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Improving treatment of women with schizophrenia: a review of the recent literature

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Abstract

Effective clinical management of women with schizophrenia is therapeutically challenging. While there have been recent advances in the understanding of neurobiological, hormonal, and female reproductive cycle factors that play a decisive role in the development and progression of schizophrenia in women, this knowledge has not yet been fully translated into treatment practice. The aim was to apply the best evidence available to optimally treat women with schizophrenia at various periods of the lifespan. A narrative review was conducted of recent advances (2018–2023) in aspects of schizophrenia in women that demand sex-specific treatment. Sex steroids impact antipsychotic absorption, distribution, metabolism, elimination, passage through the blood-brain barrier, and blood flow rate to the brain. For these reasons, premenopausal women with schizophrenia, as compared to male age peers, require lower doses of most antipsychotic drugs and suffer comparatively more adverse events (metabolic, sexual, and cardiovascular) at similar doses. Apart from pharmacologic treatment, women have specific reproductive planning needs and need protection from sexual exploitation and domestic abuse. In addition, when pregnant, schizophrenia women show a high risk of gestational diabetes and pre-eclampsia/eclampsia that requires prevention. Prevention is also needed against long-term health hazards for their offspring. Another period of therapeutic challenge specific to women is menopause. The collected evidence points to women-specific recommendations for both biological and psychosocial treatment strategies for schizophrenia.

Keywords

Schizophrenia, psychosis, women, oestrogens, menopause, perinatal, outcomes, antipsychotics

Introduction

Many gender differences in schizophrenia have been reported and reviewed [1–5]; some, but not all, point to the need for specialized treatment in women. One important treatment-relevant finding is the demonstration that reduced levels of sex hormones in women with schizophrenia are positively associated with symptom severity, psychosis relapse, and rehospitalization rates [6]. This means that positive psychotic symptoms (delusions and hallucinations) increase when oestrogen levels are low—i.e. postpartum, and during low oestradiol phases of the menstrual cycle and at menopause.

Female hormones impact antipsychotic drug absorption, distribution, metabolism, elimination, and degree of entry into the brain. They regulate the activity of some cytochrome P450 (CYP) metabolic enzymes producing, for the same dose of drug (and for olanzapine and clozapine in particular) higher plasma levels in women (pre-menopause) than in men [7]. The blood-cerebrospinal fluid (CSF) barrier, blood-brain barrier (BBB), blood-retina barrier, and blood-nerve barriers all show variations according to sex. Alterations in peripheral and central inflammation (different in men and women) can directly modulate BBB properties and, thus, represent an important mechanism underlying not only drug effects but potentially also the neurodevelopment of many mental disorders, including schizophrenia [8]. Addressing drug dose and modulating inflammation thus represent two potential sex-specific routes to effective treatment. The second route has barely begun to be investigated [9].

Preventing antipsychotic adverse events is a critical component of treatment. Relative to men, women react to these drugs with more metabolic effects, sexual dysfunctions, and cardiovascular reactions [7]. An important woman-specific treatment consideration is pregnancy. Venous thrombosis and pulmonary embolism, a potential threat for all pregnant women, are increased by antipsychotics [10].

The goal of this narrative review of literature between 2018 and 2023 is to highlight aspects of schizophrenia treatment that is specific to women and can improve their outcomes. For the scope of this review, the most recent five-year publication period was chosen on the assumption that recent studies incorporate all previous advances in the field. Before describing method and results, the history of the oestrogen hypothesis of schizophrenia is presented.

The oestrogen protection hypothesis of schizophrenia

In the early 20th century, Kraepelin [11] wrote that males suffered more often and more severely from dementia praecox (the condition that later became known as schizophrenia) than females. In 1934, Braatöy [12] noted that the peak incidence of schizophrenia was earlier in males than in females; his explanation was that men suffered more social stress in adolescence than women. Noreik and Ödegård [13] also noted the onset age discrepancy between the genders, as did Forrest and Hay [14] and Lewine [15]. Seeman [16] and Häfner [17] were the first to attribute the sex difference in onset age to oestrogen, giving rise to the oestrogen hypothesis of schizophrenia. The hypothesis was based, thanks to the work of Bruce McEwen at the Rockefeller Institute [18], on the growing appreciation of fetal activation and pubertal organizational action of oestrogens reflected in brain structure and neuroprotective function.

