Women and psychosis: A guide to evidence-based, hormone-informed care

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Summary

Psychosis is associated with sex differences that are rarely considered in routine care. Oestrogen exerts protective effects, with symptom exacerbation and increased relapse risk occurring during low-oestrogen states such as perimenstruation, postpartum, and menopause transition. Antipsychotic pharmacokinetics and response vary by sex and hormonal status, with premenopausal women requiring lower doses, and postmenopausal women showing reduced treatment efficacy. Antipsychotic-induced hyperprolactinaemia can further suppress endogenous oestrogen, compounding both mental and physical health risks. Despite this, treatment guidelines remain largely sex-neutral. This review outlines the role of ovarian hormones in psychosis and offers practical considerations to support the first steps towards implementing hormone-informed care, providing a conceptual framework to guide clinical decision-making with the aim of improving outcomes for women with psychosis across the lifespan. Key recommendations include thorough assessment of hormonal status, sex-specific prescribing, and the judicious use of oestrogen-based interventions such as hormonal contraception, hormone therapy, and oestrogen receptor modulators.

Introduction

Schizophrenia is a severe psychotic disorder which in some individuals can be associated with significant disability.[1] Although lifetime incidence is similar between sexes, with a male-to-female ratio of 1.1:1 for schizophrenia,[1] there is a robust difference in the onset of schizophrenia and schizophrenia-spectrum disorders. Men are more frequently affected before age 45, whereas incidence in women is double that in men thereafter.[2,3] While women initially respond better to medication, require lower doses, and have better outcomes, this advantage is lost over time.[4] Across the lifespan, rates of readmissions,[4] recovery,[5] and long-term functional outcomes,[6] converge with men's, with outcomes notably declining in women after reaching midlife.[4] Clinically, women tend to show milder negative symptoms, better social functioning, and less substance misuse, but more severe auditory hallucinations and a higher prevalence of affective symptoms.[7,8] Although men have a higher absolute suicide risk,[3] women show a disproportionately greater relative increase compared with the general population.[9]

Sex differences in psychosis are shaped in part by ovarian hormones. Across the lifespan, women show increased vulnerability to psychosis during periods characterised by falling ovarian hormones, such as the perimenstrual phase of the menstrual cycle (i.e., the days just before and during menstruation), postpartum, and peri- and post-menopause (Figure 1).[4,10,11] Among these hormonal fluctuations and their downstream regulated processes, the role of oestrogen, particularly (17β-)oestradiol, the biologically most active oestrogen type, has been particularly well-studied, and the 'oestrogen protection hypothesis' postulates that this hormone plays a protective role in psychosis.[12]

Despite their potential influence on disease course and treatment, sex and ovarian hormones are rarely considered in management strategies. Current guidelines neither address sex differences nor female-specific hormonal changes.[13] This review outlines clinical implications of ovarian hormones in women with psychosis across the lifespan, incorporating practical strategies for assessment and treatment in general psychiatric care. The perinatal period is excluded as this is covered elsewhere.[14–16] We first describe how ovarian hormones and times of hormonal fluctuation shape symptom expression and disease course. We then discuss the use of antipsychotic and oestrogen-based treatments, and outline initial steps to optimise care. By doing so, we aim to link existing evidence with clinical decision-making, providing a conceptual basis for understanding and addressing the influence of ovarian hormones in psychosis.

Ovarian hormones and psychosis

Hormone and symptom fluctuations across the menstrual cycle

Between menarche and menopause, women experience cyclical hormonal fluctuations, with the menstrual cycle typically spanning 25-35 days and commencing on the first day of menstrual bleeding. Psychotic symptoms tend to worsen and hospitalisation risks increase from the last quarter of the cycle into the first quarter of the next, also referred to as the perimenstrual phase,[17] when oestrogen and progesterone decline and remain low for 4-6 days (Figure 1).[11]

Menstrual cycle symptom fluctuations are thought to be driven, at least in part, by the effects of ovarian hormones on the brain. Oestrogen potentiates striatal dopamine release and increases receptor sensitivity,[18] and neuroimaging studies indicate that menstrual cycle hormone fluctuations impact corticolimbic function.[19,20] Preclinical evidence furthermore indicates that oestrogen modulates hippocampal synaptic plasticity, with spine density peaking during the phase when oestrogen levels peak.[21] While the impact of progesterone in psychosis is less established,[22] its role in premenstrual mood disorders is better characterised and of potential relevance to psychosis.[23]

