Psychopathology in Women and Men: Focus on Female Hormones

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Objective: The goal of this overview is to examine male/female differences in psychopathology in light of the known effects of gonadal steroids, especially estradiol, on neural function.

Method: The epidemiology of specific psychopathological syndromes is highlighted with respect to male/female differences and discussed against the backdrop of recent neuroendocrine findings.

Results: A number of differences between the sexes in rates of illness and course of illness are documented, with Alzheimer’s disease, schizophrenia, alcoholism, and mood and anxiety disorders each illustrating slightly different hormone-mediated risks and buffers.

Conclusions: Estrogens are neuroprotective with respect to neuronal degeneration, growth, and susceptibility to toxins. The cyclic fluctuations of estrogens and progesterone enhance the response to stress, which confers susceptibility to depression and anxiety.

This article addresses some differences in psychopathology between men and women and asks the question, Why are women disadvantaged with respect to men when it comes to certain psychiatric disorders, such as mood disorders and Alzheimer’s disease, and relatively advantaged when it comes to others, such as schizophrenia? Although there is much debate about the reasons for differing rates of psychiatric illness, it is generally agreed that most of the relative disadvantages that accrue to women do not take place until after puberty, boys being much more susceptible to psychological problems than girls (1). The marked sex differences in rates of illness that begin with the reproductive years suggest that the brain’s hormonal environment during adulthood may be an important point of departure in the search for an explanation. That being said, it is recognized that the adult brain has earlier, during fetal life, been shaped or “organized” by its hormonal environment so that postpubertal effects act on an already sexually dimorphic organ (2, 3). It is also recognized that hormonally induced propensities are always expressed in a social context that powerfully shapes their expression.

Women and men are genetically very similar, except that different hormones enter the brain at different times and at different tempos, encouraging some brain cells to sprout more than others at time periods critical to brain development. Males and females are undifferentiated until the sixth week of gestation, when testes develop in males and begin to produce androgens. Follicle-stimulating hormone (FSH) is found in the pituitary glands of both sexes by fetal week 10, and its concentration increases dramatically, but only in females, between weeks 12 and 20 (4). FSH is thought to play a key role in fetal ovarian development, but the influence of ovarian secretions on the brain during fetal life is not nearly as well understood as that of testosterone (5). In humans, maximum CNS sensitivity to the organizational effects of gonadal steroids is presumed to occur between gestational weeks 14 and 16, when peak concentrations of testosterone are found in fetal serum (4). From then until puberty, the brain’s hormonal environment is again very similar in females and males. Females reach sexual maturity earlier than males. Although the extent of this difference varies with genes, geography, and nutritional factors, it appears to be a fact in all mammals and, for good measure, in birds as well (6). During sexual maturity, hormone levels of women fluctuate cyclically over a much larger range than those of men. At female menopause, ovarian secretion shuts down. In men the testes continue to produce testosterone, which is partly converted to estradiol in the brain, but at an increasingly slower rate. In very old age, the
brain hormonal environment is once again similar in the two sexes. These male/female contrasts are thought to play a part in the expression of many neuropsychiatric illnesses.

ALZHEIMER’S DISEASE

Women are disproportionately prone to Alzheimer’s disease, even after adjustment for their longer survival (7–10). As many as 30%–50% of women older than 85 years suffer from a dementing process (7). Women’s cognitive impairments may also be more severe than men’s (11). Part of the increased understanding of the puzzle of Alzheimer’s disease lies in the clarification of the effect of estrogens on neurotrophins, proteins that play both individual and combined roles in the sustenance of neural axons and dendrites and also in the growth of new nerve cells. This hormonal modulation of neurotrophins increases the connections among neuronal branches and maintains a complex system of communication in the brain (12). When estrogen levels drop at menopause, brain cells of women begin to degenerate at a faster pace than those of men. Men are relatively spared because their continuing testosterone secretion is converted, to some extent, to estradiol in the brain. This hypothesis has been supported by studies which show that estrogen replacement therapy prevents, or at least delays, the onset of Alzheimer’s disease (13) and may even improve memory in Alzheimer’s patients (14).