Evidence from clinical trials supports this hypothesis by showing that administration of exogenous oestrogens ameliorates clinical symptoms in schizophrenia [5] and epidemiological studies show that menopause worsens symptoms and is responsible for a 2nd incidence peak at this age in women [19]. The higher the levels of sex hormones in women, the better the clinical outcomes [20]. This has been shown by the protective effect of early puberty in women, the heightened symptom severity of the pre-menstrual phase, the protective effects of pregnancy, and the adverse effects on symptoms of the postpartum and postmenopausal periods [20].

Riecher-Rössler [21] implicates (perhaps stress-induced) high prolactin levels leading to oestrogen and testosterone decline in triggering psychotic symptoms. Thomas and collaborators [22] carried out a 12-week follow-up study of 45 women with schizophrenia whose mean age was 46. This study explored the association between psychotic and depressive symptoms, and hormonal levels of oestradiol, progesterone,

follicular stimulating hormone (FSH), luteinising hormone (LH), and dehydroepiandrosterone (DHEA). Using the Positive and Negative Syndrome Scale (PANSS), they identified two trajectories for psychotic symptoms: 1) lower symptom severity associated with FSH, LH, and DHEA, and 2) higher symptom severity associated with LH. This paper highlights the fact that reproductive hormones play a role in the pathophysiology of schizophrenia and recommends stratification of patients according to endocrine variables [22].

Herceg and collaborators [23] investigated the association of hormonal status and psychopathological symptoms in 31 consecutively admitted women suffering from acute schizophrenia. All were aged 18 to 45 and their menstrual patterns were regular. Psychopathological symptoms were assessed through the PANSS and oestradiol, progesterone, and testosterone levels were also determined. The sample was divided into two groups according to the menstrual cycle phase: 1) follicular phase (high-oestrogen), and 2) luteal phase (low oestrogen). The results showed that luteal phase hospital admission occurred in 68% of the participating women, *versus* follicular phase admissions which occurred in only 32%. While oestrogens are known to serve many neuroprotective functions, one that seems particularly significant for schizophrenia is the ability of oestrogen to attenuate dopaminergic activity [24].

A recent review of studies examining ovarian hormones and midlife psychosis in women [25] concluded that the data linking oestrogen and psychosis are promising, but critical gaps in knowledge remain. For instance, many studies use only indirect or proxy measures (such as age or verbal report) to identify menopausal status or menstrual phase.

The oestrogen protection hypothesis of schizophrenia is outlined in Table 1, which summarizes epidemiological and clinical findings supporting the theory.

Table 1. Oestrogen protection hypothesis of schizophrenia

Evidence	Outcomes	Findings
Epidemiological studies	Incidence of schizophrenia in women and men	Peak of incidence earlier in men than women [3, 4]
		Second peak of incidence in women at menopause [19]
Clinical studies	Hormonal status and psychopathological symptoms	Low levels of oestrogens associated with more severe psychotic symptoms [5, 19, 20]
	Hormonal status and cognitive symptoms	Menstrual cycle irregularity associated with cognitive impairment [24]
Clinical trials	Administration of exogenous oestrogens	Positive effects of oestrogens on clinical symptoms [5]

The oestrogen hypothesis, with its biological and psychosocial implications, guided the search method for this review.

Method

This is a non-systematic narrative review using the PubMed database for English, Spanish, French, and German language papers published in the last five years (2018–2023). Included papers referred to aspects of schizophrenia in women that demand sex-specific treatment in reproductive, premenopausal, and postmenopausal stages of life, irrespective of the study design. Papers that did not contain information pertinent to treatment in women were excluded. The following search terms were used: “women,” “schizophrenia,” “hormone,” “reproduct,” “treatment,” and “menopause”. Reference lists from included studies were also manually checked for additional relevant papers. From a total of 591 initially selected abstracts, 64 studies were included. Pertinent papers were specifically selected for quality: clarity of presentation, clinical importance, the rigour of study design and data analysis, and novelty of conclusions.

The result sections of the review are organized according to the two main stages of women’s adult lives: 1. reproductive years; 2. postmenopausal years. Subsections address: Health needs in women with schizophrenia at early stages of illness; reproductive health at the early stages of illness; decision-making capacity and reproductive counselling; pregnancy and the postpartum period in women with

schizophrenia; victimization during pregnancy and postpartum; children born to women with schizophrenia. Clinical outcomes in women with schizophrenia post-menopause; oestrogen/raloxifene in schizophrenia; cancer risks as women with schizophrenia age.

Results

Specific management of women with schizophrenia during the reproductive years

Several critical aspects of the management of reproductive age women with schizophrenia are summarized in Table 2.

