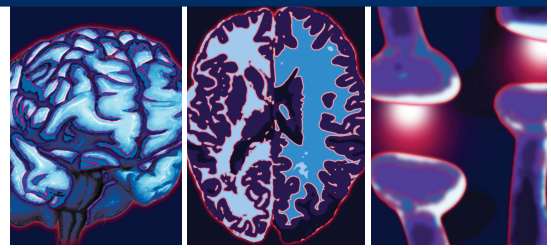


REVIEW



Women and schizophrenia: new findings

Mary V Seeman*

Practice points

- Immunity and hormonal transitions are both of potential importance to the course of lifetime schizophrenia. There is mounting evidence for significant effects of both estrogen and oxytocin.
- Cannabis use, urbanicity, migration and aging fathers are risk factors for schizophrenia in sons and daughters. Early paternal age and Rhesus incompatibility are of special risk to sons.
- Standard doses of antipsychotic medication may be too high for most women and may expose them to unnecessary side effects.
- There is no evidence that men and women differ in rates of recovery, as presently conceptualized.
- Women in the earliest stages of psychosis, women who are pregnant and women who are menopausal all have special clinical needs that call for specific interventions.

SUMMARY Schizophrenia has long been known to affect men and women somewhat differently. It has been shown that men have a higher incidence, a younger age of onset, more impaired social and vocational functioning, and poorer response to treatment. Generally acknowledged risk factors such as season of birth, obstetric complications, head trauma and substance abuse affect males more than females. This review examines other potential predictive factors, both genetic and environmental, that have come to attention over the last 5 years, and examines their relative gender risk. Recent findings pertinent to women with schizophrenia have emerged with respect to hormonal effects, antipsychotic metabolism and antipsychotic side effects. A new concept relative to outcome is recovery, which, thus far, shows no gender difference. The review also addresses the needs of specific groups of women affected by schizophrenia – those in the early stages of illness, those who are pregnant, those who are mothers and those who are in their postmenopausal years. Several new findings are advancing the field of women and schizophrenia.

Schizophrenia has long been known to affect men and women somewhat differently. For instance, the incidence of schizophrenia is 1.4-times higher in men than in women [1,2], women have a later age of onset [3,4], social and

vocational functioning is superior in women during the course of illness [5,6] and women show a better response to treatment than men do [7,8]. Generally acknowledged risk factors, such as season of birth, obstetric complications,

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head trauma and substance abuse, affect males more than females [9–12], which supports the epidemiological data. The current review will examine other potential predictive factors that have risen to prominence over the last 5 years, and will examine whether they also show a preponderance of male risk. In addition, this review will point to newly described gender differences in hormonal effects, antipsychotic metabolism and antipsychotic side effects as they pertain to schizophrenia, as well as to a new view of outcome, namely the concept of recovery. Finally, the review will focus on specific groups of women affected by schizophrenia – those in the early stages of illness, those who are pregnant, those who are mothers and those who are in their postmenopausal years.

Methods

The search terms ‘women’ or ‘men’ or ‘gender’ or ‘sex’ and ‘schizophrenia’ or ‘psychosis’ were entered into Google Scholar and all papers published in English between 2007 and 2013 were reviewed for new findings about women and schizophrenia. On average, 200 relevant papers were found for each category, with considerable overlap. Selecting only papers that addressed the topics prechosen for this article – risk genes, environmental risk factors, recovery, antipsychotic drugs, hormones and specific populations of women with schizophrenia – resulted in the 110 references cited below.

■ Risk genes

In the last several years, copy number variations in DNA have come to be an important area of genetic research in schizophrenia [13]. The most commonly known recurrent copy number variant disorder conferring risk for schizophrenia is the 22q11.2 deletion syndrome. A candidate gene for schizophrenia within the 22q11.2 region is *COMT*, previously linked to schizophrenia [14] and considered sexually dimorphic [15]. The *COMT* gene encodes the enzyme that metabolizes dopamine, as well as other catechol compounds (including estrogen). Genetic associations between *COMT* and rates of psychiatric illness have shown differences between men and women, presumably because of the role of *COMT* in cortical dopamine metabolism. *COMT* activity in prefrontal cortex has been shown to be 17% higher in men than in women, despite levels of *COMT* and mRNA being similar in the two sexes. In addition, whereas tissue dopamine

levels in the frontal cortex remain unchanged in the female *COMT* knockout mouse, they are increased almost threefold in male *COMT* knockouts. The sexual dimorphism of *COMT* is usually attributed to the transcriptional regulation of gene expression by estrogen [15], but it is now thought that this is not the only relevant factor. There are also differences between the sexes in central dopamine parameters. Compared with men, women show higher levels of presynaptic dopamine synthesis and a lower D2 receptor affinity. They also have lower amphetamine-stimulated dopamine release and a greater dopamine transporter uptake. Thus, compared with men, women appear to have elevated basal, but decreased stimulated, striatal dopamine levels. This may help to explain the dissociation between expression and activity of *COMT* [15]. Despite initial promise, however, genome-wide association studies (GWAS) have not confirmed *COMT*’s link to schizophrenia.