The neurotrophin route is only one of the ways in which estrogens may act to protect against Alzheimer’s disease. Estrogens are also antioxidants, protecting neurons against β-amyloid, one of the proteins that accumulates in patients with Alzheimer’s disease to produce neuronal degeneration (15, 16). Estrogens also modulate the secretion of acetylcholine in the hippocampus by their effect on choline acetyltransferase, an enzyme critical to the maintenance of memory functions (16, 17).

In summary, women’s special vulnerability to Alzheimer’s disease, a disease of neuronal degeneration, may be attributable—as is the case for osteoporosis and cardiovascular disease—to postmenopausal estrogen withdrawal.

SCHIZOPHRENIA

Men and women are more or less equally prone to develop schizophrenia, but the onset of symptoms is earlier in men (18). Possible explanations for this are 1) sexually dimorphic brain anatomy, 2) the disproportionately high incidence of birth injury in boys, 3) the differential effects of estrogens and androgens, 4) heavy exposure of male adolescents to alcohol and other toxic substances, and 5) the buffering action of earlier marriage among young women (19, 20). Schizophrenia in women is relatively mild in the first decade but increases in severity later, when the symptoms in men paradoxically taper off (21). This sex difference may, to some extent, be connected to the faster drop in dopamine and serotonin receptors with age in men (22). Women seem to respond better to antipsychotic drug treatment, at least when they are young (they need lower doses of antipsychotic drugs to get over an acute episode and to ward off future episodes) (23). The reason for this disparity is unknown. It has been attributed to better treatment compliance among women but also to the various antidopaminergic actions of estrogen hormones, such as the decrease in the rate of tyrosine hydroxylase gene transcription (24), tyrosine hydroxylase being the rate-limiting enzyme responsible for the synthesis of catecholamines (for a review of the several antidopaminergic actions of estrogens, see reference 25).

Not all clinical reports agree that estrogens play a protective role in schizophrenia (26). While the finding of later onset in schizophrenic women has been replicated numerous times (27), the onset age difference disappears when one studies familial schizophrenia (28–30). Do genetic influences in familial schizophrenia overshadow estrogen effects (31)? It is uncertain whether family liability in itself hastens onset age (32). Explanations other than the hormonal one exist for the sex discrepancy in age at onset, for instance, the impact of maternal obstetrical complications in bringing the age at onset forward preferentially in men. A recent study, however, suggests that maternal histories of obstetrical complications are equally prevalent among preschizophrenic men and women (33). Men have more negative symptoms than do women (34, 35) and, arguably, more brain abnormalities (36–38). These sex differences may be secondary to later environmental events but may also be primary, emerging from hormonal differences between male and female fetuses (39–42).

While late-onset schizophrenia is unquestionably more common in women, it has not been proven that this is related to estrogen withdrawal (43–45); nor has it been shown that the worsening of symptoms which sometimes occurs in schizophrenic women as they grow older correlates with decreasing estrogen levels (46). Nevertheless, Häfner’s group (47–49) provides convincing epidemiologic and experimental evidence for the role of estrogens, particularly estradiol, in women’s relative protection against psychosis. This protection is probably mediated through social factors. Estrogens have been conceptualized as protecting vulnerable neural circuits that come on-line during adolescence (50), thus delaying onset in prespsychotic females and permitting them to finish school, start a job, and establish interpersonal intimacy—all of these achievements subsequent to the various behaviors that confers an advantage (51–53). Males, by contrast, frequently develop psychotic symptoms while still in school. Consequently, they have trouble completing their schooling, they never become proficient at a job, and they never develop the social skills required to get along in the world. This early start of illness may be responsible for the greater social deficits seen in men (54).
The protective effect for women, however, wanes in the fourth decade, at approximately the same time that women's estrogen levels begin to decline. Long-term studies (15 or more years after the beginning of illness) from around the world do not support outcome differences between men and women, although at 2 years, 5 years, and 10 years into the illness, most research shows women, as a group, doing significantly better than men (55–58). The "doing better" during the first decade of illness may be more related to premorbid competence, relative absence of substance abuse, and compliance with treatment than to hormones (although such behaviors may be hormone-dependent to some extent). The decline in female advantage in the second and third decades of illness, rather than being hormone-induced, may be caused by the greater impact on women than on men of the loss of family and other emotional supports (M.V. Seeman, manuscript submitted for publication).