Despite their plausible link, few studies have directly examined how cyclical changes relate to symptom fluctuations. When attempted, they often face methodological challenges: phases when both oestrogen and progesterone are high are typically compared with phases when both are low, making it difficult to disentangle their individual effects.[24] The lack of hormonal assays and inconsistent definitions on cycle phases further complicate the interpretability and comparability of findings.[17] Symptom exacerbation may also reflect individual sensitivity to hormonal fluctuations rather than abnormal concentrations, such that even minor physiologically normal changes may trigger substantial symptoms in some individuals, as seen in premenstrual dysphoric disorder.[25]

Menstrual irregularities and hormonal dysregulation

Irregular, infrequent or absent menstruation affects 12-25% of women in the general population,[26] but occurs at about twice that rate in women with schizophrenia.[27] Antipsychotic-induced hyperprolactinemia causing secondary hypogonadism is a common cause, while elevated stress and BMI, both common in psychotic disorders,[28,29] also contribute.[30] Premenopausal women with psychosis consistently show lower oestrogen levels than healthy controls,[31–34] though small sample sizes and confounding effects of prolactin-raising antipsychotics on ovarian oestrogen production complicate interpretation. Only very few studies report lower oestrogen levels in women with psychosis independent of medication use,[35] while others report no difference.[36–39] Some studies also report reduced midluteal progesterone,[39–41] while others find no difference.[42] Menstrual irregularities have been linked to poorer cognitive performance,[43] and low oestrogen levels to greater symptom severity and worse cognitive functioning.[37,43,44]

In all women, the menstrual cycle functions as a vital sign that offers crucial health information, and cycle characteristics can predict chronic disease later in life.[45] Long or irregular cycles or absent menstruation often co-occur with endocrine disorders such as functional hypothalamic amenorrhoea, obesity, and thyroid disorders, and is linked to higher risks of developing type 2 diabetes, cardiovascular disease, and osteoporosis.[45] As such, menstrual irregularities should be recognised as a key indicator of overall health. Overlap with antipsychotic side-effects likely contributes to under-recognition, underscoring the need to address these disturbances as a vital sign to guide treatment, monitor symptoms, and inform preventive care.

A key comorbid condition to consider is polycystic ovarian syndrome (PCOS), an endocrine disorder affecting approximately 5-18% of women.[46,47] Although its prevalence in psychosis is unknown, PCOS is widely underdiagnosed and likely even more frequently missed in women with psychosis due to reduced healthcare

access and symptom overlap with antipsychotic side-effects.[48,49] PCOS features such as hyperandrogenism, insulin resistance, obesity, menstrual dysfunction, and gut dysbiosis may independently increase psychiatric vulnerability.[50] Such symptoms should therefore not be automatically attributed to antipsychotics but considered in the context of potential underlying endocrine disease.

Role of stress and trauma

Traumatic experiences increase psychosis risk in both sexes, but the risk appears to be greater in women.[7,51] Women with psychosis and a history of trauma also tend to show more severe affective and psychotic symptoms than those without trauma.[7] Under chronic stress, sustained activation of the hypothalamic-pituitary-adrenal (HPA) axis can impair hypothalamic-pituitary-gonadal (HPG) axis functioning, disrupting ovarian hormone production.[52,53] Consistent with this, childhood trauma has been associated with PCOS, highlighting a potential link between early-life stress and long-term dysregulation of endocrine function.[54,55]

Acute stress may also increase psychotic vulnerability via prolactin dysregulation. Elevated prolactin has been observed in antipsychotic-naïve individuals with psychosis and in those at clinical high risk, potentially reflecting stress-related decrease in dopaminergic inhibition of prolactin.[32,56–58] Reduced oestrogen may subsequently further exacerbate HPA-axis dysregulation, reinforcing stress sensitivity,[7,56,59] potentially contributing to psychosis pathophysiology in women.

Menopause and increased vulnerability

The steepest decline in oestrogen and progesterone occurs during the menopause transition, or “perimenopause”, typically in the late forties. Menopause, defined as 12 consecutive months without menstruation, marks a lasting drop in both hormones. Progesterone declines earlier and more steadily, while oestrogen fluctuates markedly during the perimenopause before its permanent decline.[60] Perimenopause lasts an average of four years but can extend to ten years,[61] and its course can vary greatly between women.[62] Menopausal hormonal shifts can affect physical and mental health, including vasomotor symptoms, sleep disturbance, mood and cognitive symptoms and sexual dysfunction.[63,64] Such changes can trigger or intensify psychotic, mood, and anxiety symptoms, which in turn may further disrupt sleep and overall well-being, creating a vicious circle.[65,66]

