Neuroendocrine Networks and Functionality

Margaret Altemus, MD

KEYWORDS

• Estrogen • Progesterone • Puberty • Lactation • Menopause • Menstrual cycle • Pregnancy

KEY POINTS

- Premenstrual symptoms most commonly include irritability, tension, mood lability, sleep changes, fatigue, increased appetite, and fluid retention, and are stimulated by luteal secretion of progesterone.
- During pregnancy, physiologic responses to stress are relatively suppressed but there is no reduction in rates of depression or other psychiatric disorders during pregnancy.
- After delivery, women are at increased risk for relapse or first episode of bipolar disorder. Women with antithyroid antibodies are at high risk for developing hyperthyroidism or hypothyroidism postpartum.
- The risk of major depression in increased in women compared with men from the onset of ovarian cycling at puberty until menopause, with the highest relative risk occurring in the years preceding menopause.

Women undergo developmental and cyclic changes in hormonal exposures that affect brain function and some aspects of mental health. The fluctuations in gonadal steroids and hypothalamic-pituitary-adrenal (HPA) axis regulation across the menstrual cycle and pregnancy are necessary for conception and gestation but also expose women to repeated and large perturbations of gonadal steroid and glucocorticoid responsive brain systems. In addition, the thyroid axis is at increased risk of dysregulation during and after pregnancy, which in turn increases risk for affective illness.

It is important to note that there are large individual differences in the activational effects of reproductive hormones on behavior. Although almost all women undergo the hormonal fluctuations related to menstruation, pregnancy, and menopause, few women (3%–5%) experience the intense perimenstrual negative affect that occurs in women with premenstrual dysphoric disorder (PMDD)[1] and, similarly, small subgroups of women experience postpartum or perimenopausal depression.[2,3] The bulk of research indicates that these subgroups of women experience the typical

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VA Connecticut Health Care System, Women's Clinic, Building 2, Room 7-165, 950 Campbell Avenue, New Haven, CT 06516, USA
E-mail address: margaret.altemus@yale.edu

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changes in levels of estrogen, progesterone, and other reproductive hormones but a suboptimal central nervous system response that leads to negative affect and maladaptive behaviors.[4,5] Both inherited genotype and developmental experiences likely contribute to these individual differences among women. Life experiences and cultural expectations clearly shape subjective experience, resiliency, and behavior. In addition, there is evidence that experience alters gene expression and contributes to biological changes in brain and physiology throughout the lifespan.[6] Finally, it can be difficult to tease apart the effect of hormonal changes associated with puberty, pregnancy, and menopause from the profound psychosocial changes that can accompany these life stages.

The onset of anxiety and affective disorders peaks during adolescence and early adulthood, with female patients being at significantly greater risk than male patients. Women have twice the lifetime rates of depression and most anxiety disorders.[7–10] The exceptions in term of sex ratio are obsessive compulsive disorder (OCD) and bipolar disorder, which have similar prevalence in men and women. However, even for these disorders, men and women have differences in disease presentation and course.[11–13] In addition to higher rates of affective disorders that meet full diagnostic criteria, subclinical anxiety and depression symptoms are also more common in women.[14,15] Sex differences in prevalence rates and symptom course of other psychiatric disorders are less clearly linked to adult hormonal fluctuations, with the exception of schizophrenia.

This article summarizes hormonal fluctuations in women across development and the associated impact on mental health.

PRENATAL

There are multiple organizational effects of gonadal steroid exposure during development.[16,17] In humans, exposure to fetal sex hormones starts at gestational week 7, at which point the male fetus begins to produce testosterone, resulting in differentiation of the male genitalia and sex differences in the brain and other tissues. Testosterone levels peak in the fetal serum in males between weeks 12 and 18 of pregnancy.[18] Immediately after birth, there is a second peak in testosterone in boys and a peak in estrogens in girls.[19] The testosterone levels of the male newborn are ten times higher than those of the female and this surge persists for 3 months after birth.[20] Lower amniotic fluid testosterone levels at midgestation (weeks 13–20) were associated with a negative response bias and less response to rewarding stimuli during a functional MRI task among boys studied between 8 to 11 years of age,[21] suggesting that the relatively greater levels of androgen exposure in utero may contribute to relative protection against depression later in life. Biologically determined sex differences can arise from effects of sex chromosome genes, independent of reproductive hormone exposure.[22–25] In addition, recent animal studies suggest that maternal and paternal stress that occurs even before conception can have differential effects in male and female offspring on depression and anxiety-related behaviors and stress-response regulation.[26,27] In humans, elevated levels of maternal depression and cortisol during pregnancy,[28,29] and elevated milk cortisol levels during lactation,[30] have been associated with more fearful and reactive behavior in female infants and children compared with male offspring.

CHILDHOOD

In contrast to major depression, which has an increased prevalence in girls beginning in midpuberty, the increased risk of anxiety and some anxiety disorders in girls begins