Table 2. Critical aspects of the treatment of women with schizophrenia in their reproductive years

Critical aspects	Findings	Potential strategies
Early phases of disorder	Prodromal signs of psychosis differ between men and women	Training to recognize sex-specific prodromal signs [26, 27]
	High prevalence of childhood adversities in schizophrenia women	Careful history taking and early intervention [26]
	Negative influence of hyperprolactinemia on cognition	Screening, prevention, and monitoring of hyperprolactinemia [27, 28]
Sexual and reproductive health	Sexual dysfunction	Sexual health interventions [29]
	Abortion and sexual violence	Psychoeducation, family planning [30–35]
	Sexually transmissible infections relatively high in schizophrenia women	Counselling re safe and effective protection and contraception [28, 32, 33, 36, 37]
Drug-induced hyperprolactinemia	Drug-induced hyperprolactinemia more prevalent in women than men (e.g., galactorrhea, amenorrhea)	Appropriate choice and dose of antipsychotics and regular check of prolactin levels [38]
Low fertility	Hyperprolactinemia reduces fertility	Personalized drug choice and dose [39, 40]
Repeat pregnancies	Repeated inadvertent pregnancies	Psychoeducation [39]
		Long-term contraception

Health needs in women with schizophrenia at early stages of illness

Early treatment depends on recognition of prodromal signs, which may differ from those of men; lack of recognition delays timely access to intervention services. Women who present with delusional ideas and report hearing voices but are cognitively intact and show appropriate affect and few negative symptoms (apathy, social avoidance), need careful monitoring for schizophrenia. Brand and collaborators [26] recommend physician education on male/female divergence in these respects. A second recommendation is a routine exploration of childhood adverse events in women. A third recommendation is an inquiry into symptom fluctuation over the menstrual month. Premenstrual increase in psychotic symptom severity can be addressed by a slight dose increase of antipsychotic drugs over the three-day period preceding menses [26].

Because most antipsychotics induce hyperprolactinemia, especially in women, sexual function may be negatively impacted, and galactorrhea, as well as amenorrhea, can emerge [27], confusing symptoms for women because they mimic the signs of pregnancy. Women need to be warned of these possibilities before starting treatment and to be reassured about their meaning. All things being equal, women need to be treated with relatively prolactin-sparing antipsychotics.

Nallani and collaborators [27] also investigated the risk of 25-hydroxy vitamin D deficiency and other metabolic abnormalities in women who experience hyperprolactinemia. They found that 37% of women with schizophrenia show low vitamin D levels, a consequence of high prolactin as well as infrequent exposure to sunlight. Hyperprolactinemia also exerts a negative influence on cognition [28]. Gurvich and collaborators [28] investigated the effects of hypothalamic-pituitary-gonadal axis disturbance on cognitive performance in 240 women with schizophrenia. Cognition was assessed by means of the Repeatable Battery for the Assessment of Neuropsychological Status. They found that menstrual cycle irregularity was positively associated with defective cognitive performance in three domains: psychomotor speed, verbal

fluency, and verbal memory [28]. Women may be conscious of increased cognitive deficiencies, so, again, need reassurance.

Reproductive health at the early stages of illness

High prolactin levels reduce fertility. Yu and collaborators [29] asked about reproductive concerns in 15 women with schizophrenia (age 26–40). The women's main concerns were psychological barriers to reproduction such as discouragement by their partners and by medical/psychiatric staff. Based on anxiety about the women's ability to handle the extra stress of parenting and also about their childcare competence, staff often steer women with schizophrenia away from motherhood. While this is well-intentioned, it is also a form of prejudgement or stigmatization [30]. The issue of parenting needs to be raised with women with schizophrenia, and thoroughly discussed. If children are not wanted or motherhood is unrealistic at the time, it is important to ensure that contraceptive measures are in place [31]. A systematic scoping review by Vickers and collaborators [32] investigated sexual and reproductive health in adolescents and young adults with psychotic disorders. Sexual dysfunction was attributed to psychosis, but, additionally, to the use of antipsychotic medications, especially those that markedly raised prolactin levels. Sexual risk behaviours, with their attendant risk of sexually transmissible infections, were frequently reported in this population. Sexual education is, therefore, required. Women need protective as well as contraceptive advice, access to abortion needs discussion, as do sexual violence and coercion, and sexual preference and gender identity confusion, topics that are often not broached with women with schizophrenia because of fear that they will induce delusional thinking [30].