The link between menopause and psychosis has been recognised for over a century, being first described in the 19th century and further cemented in the late 20th century, when the second incidence peak of psychosis around menopausal age was quantified epidemiologically.[12,67–69] While some studies report this peak as less pronounced,[2,3,70] psychosis at older ages remains more common in women than men. Women with a prior schizophrenia diagnosis also tend to have poorer outcomes post-menopausally, with higher relapse rates and reduced antipsychotic effectiveness than men and younger women.[4] Menopause similarly elevate risks of onset or worsening of bipolar disorder and depression,[71,72] though depressive and anxiety symptoms often improve post-menopause.[71] Women with prior postpartum depression are especially prone to symptom recurrence during perimenopause, suggesting a subgroup with particular vulnerability to hormonal transitions.[73] A similar hormonal sensitivity might apply to psychosis, with postpartum psychosis potentially heightening risks of deterioration around menopause.

Postmenopausal oestrogen decline impacts overall health by accelerating bone loss and worsening metabolic and cardiovascular health.[74] The hormonal decline increases risks of type 2 diabetes, osteoporosis, and heart disease, typically manifesting within 5-15 years after menopause onset. This creates a window for intervention during perimenopause to alter long-term risk.[75] Many of these effects of oestrogen decline, including osteoporosis and cardiovascular and metabolic changes, overlap with antipsychotic side-effects, compounding risks for women undergoing both menopause and antipsychotic treatment. Reduced antipsychotic effectiveness after menopause may additionally prompt dose increases, potentially further elevating physical health risks.[4]

Antipsychotics for women with psychosis

Pharmacokinetics and pharmacodynamics

Although antipsychotic dosing has largely remained unisex, substantial evidence shows sex differences in both antipsychotic efficacy and tolerability.[16,76] Understanding these differences is essential to optimising care for women with psychosis. Premenopausal women generally require lower doses than men and older women to achieve therapeutic effects.[4,16] Slower drug absorption, metabolism, and excretion all result in higher plasma levels as compared to men when dosed equally,[77,78] increasing the risk for side-effects, which are reported more often in women.[16]

In women, drug metabolism is modulated by hormonal status. Oestrogen can inhibit or stimulate drug-metabolising enzymes in a drug-specific manner. For CYP1A2/CYP2C19 substrates like clozapine and olanzapine,[79] oestrogen inhibits metabolism, leading to up to 40% higher plasma levels in women.[77,78] Quetiapine, metabolised by CYP3A4, shows no sex differences in younger individuals.[77,78]

Combined oral contraceptives (COCs; Box 1) with ethinylestradiol have an even stronger inhibitory effect on CYP1A2, potentially requiring halved doses of its substrates to achieve target plasma levels.[80] While similar effects are suspected for olanzapine and asenapine,[75] more research is needed.[80] Although biologically plausible, dose adjustments during the hormone-free interval have not been studied, and evidence for their effect on plasma concentrations or clinical outcomes is lacking. Other ethinylestradiol-containing combined hormonal contraceptives (CHCs) including the combined transdermal patch and vaginal ring bypass first-pass hepatic metabolism but do deliver systemic ethinylestradiol and may therefore still inhibit CYP1A2.

Lower levels of the efflux transporter p-glycoprotein in women may also increase drug accumulation in the brain and other tissues by reducing gut efflux and raising systemic exposure. The impact of this sex difference may contribute in particular to sex differences for drugs with a high affinity for p-glycoprotein, including risperidone and amisulpride.[16] Formulation excipients such as Polyethylene Glycol 400 used in paliperidone and quetiapine formulations further modulate p-glycoprotein activity differently by sex, enhancing bioavailability in men but not women.[81]

While evidence on the impact of menopause on drug pharmacokinetics is limited, The FDA recently highlighted the need for further research on menopause effects on drug pharmacology in a public workshop, highlighting this

as an important but understudied area.[82] Regarding antipsychotics, one study found sex differences in quetiapine concentrations to become more pronounced with age, with higher concentrations in women compared to men at older but not younger ages, possibly due to declining oestrogen-induced CYP3A4 activity.[78] Lurasidone might be subject to similar changes given its similar hepatic metabolic profile,[83] whereas opposing effects may be expected for CYP1A2-substrates olanzapine and clozapine. Indeed, one study found that dose-corrected olanzapine concentrations declined with age in women but increased in men.[84] Menopause may further affect excretion, as renal function declines more rapidly post-menopause, potentially increasing plasma concentrations and side-effects of renally cleared drugs.[85]