Estrogen itself has received major attention as a potential player in schizophrenia etiology and pathophysiology [16]. This hormone has been credited for preserving synaptic plasticity, improving neurotransmission, protecting against neurodegeneration and enhancing cognition [17]. Therefore, it holds promise as a therapeutic agent [17,18]. With this in mind, and because women with schizophrenia have been noted to have low estrogen levels compared with controls [19] even before the era of antipsychotic drugs (which increase prolactin levels and, therefore, further decrease estrogen levels [20]), estrogen receptor genes are being investigated with respect to potential associations with onset age in schizophrenia, expression of the illness and response to treatment [21,22]. By applying pathway analysis to schizophrenia GWAS data, Lee *et al.* have identified pathways involving estrogen biosynthesis, suggesting that lowered synthesis may contribute to schizophrenia susceptibility [23]. A potentially fertile field of investigation is the relationship between estrogen and other genes thought to be involved in schizophrenia, such as the gene that codes for the BDNF. Sex-dependent differences in schizophrenia could be modulated, for instance, through major neurotransmitter systems supported by estrogen and BDNF [24].

GWAS have implicated the MHC region at 6p21–22 in schizophrenia pathophysiology. Genes in that region are of interest to the field of women and schizophrenia because they affect immune function, neurodevelopment

and synaptic plasticity [25–27], all of which are sexually dimorphic. The kinetics, magnitude and skewing of the responses mounted against pathogens, allergens, toxins or self-antigens is said to differ dramatically between the sexes [28]. If schizophrenia risk genes play a role in resistance to infection, the fact that females show more resistance than males [29] may help to explain the later onset of schizophrenia and superior functioning of women compared with men. It may also address the issue of etiology, in that maternal exposure to infectious agents or dietary antigens during pregnancy or breastfeeding may constitute a risk factor for vulnerable offspring [30,31].

It has long been known that the brain and the immune system are in constant communication and that several psychiatric disorders, including schizophrenia, are accompanied by chronic medical conditions related to immune dysfunction, such as autoimmune diseases, diabetes and atherosclerosis [32]. There is also preliminary evidence that infective agents such as *Toxoplasma gondii* or herpes simplex virus 1 may play an important role in the pathophysiology of schizophrenia during the prenatal period [33]. Other environmental risk factors may also be transmitted prenatally from mother to child [33–36], perhaps influencing gene expression via epigenetic modulation.

Thus far, in animal models, although fetal stress in general has been convincingly shown to be sex dependent [37,38], no early environmental factor has shown specific sexually dimorphic effects on offspring.

Advanced paternal age has been repeatedly identified as a risk factor for schizophrenia and the link has been attributed to an increased rate of *de novo* point mutations and copy number variants as men get older [39], or possibly to aberrant epigenetic regulation [40]. No sex difference has been found in the offspring of older fathers [41] but, interestingly, more male than female children develop schizophrenia when their fathers were under the age of 25 years at their conception [41]. Young men may have immature sperm or low antioxidant activity and undeveloped DNA repair mechanisms. They may also be more likely to smoke cannabis than older men or be exposed to toxic substances that affect spermatozoa. If there are schizophrenia risk genes on the X chromosome, maldevelopment and disrepair will affect male offspring more than female offspring because females have a second X chromosome whose genes, in all probability,

will not be affected and will be preferentially expressed.

■ Environmental factors associated with schizophrenia prevalence

Urbanicity/migration

Several studies have demonstrated that growing up in an urban area raises the risk of schizophrenia compared with growing up in a rural area [42,43]. The pathways linking urban living with mental illness are thought to be a combination of adverse living conditions, more stressful life events, social isolation, presence of pathogens, nutritional deficiency and unsafe neighborhoods. No gender differences have been reported in the urbanicity risk.

