$) downregulation by antidepressants. This is the understood antidepressant mechanism of action. In addition, oestrogen has effects on intracellular signal transduction. Ovariectomised rats cannot downregulate serotonergic receptors thus impairing antidepressant action which is restored by oestrogen. Serotonin receptors are desensitised in postmenopausal women; this is normalised with oestrogen supplementation. This may explain the synergy of oestrogen and antidepressants in some depressed women. Both oestrogen and serotonin exert their effect via transcription factors which alter gene expression

Many of the effects of oestrogen, especially on cognition may be via acetylcholine. Oestrogen enhances acetylcholine synthesis, increases choline acetyltransferase activity, and alters muscarinic receptors and firing rates in the hypothalamus. There is a suggestion that oestrogen may prevent or delay Alzheimers disease, with studies demonstrating improved memory with oestrogen. The question of whether oestrogen should be used as part of the treatment of Alzheimers disease deserves further study.

Oestrogen in addition has an effect on noradrenaline (NA). It Alters tyrosine hydroxylase activity, NA turnover and NA reuptake. It also decreases activity of, the catabolic enzymes of NA. Oestrogen alters $alpha_2$ and $beta_2$ adrenoreceptor binding sensitivity as well as dopamineD_2 receptor sensitivity. It may modulate mood through these mechanisms

Oestrogen induces neuronal growth in the rodent brain. In addition, oestrogen builds synapses at commencement of the menstrual cycle; progesterone dismantles them. Progestins have benzodiazepine like effects acting as a partial agonist at appropriate receptors, which led to speculation that it could be anxiolytic. More importantly progestrone appears to mitigate oestrogens effects, and can have mood destabilising effects. Dysphoric effects of progesterone are well documented with contraceptives and hormone replacement therapy (HRT). Adding progesterone to oestrogen can counteract oestrogens effects, especially if given sequentially. However there are multiple progestins and metabolites which may differ significantly; there is minimal data in this regard. Progesterone antagonists such as mifiprestone are thus potentially psychotropic; only one study of this agent in premenstrual syndrome was however negative.

A double blind randomised placebo controlled trial of norethisterone in the postnatal period involving 180 postnatal women showed that there was a significantly higher depression rating scale (MADRS) score in the norethisterone

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(8.3) group compared to placebo (4.9). Significantly, 11 vs 5 women respectively met threshold criteria for a depressive episode. Rates of emergent postnatal depression were thus double in the norethisterone group compared to placebo. This confirms the possible mood destabilising effects of progesterone.

Premenstrual syndrome

Cyclical mood changes, such as in the late luteal phase are frequent. Oral contraceptives, menopause, and HRT also impact on mood. Many such changes are normal and there is a dilemma. Setting the diagnostic threshold too low pathologises physiology, while setting threshold too high leaves people with disabling and treatable symptoms.

Approximately 20-80% of women report mood or somatic symptoms in late luteal phase. Premenstrual dysphoric disorder (PMDD) [DSM-IV] has severe cut offs; using these criteria, 5% rates are reported in epidemiological studies. The onset is typically in the teens to 20's and peaking in the 3rd to 4th decade. PMDD may progress to a major depressive disorder. The aetiology of PMDD is unknown, and is thought to be an effect of hormones on neurotransmitter, circadian and neuroendocrine systems. Studies show that irritability is the core feature of the syndrome. The symptom profile differs from mood or anxiety disorders, and tends to be stable across cycles. Biological markers such as the hypothalamic pituitary adrenal (HPA) axis appear normal in PMDD, unlike in depression

Many treatments for PMDD have been studied, including diuretics, progesterone, B group vitamins, evening primrose oil, all of which have received inadequate support from well designed randomized controled trials (RCT). Cycle abolition stops PMDD, using agents such as danazol. There is some evidence of efficacy of gonadotrophin antagonists (leuprolide) alone and with conjugated oestrogen and medroxyprogesterone. However there are cases of depression and panic with leuprolide.