Once in the brain, antipsychotics may exert stronger effects in women. Dopaminergic neurotransmission, including synthesis, release, reuptake, and receptor responses all vary by sex and is modulated by ovarian hormones.[86] Women show higher D2-receptor binding in extra-striatal regions,[87] and PET data suggest that premenopausal women achieve optimal receptor occupancy at half the olanzapine dose required in men.[88] A systematic review indicated higher overall antipsychotic efficacy in women,[76] which was most consistent for olanzapine: four out of 12 studies reported superior responses in women whereas none favoured men. Risperidone, aripiprazole, and clozapine show no consistent sex differences in efficacy, but many antipsychotics remain understudied. A key limitation is the lack of stratification by menopausal status, potentially masking reduced treatment response in postmenopausal women.[4] Even without power for subgroup analyses, reporting outcomes by menopausal status would enable future pooled analyses.

How to prescribe antipsychotics for women with psychosis

When initiating antipsychotic treatment in women it is advisable to start at the lowest possible effective dose, which is lower than in men for most antipsychotics, except for quetiapine and potentially lurasidone based on their pharmacokinetic profile. Dose adjustments guided by side-effects can therefore be particularly helpful to optimise tolerability in women.

Starting ethinylestradiol-containing CHCs with CYP1A2-substrate clozapine may require dose reduction of clozapine.[80] Where available, plasma levels can be monitored on initiation or discontinuation to guide adjustments. Without monitoring, halving the clozapine dose at initiation and/or doubling it on discontinuation of COCs with vigilance for side-effects or loss of efficacy, has been recommended,[89] and similar caution may apply to asenapine and olanzapine. Initiation of oestrogen-containing COCs or hormone therapy (HT; Box 1) may also require dose adjustments, though effects may be less pronounced, especially with transdermal delivery. Intramuscular antipsychotics similarly bypass first-pass metabolism, minimising oestrogen-related hepatic effects, yet other described sex differences remain equally relevant.

During menopause, declining oestrogen may alter plasma concentrations of some antipsychotics, although research on this topic remains limited. For CYP1A2 substrates such as olanzapine and clozapine, loss of oestrogen may increase metabolism and therapeutic drug monitoring may help guide dose increases if symptoms re-emerge. Conversely, metabolism of CYP3A4 substrates such as quetiapine and potentially lurasidone,[79] may decrease, and monitoring plasma levels may inform downward dose adjustments if adverse effects arise.

Management of side-effects: Hyperprolactinemia

Women are more susceptible to antipsychotic-induced hyperprolactinaemia due to higher baseline prolactin levels and greater dopamine sensitivity.[90] Elevated prolactin suppresses the HPG-axis, reducing ovarian hormone production, causing many adverse effects, including breast tenderness, galactorrhoea, menstrual irregularities, subfertility, sexual dysfunction, and endometrial changes.[91] Prolonged use of prolactin-raising agents increases breast cancer risk after >5 years,[92] likely due to sustained prolactin elevation,[93] and reduces bone mineral density after >10 years due to chronic oestrogen deficiency.[94] Additional consequences include weight gain, dyslipidaemia, insulin resistance, and metabolic syndrome.[95] In postmenopausal women, symptoms may go unnoticed due to absent cycles and overlapping menopausal changes.

The literature on hypo-oestrogenic symptoms (mood, cognitive, and vasomotor symptoms, genital changes, and sleep disturbance) in women with antipsychotic-induced hyperprolactinemia is scarce, but women on prolactin-raising antipsychotics do show lower oestrogen than controls or those on prolactin-sparing antipsychotics.[37] Oestrogen levels correlate negatively with psychotic symptoms, suggesting a protective role, while high prolactin correlates with poorer processing speed.[37,96] This negative link with prolactin is also observed in unmedicated individuals,[44] indicating a specific role for prolactin rather than a general antipsychotic effect.[97]

The adverse physical and mental health effects of hyperprolactinaemia and hypo-oestrogenic states highlight the need to minimise prolactin elevation. Partial dopamine agonists (aripiprazole, cariprazine, and brexpiprazole), typically do not raise prolactin, whereas clozapine, quetiapine, and asenapine rarely cause sustained increases. Olanzapine, ziprasidone, and lurasidone can cause transient increases that may normalise within three months.[98]

When prolactin is raised, switching to a prolactin-sparing agent is preferred, as dose reduction is often ineffective.[99] If switching is inappropriate, adjunctive low-dose aripiprazole (from 5 mg/day) can effectively lower prolactin and reverse symptoms.[100] Prolactin levels should be monitored after initiation to confirm response.[101] Though evidence is mainly derived from studies in men,[100] high-dose vitamin B6 (600 mg/day) may also be effective,[102] yet such doses are only recommended short-term and carry a significant risk of peripheral neuropathy.[103] Other options include metformin, Paeonia–glycyrrhiza Decoction, or dopamine agonists.[100,104]