An attempt was made by Posada Correa and co-workers [33] to address sexual and reproductive health issues and the use of contraception and sexual counselling in patients with schizophrenia and bipolar disorder. Although relatively few patients with schizophrenia reported having an active sexual life, almost all who did report, in this sample, to be using contraception. The majority of patients stated that they had never received information about family planning from their physicians. Nevertheless, 78.8% of those with schizophrenia considered themselves well-informed on the subject. The authors of the study recommended the provision of psychoeducation in areas such as contraception, family planning, and sexually transmitted diseases. This is an important issue for both men and women. Because women with schizophrenia show low rates of sexual satisfaction and high rates of both sexual dysfunction and sexual coercion [34], sexual health interventions are particularly recommended for women. A systematic review and meta-analysis that included 10 observational studies of 3,570 patients, 1,161 of whom suffered from schizophrenia [35], found statistically significant correlations between schizophrenia and sexual dysfunction in both men and women and advocated for psychological as well as pharmacological (prolactin-lowering) interventions. Therapeutic conversations about sex need to be attuned to age, and cultural context, to intimate partner status, and to the different needs and potential risks of sexual activity in men and women.

Decision-making capacity and reproductive counselling

Attention has been paid in recent years to decision-making capacity with respect to pregnancy and abortion in women suffering from mental disorders [36]. While many women with severe mental illness retain their decision-making capacity despite the presence of psychotic symptoms, the appointment of a guardian or surrogate decision-maker may be necessary, especially when termination decisions need to be made within a short time period. Such decisions benefit from consultation with ethics experts [37].

As mentioned, antipsychotic treatment, via hyperprolactinemia [38] lowers fertility and needs to be addressed by a judicious choice of drug treatment and also by stress reduction techniques and social support because stress itself raises prolactin levels [30]. Some women with schizophrenia, however, perhaps especially those who are not adherent to their antipsychotic regimen and/or who lack effective contraception, go through repeated pregnancies [39]. In these cases, the postnatal period has been touted as an ideal opportunity to initiate the implementation of contraceptive measures to prevent what often leads to repeated maternal loss of offspring to adoption services or foster care [30]. Such losses intensify psychotic symptoms.

It is important to reiterate that women with schizophrenia require reproductive counselling. Frayne and collaborators [40] carried out a cross-sectional survey of an antenatal clinic in Australia consisting of 38 women participants with severe mental illness. The following variables were noted: unintended pregnancies, initiation of immediate postpartum contraception, use of prenatal and pregnancy vitamins, presence of obesity, use/discontinuation of smoking, alcohol, and street drugs, and presence of comorbid medical conditions. In 56% of women with schizophrenia, the pregnancy was unintended (compared to 26% to 40% of all Australian women) [41, 42]. Contrary to recommendation, 45% of the women had not started contraception prior to postnatal discharge. Twenty-one percent smoked during pregnancy (compared to 8.6% in Australian pregnant women in general) [43] and 35% were obese (compared to 22% of pregnant women in Australia), statistics that indicate inadequate care [40]. The reasons for poor adherence to antenatal health may be partly due to the positive, negative, and cognitive symptoms inherent in psychotic disorder and reduced by effective treatment, but also to the associated social risk factors—poverty, social exclusion, lack of support, lack of education [44, 45], a change of which requires strong advocacy and political will.

Pregnancy and the postpartum period in women with schizophrenia

A recent systematic review and meta-analysis examined the evidence on pregnancy, delivery, neonatal complications, and infant mortality in schizophrenia women, pregnancy in schizophrenia being considered high risk [46]. The findings were that this population experiences a disproportionally high rate of gestational diabetes, pre-eclampsia and eclampsia, antepartum and postpartum haemorrhage, placental abruption, and premature rupture of membranes. Infants of schizophrenia mothers have been found at risk for neonatal and early death, all of which make effective intervention a public health priority. A minority of women with schizophrenia show a psychotic denial of pregnancy [47], which, for this subgroup, explains the lack of prenatal care.

Simoila and collaborators [48] compared the reproductive health of women with schizophrenia and schizoaffective disorder, focusing on pregnancy, delivery, and postpartum outcomes. Women with schizophrenia were younger at the time of giving birth than those with schizoaffective disorder, but no other differences were found. Compared to the general population, women with schizophrenia have been found to have fewer pregnancies and higher rates of induced abortions, but the pregnancy rate in this population is increasing, perhaps because newer antipsychotics interfere less with fertility than older drugs [49]. It is important in schizophrenia pregnancies to monitor antipsychotic levels and health indices across the three trimesters. Schizophrenia-induced and drug-induced risks both result in obstetric complications that can negatively affect infant development [50].