The most effective treatment in RCT's are the selective serotonin reuptake inhibitors (SSRI). There are at least 17 positive randomised controlled trials for all SSRIs including fluoxetine, paroxetine, citalopram sertraline fluvoxamine and clomipramine. Of interest, they are effective for somatic (breast tenderness, bloating) and psychic symptoms (irritability). New data suggests that SSRIs used only in the luteal phase may be as effective as continuous administration.

Depression and pregnancy

Rates of depression in pregancy approximate those in nongravid women. Depression in pregnancy is associated with poor perinatal outcome,e.g low birth weight and preterm delivery and may be associated with decreased appetite and self medication with alcohol, cigarettes, and over the counter drugs. Depression in pregnancy is associated with a clearly increased risk of postnatal depression. There are complex interactions between pregnancy and anxiety. Some studies indicate a decrease in panic symptoms in pregnancy. On the other hand, a number of studies indicate that pregnancy may be associated with de novo obsessive compulsive disorder (OCD)or exacerbation of OCD symptoms.

Animal studies show maternal stress may lead to long term behavioural changes in infants. There is greater HPA axis reactivity, greater fearfulness in novel environments, and abnormalities in social behaviour. The course and treatment of depression in pregnancy is poorly studied.

Perinatal mood disorders are traditionally divided into the baby blues, postpartum depression and postpartum psychosis. Baby blues is the mildest of the postnatal mood disturbances. It occurs in 26-85% of all mothers, begins in first week, peaks on day 5, and resolves by day 12. It is transient and does not cause significant impairment in functioning. No specific management is usually necessary.

Postnatal depression occurs in 10-15% of mothers, occurs within weeks of delivery and tends to resolve within 3-6 months. The symptoms resemble typical major depression. It is, however, unique in timing, and involves the mother child dyad although often the whole family. This should be treated as per the condition at any other time. However, in addition to routine management, specific psychological factors may need to be addressed. Oestrogen patches were useful in one study.

Postpartum psychosis is the most rare and severe form occurring in 1:500 to 1:1000 births. It has a rapid onset within a few days to 2 weeks. It most commonly represents an episodic presentation of bipolar disorder. There is a substantial impairment of function and a high risk of suicide and infantacide. Hospitalisation is typically necessary.

The aetiology of postnatal depression is unclear. There is no consistent link to hormonal changes, or strong evidence of genetic factors. It may be associated with rapid beta endorphin withdrawal. Interestingly, there are very high levels of cytokines in the postnatal period, and cytokines are thought to be linked to the aetiology of depression. Altered serotonin receptors, alpha 2 adrenoceptors and dopamine receptors are described. Altered oestrogen may modulate these neurotransmitter changes.

Psychological factors such as lack of social support, negative life events, occupational instability, little experience with children, unplanned pregnancy, poor marital relationship, disaffection with being single, or a poor relationship with own mother appear to be related to the aetiology of postnatal depression.

Major depression is typically undetected. Most patients in primary care are neither adequately diagnosed or treated. This is more likely to happen when: there is concurrent physical illness, when symptoms are mentioned late in the consultation, the doctor listens less, and there is a lower index of suspicion and awareness

Menopause

For most women, mental health is not adversely affected by menopause. Rates of depression actually fall after menopause, although peak at the menopausal transition and with childbirth. Rates of depression roughly track plasma oestrogen levels. The perimenopausal period is associated with both new onset of depression and recurrence.

Oestrogen deficiency may decrease serotonergic activity in the menopause. Infusion of a serotonin agonist is associated with a blunted prolactin response in postmenopausal women compared to premenopausal women. Oestrogen deficiency may also desynchronise circadian rhythms, which is a finding in depression.

Epidemiological data from oestrogen replacement therapy (ORT) studies of women over 60 suggest that oestrogen has antidepressant effects. The response is more dramatic in

oophorectomised women than with natural menopause. This is strongly suggested by a trial that found that ORT in elderly depressives is associated with higher response rates with fluoxetine treatment.

Testosterone levels decline with age, and there is provisional data suggesting utility of androgens in postmenopausal and women after surgical menopause. There may be possible beneficial effects on bone mass and sexual function. Further study is however needed. There is a small literature on the use of androgens in male depression, a field that also deserves further study.