Migration is another important factor that has been increasingly found to confer greater risk for schizophrenia, equally so for men and women [44,45]. One study found that female refugee immigrants from low-income countries were at greater risk for mental health illnesses than men. Mental health illnesses in this study were measured with the proxy variable, amount of psychotropic drugs purchased [46]. The pre- and post-migration stress that accompanies a move to a new country is considered to be a highly gendered experience, with effects on women and men varying markedly in different migration situations, particularly with respect to the economic outcome of migration [47,48].

Early psychological trauma

Early childhood trauma, such as physical or sexual abuse, or bullying by peers, has also increasingly been linked to schizophrenia incidence [49–52]. One study reported that approximately 70% of a high risk of schizophrenia population had experienced at least one type of trauma, and that the rates of conversion to psychosis significantly increased when the type of trauma was sexual abuse, which is known to be more prevalent in females than males [53]. Despite this, no sex differences have been reported in the link between the larger category of early childhood trauma and psychosis.

Maternal/fetal incompatibility

Maternal–fetal Rhesus incompatibility is a risk factor for schizophrenia that does show a gender difference. This mother–child incompatibility has been reported to increase the risk of schizophrenia more in male than in female offspring [54].

Exposure to brain toxins

Among the various substances of abuse, cannabis has assumed importance as a factor that can predict the transition to schizophrenia in vulnerable individuals [55,56]. Young men use more cannabis than young women [57], which gives credence to this explanatory factor. In a study of individuals at high genetic risk for schizophrenia, early cannabis use was the most significant predictor of transition to clinical high-risk status [58].

Many other potential brain toxins besides cannabis are ingested or inhaled by humans. Harm to brain development is especially high *in utero* or in early life but these substances may exert a noxious influence when exposure occurs in adolescence or early adulthood. Men and women can be exposed to somewhat different forms of inhaled and ingested toxins, men to substances of abuse and to industrial toxins, women to cosmetics, perfumes, hair dyes and diet pills.

■ Recovery

In the past, women were said to have a better schizophrenia prognosis than men, but the concept of outcome has changed. It now includes not only symptom scores and indices of function but also subjective quality of life as embraced in the concept of recovery. Recovery has been defined in many ways and no standard measure for it exists, making male–female comparisons difficult. One team has tried to do a meta-analysis of relevant studies and found no gender differences in recovery [59].

Despite earlier findings, no significant difference has recently been found between females and males in the rate of symptomatic or functional remission in schizophrenia [60,61], which is surprising because negative symptoms are associated with poor prognosis [62] and they are more prevalent in men than in women [63].

■ Antipsychotic drugs

Some have argued that the superior female outcome in schizophrenia is attributable, at least in part, to their response to antipsychotic drugs [64,65]. There are differences in absorption and metabolism of antipsychotics between men and women, with the result that, at standard doses, women may be overdosed and, as a result, experience more side effects [66–76]. There are also side effects such as amenorrhea [77] and breast cancer [78] that are female specific.

Metformin is proving to be a useful adjunct to treatment in women who are suffering from antipsychotic side effects. Not only does it help to prevent the side effect of diabetes [79], but it also reverses amenorrhea [80].

■ Hormones

Estrogen is considered the most biologically active of all hormones in relation to psychiatric disease. Its neuroprotective aspects in relation to brain morphology, reparative brain processes, neurotransmitter activity and behavior have been well demonstrated [81]. Although much schizophrenia research continues to be devoted to gonadal steroids [82,83], synthetic estrogens [84] and even melatonin [85] are being investigated.

Oxytocin, however, is the ‘hottest’ new hormone that promises to explain some of the male–female differences in schizophrenia. Intranasal oxytocin has been shown to reduce psychotic symptoms and improve theory of mind and social perception in schizophrenia [86,87]. In female patients with schizophrenia, higher oxytocin levels are associated with less severe positive symptoms and overall psychopathology [88].

■ Specific populations of women with schizophrenia

Early psychosis

More and more, clinicians are attempting to identify psychosis predisposition early and to intervene before the start of overt illness. The risk states of premorbidity and prodrome are being increasingly investigated, as is first-episode psychosis, where gender differences have been reported [89–92].

The gender differences reported in first-episode cohorts are similar to those described for schizophrenia, in general: males have more negative symptoms, are more likely to live alone and suffer more than females from substance abuse. On follow-up, women are more likely to be employed than men, to be in school and to function well socially. Compared with men, women are more likely to be medication adherent, to be a parent and to report a subjective state of recovery [93–96].

Pregnancy

A cross-sectional population-based study using administrative databases from Ontario, Canada (1996 to 2009) showed that the fertility rate among women with schizophrenia has risen [97], probably because of a decrease in stigma

associated with the illness, improved social functioning and new therapeutic drugs that do not interfere with fertility. This means that more women with schizophrenia are becoming pregnant.