The hypothesis about the protective effects of estrogens is bolstered by the observation that in pregnancy, when estrogen levels are steadily rising, women who have had recent acute episodes of schizophrenia do not usually break down (59, 60). However, they do suffer postpartum psychoses when estrogen levels have abruptly plummeted (61). In addition, psychotic symptoms are relatively exacerbated when estrogen levels are at their lowest during the menstrual cycle (62–64), and estrogen treatment has been shown to produce some beneficial effects in patients with schizophrenia (65).

Schizophrenia is thought to be a neurodevelopmental disorder with roots in critical phases of embryonic life, during which neurons fail to grow, to migrate to their appointed sites, or to make appropriate synaptic connections. As noted in the section on Alzheimer's disease, estrogens stimulate nerve growth factors and enhance neuronal survival. This occurs throughout the life cycle, from fetal development through puberty and into old age (42). The neural protection during the epoch of brain organization may be central to sex differences in schizophrenia (40).

In summary, in schizophrenia, the presence of estrogens at crucial time periods appears to confer an advantage that is lost upon estrogen withdrawal.

**ALCOHOL DEPENDENCE**

Like schizophrenia, alcohol dependence also starts earlier in men; but unlike schizophrenia, it remains three to five times more common in men than in women throughout the lifespan. In the United States, 24% of men, versus 5% of women, suffer an alcohol-related disorder during their lifetimes (66). While it has been reported that this ratio is rapidly changing, in conformity with social changes occurring in North America, it is also possible that social factors will never obliterate the sex difference. Androgens enhance the activity of alcohol dehydrogenase, the liver enzyme that is responsible for the elimination of alcohol (67). Efficient elimination protects against immediate subjective negative consequences and, thus, favors the early development of alcohol dependence in males. Alcohol dehydrogenase is less active in women, thereby discouraging heavy drinking but, by the same token, allowing greater absorption of the alcohol that is consumed and increasing the risk of alcohol toxicity.

Female alcohol users drink lesser quantities, which in the early years leads to fewer social, occupational, and legal problems. But the dependence process in women becomes "telescoped" (starts later than in men but reaches end stages sooner), so that long-term secondary effects of alcohol on internal organs are expressed at an earlier chronological age. In women, cognitive impairment secondary to alcohol-induced neuronal toxicity shows a pattern similar to that in men but occurs earlier in the course of a lifetime of drinking (68, 69).

Alcoholic women develop medical consequences and die as a result of them at a greater rate than alcoholic men. Women who drink shorten their lives by an average of 15 years, and their death rate is five times that of the general population of women; alcoholic men's death rate is three times that of other men (69).

In summary, while incidence and prevalence rates are greater among men, alcoholism leads to severe problems in the individual woman earlier than in the individual man.

**ANXIETY DISORDERS**

Women are more prone than men to essentially all anxiety disorders (70–73). Simple phobia is twice as common in women as in men. Phobic objects tend to be the same for men and women (animals, heights, blood, airplanes), but women score somewhat higher on fear questionnaires such as the Fear Survey Schedule (74), commonly used to assess the severity of phobias. The lifetime prevalence of social phobia is about 2% in the general population, and 70% of those affected are women (75). Uncomplicated panic disorder occurs in 20,000 women and about 8,000 men. A goraphobia with or without panic attacks is found in nearly 8% of women versus 3% of men. The number of episodes increases premenstrually in affected women. The 1-year prevalence of generalized anxiety in the community at large is 1%–2% among men and 2%–5% among women (75).

A large study of a treated study group with posttraumatic stress disorder (PTSD) showed a rate of 11% in women and 7% in men (76). The investigators extrapolated from their data to estimate that 31% of women and 19% of men who are exposed to major trauma develop PTSD symptoms. In other words, when exposed to a traumatic life event, more women than men develop PTSD, and in addition, women make up 85% of the group whose symptoms last for over a year.