Harris and collaborators [51] carried out a retrospective study of 98 pregnant women with schizophrenia in order to determine hospitalization risk during the gestational period. Approximately 41% of the women required hospital admission during pregnancy, the first trimester being the period of greatest risk. Inadequate prenatal care, drug and alcohol use disorders, and the intervention of child protection services were the three most common factors responsible for psychiatric admissions. A multidisciplinary approach to these problems was recommended. Active collaboration between psychiatrists and gynaecologists and childcare agencies during pregnancy has been suggested [52].

One of the more controversial aspects of treatment during pregnancy is the use of long-acting injectable antipsychotics (LAI, whether 1st or 2nd generation). Nguyen and collaborators [53] conducted a case-series study in a tertiary maternity hospital with the aim of examining pregnancy, neonatal, and psychosocial outcomes of women receiving LAI, between 1999 and 2017. Measures included: socioeconomic variables, smoking, alcohol and other substance use disorders, pregnancy complications, and child protection involvement. Thirty-eight pregnancies of 36 women treated with LAI were compared to pregnancies of women in the general population. The LAI-treated women were more likely than controls to experience gestational diabetes and preeclampsia. The percentage of congenital malformations did not differ. The authors reported high rates of psychiatric admission in these women, with similar outcomes between those exposed to first- and second-generation antipsychotics. A recent descriptive observational

study investigated neonatal outcomes in women suffering from bipolar and other psychotic disorders who received LAI during pregnancy [54]. Assessment at follow-up consisted of an interview with either the patient or the physician-in-charge. Here again, it was found that treatment with LAI was not associated with an increased risk of malformations. Importantly, pregnancy outcomes of LAI have not been compared to those of women with schizophrenia in general, whether untreated or treated solely with oral medications. The assumption that a history of non-compliance to oral antipsychotics necessitates LAI and that this precludes a treatment switch to oral meds during pregnancy is worth noting. It has been found that close monitoring during pregnancy allows switching to oral meds, at least for the critical time period of the third trimester [55], which would avoid high drug levels in neonates.

The postpartum period of a woman's life is a period of high vulnerability to the occurrence of psychiatric symptoms and exacerbation of mental disorders, which may be partly explained by the decline of circulating oestrogens [56]. In fact, the rapid drop of oestradiol at the end of pregnancy has been implicated in the aetiology of postpartum disorders, and oestrogens combined with progesterone have been tested as potential treatments for these conditions [57].

With regard to breastfeeding in women suffering from schizophrenia, recent work highlights the relative lack of evidence in this field. A cross-sectional descriptive study [58], using self-report questionnaires, investigated attitudes towards breastfeeding among women with schizophrenia among health professionals (nurses, midwives, health visitors) from health care settings in Athens. In general, healthcare professionals showed favourable attitudes towards breastfeeding and recommended a rating scale to evaluate the effect of breastfeeding on outcomes in both mothers and children. Despite acknowledged benefits to the infant (and to the mother) of breastfeeding, there are concerns, on one hand about antipsychotic drugs being transmitted to the infant, and, on the other, about women stopping their much-needed medications to avoid child exposure. There are dose and feeding schedules that will minimize the dangers of exposure, and many experts are now leaning toward encouraging breastfeeding in all women, including those being treated for schizophrenia [59].

Rarely, psychosis, especially postpartum psychosis, can lead to pathological filicide—a mentally ill mother killing her child. A recent study investigated the characteristics of 17 mentally ill filicidal mothers by retrospective chart review conducted in a secure unit in France [60]. Forty-one percent of the sample suffered from schizophrenia, 41.2% from bipolar disorder or depressive disorders, and 17.6% from personality disorders. Two different profile groups were identified. In the first group, filicide was attributed to a defensive response to a perceived threat to the child induced by delusional beliefs or auditory hallucinations. In the second group, the act was precipitated by the mother's belief, real or imagined, that the child was about to be taken away from her. In 39% of filicide cases, women are reported to also attempt suicide [61]. In general, filicide is considered multifactorial in aetiology, with aggressive/violent relationships and social isolation playing an important part in the behaviour. Study authors underline the importance of maintaining contact with new mothers with mental illness whenever they fail to attend scheduled visits.

One relatively unusual syndrome in high income countries, but frequent elsewhere, especially in women with schizophrenia, is delusional pregnancy, an insistence by the woman that she is pregnant, frequently accompanied by signs of pregnancy (amenorrhea, nausea, breast swelling, and galactorrhea, abdominal swelling, urinary frequency) without evidence of a fetus [62]. This is a delusion that may be difficult to manage because the woman, considering herself pregnant, will not agree to take antipsychotic medications.

The complexity of management of women with schizophrenia during the perinatal period has led to very much needed recommendations for decision-making models and international guidelines with respect to optimal care during this vulnerable time period [63].

