REVIEW ARTICLE

Insights into Reproductive Psychiatry: A Literature Review

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ABSTRACT
This review article scrutinizes the role of male and female reproductive hormones on behavioural and psychological levels. Research suggests that estrogen serves as a protective hormone against psychosis in females, and that women are most prone to acute psychotic states during their menopausal years. Estrogen-driven dopamine levels are regulated, as shown by strong evidence that younger females are less likely to experience psychosis than older women. However, higher testosterone levels in males can cause an upsurge of dopamine levels, making younger men more prone to psychosis than older males. The role of other reproductive hormones (such as pregnenolone) on dopamine levels and therefore risk of psychosis is also explored from a psychiatric angle.

Hena Jawaid

INTRODUCTION

A woman achieves a variety of reproductive milestones throughout her life. From the time of her birth, ranging from puberty with the onset of menarche, all the way to pregnancy until the stage of menopause, hormonal disturbances continue. The intricacies and upheavals of estrogen, progesterone, oxytocin and gonadotrophic hormones play significant roles in conjunction with neurotransmitters. The dramatic highs and lows generate a psychiatric spectrum ranging from premenstrual depression (premenstrual syndrome or premenstrual dysphoric disorder) to postnatal depression/psychosis and peri-menopausal depression.

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Outline of the Reproductive Lifespan

Stages of the menarche comprise of the 1) follicular phase and 2) the luteal phase. The surge of estrogen in the follicular phase under the influence of follicular stimulating hormone and luteinizing hormone (LH) proliferate the inner layer of the uterus, the endometrium. The surge of LH increases estrogen and here, ovum is released from the ovaries. The cycle then enters the luteal phase where the progesterone rise enriches the endometrium with capillaries. Gonadotrophic hormonal influence declines here. The proximity with sperm defines the fate of cycle from here. The process of fertilization leads to impregnation, otherwise the superficial layers of endometrium shed off secondary to lower levels of progesterone, giving rise to menstruation. Menopause is one of the most important milestones of a woman's life; the term menopause transition (MT) was recently coined to elaborate peri-menopusal changes. The hormonal instability manifests itself psychologically via mood changes (mainly depression), but in other cases where there is a history of frequent manic episodes, mood elevation can occur during the MT phase.[1]

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Estrogen and the Brain

Estrogen has an excitatory effect on the brain. Various studies have shown substantial improvement in psychosis during the luteal phase of the menstrual cycle.[2] During the menstrual cycle, changes in the estrogen level cause exacerbation or remission of psychosis or seizures among predisposed individuals. Estrogen also serves as a protective hormone and has been included in various trials as an antipsychotic.[3]

Estrogen provides a dimorphic insight into schizophrenia as a sexual and a psychiatric illness. The presence of estrogen receptors in the limbic system (emotional hub), basal ganglia (impulsivity) and many areas of the cerebral cortex (rational hub) defines its role in mood, behavior and perception.[4] In another study, the presence of androgen and estrogen receptors were found in the medial amygdala, bed nucleus of stria terminalis, and lateral septum in the basal forebrain.[5] The pulsatile increase in estrogen and androgen reshapes axons and receptors in different brain areas, which affects a person on behavioral, physical and cognitive levels. This pulsatile release of LH correlates with the bursts of neuronal discharge in the arcuate nucleus of the hypothalamus, amygdala, bed nucleus of Stria Terminalis, and septal limbic nuclei. The phenomenon is active during phases such as sexual intercourse and ovulation.

Molecular level mechanisms include changes in serotonin transmission, binding, and metabolism by estrogen, which affects mood and cognitive functions. The extra-hypothalamic regulatory system comprising of the anterior basal forebrain network (containing gonadotropic hormones and androgen and estrogen receptors) have a direct influence on reproductive behavior at the sensory, motor, and affective levels. Two lines of thought begin to surface within this hypothesis.

1. Estrogen Protective Hypothesis

This concentrates on the pre-menstrual phase, which defines natural psychosis protection in young females due to the presence of estrogen. Increased incidence of psychosis during postmenopausal age is due to the decline of estrogen.

2. Hypoestrogenism

This hypothesis stands on the phenotypic dysfunction of estrogen and gonadal axis. A prospective observational study with a 24-month follow-up period was conducted in women suffering from delusional disorder. The purpose was to investigate the differences between premenopausal onset and postmenopausal onset psychosis in terms of socio-demographic differences. Table 1 outlining differences in symptomatology between pre-menopausal and post-menopausal psychosis.