Physiological data suggests a role for oestrogen as an antidepressant. Unfortunately, evidence for its role as an antidepressant remains unclear. Studies of monotherapy are mainly disappointing. Nevertheless over 30 studies exist suggesting oestrogen stabilises mood and increases wellbeing in non-depressed postmenopausal women. Serotonin downregulation is the major hypothesis of antidepressant mechanism of action. Oestrogen can alter the ability of serotonin to downregulate receptor responsivity in postmenopausal women. There may be synergy between serotonin and antidepressants. This suggests that supplementation in oestrogen deficient postmenopausal women may be useful.

Few studies of oestrogen in resistant depression exist mainly with the older tricyclics. The data is limited by a number of methodological difficulties. There are case reports and uncontrolled studies only, various oestrogens have been used, often at high doses and pre, peri and post menopausal women have been combined. There is conflicting data which is largely negative. One study using fluoxetine study (N=658) reported 3 times greater response rates in women receiving oestrogen. Controlled data, especially with serotinergic agents is needed.

In mild depression with prominent vasomotor symptoms, some authorities advocate using oestrogen first followed by antidepressants if there is no response. In major depression in a perimenopausal woman, antidepressants and psychotherapy should arguably be used first with oestrogen for vasomotor, bone and heart indications. This practice would utilise the possible synergistic effects of oestrogen and antidepressants on mood.

New data is clarifying the role of reproductive hormones in CNS. This is impacting on the understanding of mood and the treatment of mood disorders. Rational use of hormones as psychotropic agents is clinically necessary. However this remains a neglected area, and much data is still needed.

Bibliography

1. *Chakravarti, S., Collins, W.P., Thom, M.H., Studd, J.W. (1979). Relation between plasma hormone profiles, symptoms, and response to oestrogen treatment in women approaching the menopause. British Medical Journal, 1, 983-5*
2. *Genazzani, A.R., Petraglia, F., Facchinetti, F., Grasso, A., Alessandrini, G., Volpe, A. (1988). Steroid replacement treatment increases beta-endorphin and beta-lipotropin plasma levels in postmenopausal women. Gynecologic and Obstetrics Investigation, 26, 153-59.*
3. *Khastgir, G., Studd, J., (1998). Hysterectomy, ovarian failure, and depression. Menopause, 5, 113-22.*
4. *Palacios, S., Menendez, C., Jurado, A.R., Castano, R., Vargas, J.C. (1995). Changes in sex behaviour after menopause: effects of tibolone. Maturitas Journal of the Climacteric & Postmenopause, 155-60.*
5. *Panay, N., Studd, J.W. (1998). The psychotherapeutic effects of estrogens. Gynecological Endocrinology, 12, 353-65.*
6. *Sands, R., Studd, J.W. (1995). Exogenous androgens in postmenopausal women. American Journal of Medicine, 98, 76S-79S.*
7. *Sherwin, B.B. (1985). Changes in sexual behaviour as a function of plasma sex steroid levels in menopausal women. Maturitas, 7, 225-33.*
8. *Sherwin, B.B. (1985). Sex steroids and affect in the surgical menopause: a double-blind, cross study. Psychoneuroendocrinology, 10, 325-35.*

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COMMENTARY

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The article is a summary of current science on the subject. It is important to emphasize the extent to which the presentation, symptoms, treatment and course of mental illnesses in women are different from men. These factors should always be considered in the management of mental disorders in women.

Hormonal factors are particularly important in illnesses related to the premenstual peripartum and perimenopausal periods.

The paper emphasizes the high incidence of major depression in the post partum period of which much goes unrecognised; probably explained away. This leaves many depressed women untreated.

While oestrogen may play an important role in the management of depression in perimenopausal woman, psychiatrists need to be knowledgeable about the indications for and problems associated with hormone replacement. It is wise to be working in close association with the gynaecologist treating the patient and to avoid solo management in cases which can be very complex. The complexities lie in the interactions of hormones with psychotropic drugs and in the possible unwanted systemic effects of the hormone therapies. SAPR

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