Victimization during pregnancy and postpartum

Women with schizophrenia are at considerable risk for interpersonal violence, a risk that increases during pregnancy. A recent population-based cohort study in Canada compared rates of interpersonal violence in

women with and without schizophrenia who attended an emergency department (ED) while pregnant or within one year postpartum [64]. Measures taken were sociodemographic characteristics, history of substance use disorders, and interpersonal violence. From a total sample of 1,802,645 pregnant women, 4,470 had a diagnosis of schizophrenia, of whom 137 (3.1%) visited an ED prenatally due to interpersonal violence. Pregnant women suffering from schizophrenia were more likely to report interpersonal violence compared to women without schizophrenia, confirming that pregnancy is a period of special risk in this population, perhaps attributable to risky marital choices [65]. All women with schizophrenia need to be tactfully questioned about their intimate relationships with the possibility of domestic abuse in mind, especially during pregnancy.

Zerihun and collaborators [66] carried out a cross-sectional study of reproductive-age women suffering from chronic mental illnesses and intimate partner violence (IPV). One hundred seventy study participants were diagnosed with schizophrenia, and 116 with bipolar disorder. A structured questionnaire was used to assess IPV, as well as sexual, physical, and emotional abuse. Lifetime IPV was present in 62% of the women, emotional abuse being the most common form (60%). Marital status, occupation, duration of illness, and degree of control exerted by the male partner were all significantly associated with IPV. This is a significant safety issue that needs to be sensitively probed during psychiatric visits and any visible sign of abuse investigated; patients often do not reveal abuse voluntarily [67].

Children born to women with schizophrenia

Practices that have been recommended by the World Health Organization for all neonates, such as breastfeeding and skin-to-skin contact, have not, until recently, been investigated in new mothers with schizophrenia. Taylor and collaborators [59] carried out a population-based cohort study based on medical records of new mothers with (n = 471) and without (n = 218) schizophrenia to determine whether skin-to-skin contact and breastfeeding were started within the first 2 h after birth. The findings were that maternal schizophrenia was associated with lower skin-to-skin contact and lower rates of breastfeeding immediately postpartum when compared to the rate of these behaviours in new mothers in the general population. These are behaviours that exert a theoretical impact on mother-child bonding and the finding suggests that new mothers with schizophrenia require individualized support that actively promotes best practices. As mentioned earlier, best practice has now swung toward recommending breastfeeding for mothers with schizophrenia taking antipsychotics.

The need for specialized care for mothers with schizophrenia is underscored by the finding that maternal schizophrenia is positively associated with perinatal complications [68]. Vigod and colleagues [68] conducted a population-based cohort study of 5,066 children of mothers with schizophrenia and 25,324 children of mothers without schizophrenia. Maternal age, parity, immigrant status, income, region of residence, other maternal medical and psychiatric conditions, and childhood chronic health conditions (Childhood-CC) were all noted. A significantly larger percentage of children of mothers with schizophrenia developed Childhood-CC when compared to children of schizophrenia-free mothers. This is consistent with another recent study investigating the prevalence of complex chronic conditions in children born to women with schizophrenia. In this population-based study of 5,066 children of women with schizophrenia and 2,939,320 control children [69], complex chronic conditions were again more frequently reported in the index children. These conditions tended to be neuromuscular, cardiovascular, respiratory, and immunodeficiency disorders. Preconception psychoeducation for mothers and counselling that targets strict adherence to prenatal instructions is strongly recommended.

Maternal schizophrenia has been also associated with an elevated risk of child injury. Taylor and collaborators [70] stratified children according to sex and age: infancy (0–1 years), pre-school (2–5 years), primary school (6–9 years), and early adolescence (10–15 years). All forms of child injury were noted—e.g., accidental injury, self-injury, assault. Accidental injury and self-injury were most commonly associated with maternal schizophrenia in the 10–15-year-old group, whereas assault was associated with exposure to maternal schizophrenia in infancy and pre-school. It has been emphasized that mothers with schizophrenia

need support, aid, and monitoring to prevent accidental child injuries and injuries that result from neglect or abuse [71]. Referrals to childcare agencies may be required.

The Taylor and colleagues' group [72] also investigated adherence to infant check-up schedules and vaccination schedules (up to age two) in mothers with or without schizophrenia, using provincial medical records. The recommended rate of well-baby visits was achieved in 50.3% of children exposed to maternal schizophrenia compared to 58.6% of control children. Full vaccine schedule adherence occurred in 40% of children of mothers with schizophrenia *versus* 46% of children of controls. Close liaison with paediatrics is recommended for mental health practitioners when treating mothers with schizophrenia. Mental health staff are also encouraged to make home visits for mothers with schizophrenia whenever there are children who live at home.