Because women complain of premenstrual and postpartum exacerbations of anxiety and panic states, hormonal fluctuations have been advanced as possible contributors to understanding the difference between the
sexes in anxiety disorders. All steroids modulate the γ-aminobutyric acid (GABA) receptor, with progesterone metabolites acting as agonists and, therefore, as anxiolytics (77). In addition, estrogens have been shown to up-regulate the GABA receptor (78). It is possible that the cyclic withdrawal of progestins and estrogens “kindles” neuronal systems and promotes anxiety states by mechanisms similar to those which have been implicated in the provocation of perimenstrual epilepsy (79).

In summary, women suffer more than men from anxiety states, and there is some indication that women become more anxious during times of relatively low levels of circulating estrogen and progesterone. Ovarian steroids appear to act as anxiolytics. Their periodic physiologic withdrawal mimics anxiolytic withdrawal and could be responsible for women, as a group, being more sensitive than men to the anxiogenic effects of nonspecific stress.

Mood Disorders

While the lifetime risk of bipolar or manic-depressive illness is approximately 1% for both sexes, unipolar depressions are twice as common in women as in men (80). Dysthymia is also twice as common in women. These differences between the sexes in prevalence are true, however, only for adults and do not emerge until adolescence (81). The meaning of puberty to adolescents is, of course, far more extensive and complex than could be surmised from studying only the direct effects of hormone levels on the brain. It has been suggested that the alterations in body shape that accompany puberty are, for cultural reasons, welcomed by young men but dreaded by young women, at least in industrialized countries (82). Males’ and females’ relationships with parents during the adolescent period also vary, with new-found independence perceived as positive in men and stressful in women (83). The literature on help seeking suggests that young women, once they are old enough to do so independently, seek treatment for psychological problems more frequently than young men (84). However, this fact alone could not explain the differential variance in community rates of both depression and anxiety. It is interesting that studies in developing countries such as India, Iraq, and New Guinea have not shown the doubling of rates of depression in women relative to those in men, but these surveys are confined to treated populations (85). A recent article from the National Institute of Mental Health Epidemiologic Catchment Area study (86), in which only the Los Angeles and New Haven data were reported, reported that among Jews there was a 1:1 female/male ratio, which, the authors speculated, was due to low rates of alcoholism among Jewish males and, consequently, more depression among them. Social role, access to health care, and birth cohort effects have all been implicated in the determination of sex differences in depression in different population samples (87–89).

A few sex differences in course of illness in depression have also been noted. Women have more frequently recurring episodes. Women also report a greater number of individual symptoms. But when symptom severity is rated by the clinician rather than the patient, it is the same for both sexes (90).

Because of increasing awareness that both biological and sociocultural sex variables shape personality, investigators have searched for personality factors associated with sex role that are capable of explaining women’s special vulnerability to depression (91, 92). It has been observed that women, to a greater degree than men, invest their emotions in interpersonal relationships. Consequently, they suffer from the impact of life events that take place not only in their own lives but also in the lives of their extended network of friends and relatives. However, this interesting hypothesis of why women might be more prone to depression, despite men and women experiencing equal numbers of personal life events, is not supported by the evidence, which suggests, to the contrary, that strong social networks (more prevalent among women than among men) protect against depression (93).

Another reported personality difference is that women internalize their feelings to a greater degree than do men and blame themselves for incompetence or failure, which leads to depression, while men blame others, which leads to anger. This is a classic view of depression that has been difficult to prove empirically. Still another difference between the sexes is a passive, ruminative style of coping with problems, which is more prevalent among women, and an active, distraction-oriented style, which is more common among men (94). Nolen-Hoeksema has argued that this personality difference accounts for at least some of the sex variation in depression (94). Conflicting and changing social expectations of women and the higher rates of sexual abuse of girls during childhood and adolescence have also been considered as possible explanations for high rates of depression, and also of anxiety disorders, in women (75, 90). Psychological and social variables that distinguish women and men almost certainly apply to psychiatric disorders other than mood disorders, but they have been most intensely studied in the context of depression.

In summary, many factors seem to play a greater direct role in mood disorders than do female hormones. Personality and responses to stress are, however, influenced to some degree by hormones.