At a speciality antenatal clinic, pregnant women with schizophrenia were found to suffer more psychiatric relapses during pregnancy, and have more involvement with child welfare than mentally ill women without psychosis or women with bipolar disorder [98]. All pregnant women with severe mental illnesses at this clinic, but particularly women with schizophrenia, were overweight, had high rates of gestational diabetes and pre-eclampsia, and the neonates showed adjustment difficulties despite infant birth weights that were in the normal range [98].

With respect to treatment considerations for women with schizophrenia during pregnancy, careful adjustment of antipsychotic drug doses are needed [99], as well as further research into placental transmission of drugs to the developing fetus [100]. More important than drugs is the patient–physician relationship during this critical period. It is recommended that physicians listen to the voiced needs of the women themselves [101].

Motherhood

While pregnancy is a critical period, motherhood constitutes an extended period during which a woman with schizophrenia needs to stay healthy for her own sake and for the sake of her family. A synthesis of eight recent papers on the subject of motherhood and schizophrenia categorizes the current views of health professionals into four themes: discomfort, stigma, need for education and integration of services. Care providers are uncomfortable with the topic because of their ambivalence about women with schizophrenia being capable of adequate mothering. They recognize the stigma associated with the illness and especially with parenting when diagnosed with schizophrenia. They realize they are not fully knowledgeable on the topic and they are aware of the division between child and adult services. Clinicians who care for children see danger in mothers with schizophrenia rearing their children while clinicians who care for adult women believe that the majority of these women are capable of adequate parenting if they are supported. Resolution of these issues is needed in order to inform service development and provision [102]. In a telephone survey, over 2000 community psychiatric service users in the UK were

asked about the discrimination they experienced over the course of the previous year with respect to either starting a family or to their ongoing parenting role. In both social and professional contexts, participants were able to give 89 examples of discrimination about starting a family and 228 examples about parenting. As patients, they were routinely discouraged from having children and were not supported when they did. Their children's difficulties were automatically blamed on their mental health problem [103]. Those who lost custody of their children were not instructed on how to regain it, even though this is often in the best interests of the child [104] and parent training designed specifically for this group of mothers is increasingly available [105].

Menopausal women

It has long been known that, as women with schizophrenia grow older, they lose the advantages they once had over men with the same condition. Two recent reviews point to the lack of medical attention to the effect of the menopause on women with schizophrenia, both with respect to their general health and, more specifically, to their psychiatric condition. There is evidence that antipsychotic treatment may need to be modified in the postmenopausal period and that cardiac and metabolic health indices need to be closely monitored [106,107].

Fukuta *et al.* investigated the influences of the menopause on brain morphological changes in 20 premenopausal and 20 postmenopausal women with schizophrenia (as well as 50 control women) using MRI. The gray matter of postmenopausal patients was significantly smaller than that of premenopausal patients in the left middle frontal gyrus, suggesting an impact of estrogen loss on brain structure [108].

The gender of patients is a relevant variable in the use of mental health services by patients with schizophrenia [109], but age is also important.

Despite considerable overlap between the needs of younger and older women with schizophrenia, a recent review emphasized that younger women require preventive strategies to stop the escalation of illness while older women require recovery strategies to regain lost aptitudes and abilities [110].

Conclusion & future perspective

As research into schizophrenia focuses on new techniques, such as GWAS, or new areas of interest, such as recovery and migration, the issue of

male–female differences in this illness will continue to intrigue researchers. It is expected that in the future sexually dimorphic genetic and environmental risk factors for this illness will be identified. The contribution of estrogen-related genes and immune-related genes will likely be confirmed and environmental factors such as urbanicity and migration will be shown to affect men and women in somewhat different ways. Evidence will continue to accumulate for the involvement of estrogen, oxytocin and perhaps other hormones, in the expression of schizophrenia. Gender differences will be better identified from the start of illness in young adolescents at risk of schizophrenia. In the near future, gender-specific antipsychotic treatment regimens will probably be established, as well as specific regimens for pregnant and postmenopausal women. Healthier mothers will mean greater support for women with schizophrenia who wish to become

mothers and less separation of children from their mothers. As clinical outcome, at least in younger years, has been shown to be superior in women compared with men, it is likely that the wider concept of ‘recovery’ will also be found to favor women. Addressing gender differences is the first step toward recognizing specific individual needs among those who suffer from schizophrenia.

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