Postmenopausal years in women with schizophrenia

The impact of menopause and aging on clinical outcomes in women with schizophrenia is presented in Table 3.

Table 3. Influence of menopause and aging on clinical outcomes in schizophrenia

Aspect	Outcomes	Findings
Epidemiology	Reduced levels of oestrogens on schizophrenia incidence	Second peak of incidence at menopause in women [25, 73]
Psychopathological symptoms	Symptom severity and clinical stability	Menopause correlates with 1) increased severity of psychosis [74] and 2) antipsychotic resistance [74–82]
Physical health	Breast cancer—incidence and mortality	Increased incidence attributed to drug-induced hyperprolactinemia. Increased mortality attributed to low rates of cancer screening and medical neglect [83, 84]
	Medical co-morbidity	Osteoporosis and type 2 diabetes attributed to antipsychotics [82]

Clinical outcomes in women with schizophrenia post-menopause

The diminishing levels of oestrogen that begin at pre-menopause are thought to be responsible for the 2nd incidence peak of schizophrenia in women [25]. For women whose symptoms began earlier in life, menopause is associated with an increase in symptom severity and, frequently, the advent of antipsychotic resistance [73]. Oestrogen loss may also decrease the efficacy of specific CYP enzymes that metabolize individual antipsychotic drugs [74].

Sommer and collaborators [75] carried out a nationwide cohort study of 61,889 individuals investigating clinical outcomes in schizophrenia/schizoaffective disorders. The sample was divided into two groups according to: age < 45 years, and > 45 years. The investigators hypothesized an increase in relapse risk and a reduction of antipsychotic effectiveness leading to hospitalization in women over age 45 when compared to both male age peers and women under age 45. They saw a decrease in antipsychotic efficacy for four drugs—clozapine, olanzapine, quetiapine, and risperidone.

González-Rodríguez and colleagues [76] reviewed the impact of menopause on psychopathological symptoms and comorbidity in women with delusional disorder (DD), a schizophrenia-related disorder. They found an increase in depressive symptoms and also an increase in all psychiatric co-morbidity. Both physical symptoms (vasomotor, physical, sexual) and psychiatric symptoms (depression, insomnia, cognitive, and psychosocial difficulties), in addition to oestrogen decline, appear to trigger the emergence of psychotic symptoms at the time of menopause. Chronic medical problems such as obesity, type 2 diabetes, osteoporosis, and osteoarthritis also emerge at this time, often aggravated by antipsychotic medication [76].

Oestrogen/raloxifene in schizophrenia

The selective oestrogen receptor modulator (SERM) raloxifene has been described as a promising treatment option for women with schizophrenia for whom replacement oestradiol is contraindicated [77]. It has been shown that raloxifene improves cognitive symptoms in postmenopausal women with

schizophrenia, but the results may be inconclusive [78]. The meta-analysis of randomized controlled trials of raloxifene by Wang and collaborators [79] and the meta-analysis of randomized, double-blind, placebo-controlled trials with oestradiol and raloxifene as adjunctive treatment for women with schizophrenia by Li and collaborators [80] demonstrated a significant improvement of symptoms [79, 80]. Adjunctive oestradiol improved total PANSS scores, in addition to improving positive, negative, and general psychopathology scores. Adjunctive raloxifene improved the PANSS total scores, and general psychopathology scores [80]. Both adjunctive treatments were shown to be safe, but, at the moment, aspects such as timing and dosage remain unclear [80].

The effect of add-on raloxifene has been studied in schizophrenia even prior to menopause. Brand and collaborators [81] recently used raloxifene *versus* placebo adjuncts to antipsychotics in a sample of relatively young men and women with schizophrenia-spectrum disorders (placebo age 39.3 years ± 11.2 years, and raloxifene age 42.0 years ± 11.9 years). The study consisted of 72 men and 28 women in a parallel, randomized, double-blind, placebo-controlled trial across the Netherlands and Belgium. Participants were stratified by age, sex, and global functioning and randomly assigned to 12-week adjunctive raloxifene 120 mg/d or placebo. Intention-to-treat analyses were performed using linear mixed-effect models [81]. Results showed no main effect of raloxifene in the sample as a whole, but, in secondary sex-specific analysis, women on raloxifene showed significant beneficial effects on negative symptoms and working memory, while the working memory of men on raloxifene deteriorated. This potential sex-disparate effect needs to be further studied. There may be women with schizophrenia who respond better to raloxifene than others but it is presently unknown whether that is the case.