The parallel play of estrogen-derived dopamine regulation can be reflected via loss of 30% of dopamine neurons from the substantia nigra after oophorectomy in a study conducted on monkeys.[6] other studies have also suggested some other important markers of psychotic illness in premenopausal women. Table 2 highlights the symptomatology of premenopausal psychosis, estrogen-led serotonin changes produce antidepressant effects, too. This is enhanced in peri-menopausal women more than in postmenopausal women.[7] This finding on mood disturbances in peri-menopausal phase is more in line with the hormonal changes and thus the response is better with hormonal interventions. The use of transdermal estrogen (continued with monthly Progestogen for endometrium protection) is highly suggested for the reproductive depression (perimenopausal) to avoid the hepatic phase and the eventual risk of deep venous thrombosis.[8]

However, this abovementioned pattern of estrogen-led serotonin-based changes can be misdiagnosed as bipolar disorder because of the cyclical nature of depression, whereas remission phases can be mistaken for hypomanic states.[9] Misdiagnosis and maltreatment (use of antidepressants) can lead to decreased libido and hypoenergia. However, the markers that can help differentiate between these two may be 1) the presence of dysphoria before onset of a cycle, 2) a regular cyclical pattern, 3) the mood symptoms occur simultaneously with somatic symptoms, 4) symptomless pregnancy followed by post-delivery (post-natal) depressive symptoms and 5) the presence of good functioning between periods.

The neuro-protective role of estrogen facilitates synaptogenesis, neural plasticity, dendritic branching and axonal myelination.[10] This has been referred to as the "organizational effect of sex steroids". The activational effect

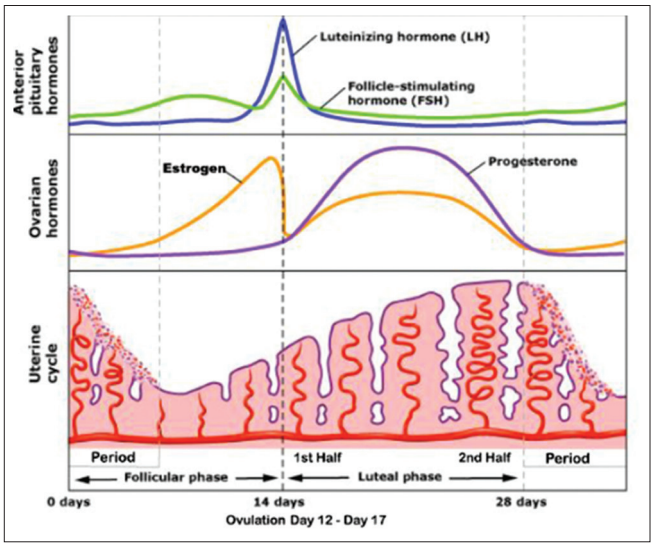

Photo credit: http://nicolejardim.com/lengthen-your-luteal-phase/

Table 1: Differences between pre-menopausal and post-menopausal psychosis

Pre-menopausal onset - psychosis	Post-menopausal - psychosis
Longer duration of psychosis (DUP)	Shorter DUP
Higher educational level	Lower educational level
Erotomanic type delusions	Jealous and somatic type delusions Tactile and visual non-prominent hallucinatory phenomena (A. Hasset, 2002)
Better insight	Poorer insight
More depressive symptoms	
Higher psychotic relapse rates	

Table 2: Pre-menopausal psychosis - a summary of Morgan et al., 2008 and Cotton et al., 2009

Criteria	Pre-menopausal psychosis
Course of illness	Benign
Levels of psychopathology	Less severe
Insight	Partial to present in most cases
Functioning	Less compromised
Treatment	Better response to antipsychotics

of sex steroids comes into play during adolescence.[11] The plummeting of estrogen at menopause causes degeneration and atrophy of neural structures with retention of protein material (which should be expelled from the cell bodies), thereby affecting cognition, memory, judgment and behavior. The higher incidence of Alzheimer's in females denotes this psychopathology. In men, the part of dihydroepiandrosterone (DHEA) changes into estrogen, which eventually has a protective role.

Testosterone

Procedures such as hysterectomies (female androgen deficiency syndrome) are also used as a management strategy for cyclical or hormonal depression. The intermittent use of testosterone (because of its mood-enhancing effect) with or without estrogen is quite helpful in terms of elevating sexual desire and energy.[12] However, testosterone in schizophrenia proves to be counter-productive as it regulates and increases dopamine synthesis.[13] The somato-dendritic control of dopamine neurons by testosterone also includes higher expression of dopamine receptors in the midbrain.

Pregnenolone

Pregnenolone, a precursor of progestogens is also under investigation. Psychotic patients demonstrate lower levels of pregnenolone. An antipsychotic use increases pregnenolone levels, causing remission of symptoms.[14] A study indicates that the higher the level of oxytocin, the lower the symptom morbidity will be.[15] In another interventional approach, the intranasal oxytocin supplement decreased the positive symptoms of psychosis.[16]

Androgen enhances the activity of alcohol dehydrogenase. This increased activity causes more alcohol excretion and predisposes a person to develop substance dependence. The phenomenon is reversed in female bodies where lower metabolic activity of alcohol dehydrogenase causes greater absorption of alcohol and thus renders them to develop toxicity.[17] Thus there is a higher prevalence of neurological, medical complications, early dependence and mortality risks.

CONCLUSION

The discovery of reproductive hormones and their roles in psychiatric illnesses has initiated an avenue of devising new psychiatric/therapeutic strategies for psychosis and mood disorders. The course of treatment has been modified with respect to reproductive age. The idea that psychiatric illnesses are the result of impaired hormonal levels has now led to the concept of hormonal therapy for mental diseases. Along this line of thought, the protective effect of reproductive hormones such as **estrogen** on neurons is significant for further exploration in terms of psychiatric disease management.

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