Discussion

It appears that female hormones—estrogens in particular—exert potent effects on the expression of various forms of psychopathology. The literature on schizophrenia suggests that estrogens preserve the integrity of neuronal circuits. The literature on Alzheimer’s disease suggests that estrogen withdrawal renders women especially vulnerable to that disorder. In
alcoholism, the absence of male hormones interferes with liver enzyme elimination of alcohol and, consequently, increases the risk of toxicity in women. The literature on depression and anxiety holds female hormones indirectly responsible for the greater prevalence of these disorders in women. It is not that estrogens directly dampen mood, although progestins may (95), but that the off-and-on binding to intranuclear estrogen receptors in the brain somehow renders women vulnerable to stress, perhaps through glucocorticoid-induced neuronal toxicity.

Estrogens—notably estradiol—play an active organizing role in the developing brain and a crucial maintenance role in the aging brain. Among other functions, they protect neurons against both developmental dysfunction (i.e., schizophrenia) and degenerative dysfunction (i.e., Alzheimer’s disease). This action, as well as the antioxidant, antiodaminergic, and cholinergic actions of estradiol, can explain most of the sex differences seen in these two diseases. Parallel to their protective role against neuronal degeneration and/or impairment of neuronal development, it is likely that estrogens are also protective against the toxic effects of alcohol on nerve cells. But the higher blood levels of alcohol and the early menopause brought about by heavy alcohol use may account for women’s cognitive decline after relatively short drinking histories. Men are supplied with estradiol into their old age, because estradiol continues to be synthesized intraneuronally from testosterone through the conversion enzyme neutral aromatase.

The cyclic nature of estrogen secretion from puberty to menopause and, subsequently, its almost total withdrawal may account for the special vulnerability of women to mood and anxiety disorders. Recurrent estrogen withdrawal, starting in the early teens, may interfere with one of the natural functions of estrogen, the ability to neutralize the effects of glucocorticoids released during stress (96). This explanation is speculative but fits the epidemiologic evidence that the high prevalence of these conditions in women is evident only after puberty.

Hormone receptors are present from early fetal life in the hypothalamus, organizing brain circuitry, setting the stage for puberty, regulating subsequent adult sexual behavior, and controlling the interaction of the hypothalamic-pituitary-adrenal-gonadal axis from puberty onward. Most relevant to psychiatric disease, gonadal hormone receptors are seen in regions of the brain that mediate both cognition and affect. During development and also during adult life (with variations from one time period to another), gonadal steroid receptors are expressed in the nuclei of the septum and the diagonal band of Broca, the hippocampus, the allocortex, the isocortex, and the amygdaloid complex (97). The best-studied receptor is the one for estradiol, known to regulate neuronal function in a number of important ways. Gonadal hormone receptors act as genetic transcription factors. The attachment of estradiol to its receptor is accompanied by a receptor phosphor-

ulation that leads to a conformational change in the receptor and the subsequent binding of the estradiol receptor complex to many DNA sequences at a variety of chromosomal sites, all of which respond to the hormone stimulus (98). In addition, more is now known about indirect (nongenomic) effects of estrogens on nerve cells in the brain. For example, by acting directly on membrane receptors, estrogens decrease behaviors mediated by the dopamine D2 receptor (25).

Various neurotrophins, known to be neuroprotective, up-regulate the density of nuclear estrogen binding sites, while at the same time, estradiol up-regulates the level of the neurotrophins, synergizing their neuroprotective role (97). That role is to prevent cell death, to promote growth of cells and parts of cells, and to enhance neural communication. There is evidence that women are more sensitive to perceived stress than men—for instance, that more women than men develop posttraumatic stress syndromes after being exposed to a stressor (76). While the interaction among glucocorticoids, neurotrophins, and estrogens is complex and as yet unclear (99), it is possible that estrogen cyclicity may render women inherently more vulnerable to the neurotoxic processes engendered by stress hormones. Indeed, recent life stresses were found to be the most important determinants of depression in the 1993 study of depression in female twins by Kendler et al. (100).

In summary, there are many reasons to believe that evolutionary imperatives have assigned a special neuroprotective but also a stress-sensitive mediating role to female hormones (specifically to their cyclicity), which consequently confers both psychiatric advantage and disadvantage to women. During the childbearing years, women are comparatively shielded from the more severe psychotic illnesses but are more vulnerable than men to depression and anxiety.

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