Cancer risks as women with schizophrenia age

An important health concern for individuals with schizophrenia as they age is cancer screening, with relatively low rates of breast and cervical screening being characteristic for this population [82]. Delays in screening postpone effective treatment and decrease survival time. Breast cancer is the main concern in women. In women suffering from schizophrenia, breast cancer has been attributed to genetics, lifestyle (smoking, alcohol use, sedentariness, and unhealthy eating leading to obesity), and other factors associated with schizophrenia such as relatively low parity. Antipsychotics are a concern because these drugs raise prolactin levels. A recent Finnish nationwide register study investigated the potential contribution of prolactin-raising antipsychotics to the breast cancer risk [83]. While exposure to prolactin-sparing antipsychotics was not associated with increased risk, five or more years' exposure to prolactin-raising antipsychotics was positively associated with the development of breast lobular adenocarcinoma [83]. These results underscore the need to use prolactin-sparing antipsychotic drugs for schizophrenia in women whenever possible [84].

Using data from the New York State Cancer Registry of 10,444 women with breast cancer, Lawrence and collaborators [85] found that the mortality rate from breast cancer of women with pre-existing severe mental illness was significantly higher than that seen in the general population of women. This can be attributed to a combination of patient factors (low screening rates and mistrust of doctors leading to late diagnosis, cognitive problems preventing treatment adherence), physician factors (failure to follow up on missed appointments, failure to recruit women with severe psychiatric illness into chemotherapy trials, diagnostic overshadowing—a form of stigma that attributes all complaints in schizophrenia patients to delusional thinking) and system failures (communication silos between psychiatry and primary care/oncology/surgery). All these factors need reform. Achieving optimal physical healthcare has been considered a major challenge in the management of individuals with severe mental illness; this is being increasingly recognized and addressed. A recent example is the introduction of exercise programs into standard care for schizophrenia patients, an intervention that benefits cognition by reversing hippocampal volume loss and improving memory scores [86]. Exercise-induced weight loss also protects against antipsychotic-induced metabolic complications. Exercise is, of course, important to both men and women but the tendency to drug-induced weight gain and metabolic disturbance is more pronounced in women [87]. Moreover, it has been hypothesized that men and women respond somewhat differently to different

kinds of exercise programs [88]. This may, in the future, be important in the optimization of women-specific treatment for schizophrenia.

Conclusions

Treatment best practices in women with schizophrenia and related psychotic disorders differ in important respects from those of men. Pharmacologically, women usually require lower doses of antipsychotics than men and, when prescribed standard doses, they suffer from antipsychotic adverse metabolic, sexual/reproductive, and specific cardiovascular effects. Regarding reproductive aspects, schizophrenia women need female-specific contraceptives as well as relationship advice. When pregnant, they show disproportionally high risk relative to other women for gestational diabetes, pre-eclampsia and eclampsia, antepartum and postpartum haemorrhage, placental abruption, and premature rupture of membranes; knowledgeable prenatal and obstetric care is vital for the women and for their children. Infants of schizophrenia mothers are more likely than other newborns to experience neonatal and infant health problems, making paediatric referral essential.

Women with schizophrenia, especially during pregnancy, are at risk for interpersonal violence, which requires continuous psychoeducation and a raised index of suspicion when women present with bruises or broken bones. Social issues such as decisions about parenthood, parenting guidance, dealing with stigma, and ensuring social support all loom large in the treatment of women with schizophrenia.

A difficult life stage for this population of women is the approach of menopause and, subsequently, the postmenopausal period. This is due to the effect of declining levels of oestrogens on brain health and physical health, combined with the effects of age itself and the cumulative negative consequences of social and lifestyle and treatment factors. Drug treatment often needs changing at this time. To counteract adverse drug effects, prolactin-sparing antipsychotics and exercise programs are recommended. Adjuvant treatment with oestrogens or selective oestrogen receptor modulators shows therapeutic promise. Strides are being made in sex-specific therapies.

Abbreviations

IPV: intimate partner violence

LAI: long-acting injectable antipsychotics

LH: luteinising hormone

PANSS: Positive and Negative Syndrome Scale

Declarations

Author contributions

AGR and JC: Conceptualization, Data curation, Writing—original draft, Writing—review & editing. MVS: Conceptualization, Data curation, Writing—original draft, Writing—review & editing, Supervision.

Conflicts of interest

AGR has received registrations for congresses or travel funds from Janssen Global Services, Lundbeck, Otsuka Pharmaceutical, and Angelini Pharma, and honoraria for lectures from Lundbeck and Otsuka.

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