If hyperprolactinaemia is unavoidable, bone mineral density should be monitored. Additionally, to mitigate the long-term consequences of hormone deficiency, transdermal oestradiol-based hormone therapy (HT) may be considered,[104] consistent with guidelines for persistent hypo-oestrogenism in functional hypothalamic amenorrhoea, and current practice for treating macroprolactinoma, where oestradiol-based HT is recommended when amenorrhoea persists for more than 6-12 months.[105,106]

Management of side-effects: Cardiometabolic health and weight gain

Women face a disproportionately high cardiometabolic burden from antipsychotic treatment. Antipsychotic use increases cardiovascular mortality more in women compared to men,[107] possible due to greater weight gain and

metabolic dysregulation, both especially common in women.[16,76] Weight gain is of particular concern as it is among the most distressing side-effects in women with psychosis, frequently linked to negative body image.[108,109]

Most studies indicate a higher burden of cardiometabolic side-effects in women, except for hypertension.[76] Antipsychotics with an unfavourable metabolic profile may also catalyse PCOS-like phenotypes through their effects on weight gain and insulin sensitivity.[107] Cardiometabolic risk is further amplified during menopause, when declining oestrogen removes cardiovascular and metabolic protection mediated through endothelial support, anti-inflammatory effects, arterial health, fat distribution, and insulin sensitivity.[110,111]

To minimise cardiometabolic side-effects, lifestyle interventions should be encouraged, but if insufficient, options include switching to a lower-risk antipsychotic, adding metformin (500-2000mg/day), or considering a glucagon-like peptide-1 receptor agonist.[97] Metformin should be titrated slowly, particularly in women who appear more susceptible to its side-effects.[101,112] It may be especially beneficial in women with hyperprolactinaemia, as it also lowers prolactin and restores menstruation.[113]

In peri- and postmenopausal women, statins remain commonly prescribed to prevent cardiovascular disease despite their link with diabetes risk.[114] Although not recommended for primary prevention in the general population, oestradiol-based HT may reduce cardiometabolic risk, improve insulin sensitivity, and lower type 2 diabetes incidence.[115,116] It may therefore counteract antipsychotic-induced metabolic side-effects, particularly when initiated within ten years after menopause.[115]

Oestrogen-based treatments for women with psychosis

Hormone therapy and raloxifene

Given the protective effects of oestrogens in psychosis, oestrogen-based treatments may offer therapeutic benefits, particularly for women who experience worsening mood or psychotic symptoms perimenstrually or during perimenopause, as well as those with consistently low levels of oestrogen due to oligomenorrhoea/amenorrhoea due to oestrogen deficiency or menopause. Here, we review the current evidence on oestrogen-based treatments, including selective oestrogen receptor modulators and hormone therapy (HT). We use the term HT to encompass oestrogen-based hormone before and after menopause.

Raloxifene, a selective oestrogen receptor modulator approved for osteoporosis in many countries since the late 1990s, acts as an oestrogen agonist in brain and bone but as an antagonist in other tissues. It has shown promise in reducing psychotic symptoms in postmenopausal women.[117–121] The most recent meta-analysis (k=6, N=460) supports its efficacy in this population,[122] although the largest trial (N=200) included reported no effect, possibly because it included a severely decompensated and unstable sample.[123] Current evidence does not consistently demonstrate that a dose of 120mg/day offers greater benefit than 60mg/day.[122,124]

Limited evidence exists for raloxifene augmentation in premenopausal women, as one trial found no effect in a mixed-sex sample (N=79, 38% premenopausal women),[125] and another reported improvement in negative

symptoms only (N=30 females, 50% premenopausal).[126] Raloxifene's effects on cognition are mixed,[126–128] but imaging studies suggest raloxifene enhances prefrontal and hippocampal activity during cognitive tasks.[129–131] Variability in age at treatment initiation may explain these inconsistent findings, as oestrogen-based treatments appear less effective when started long after menopause, potentially due to reductions in hippocampal ER-α levels.[132] This underpins the 'therapeutic window' hypothesis, also described in Alzheimer's disease[133] and mood disorders.[134]

Menopausal HT has been used since the 1950s to treat menopausal symptoms, consisting of an oestrogen and requiring a progestogen in women with endometrial tissue to prevent endometrial hyperplasia. Its use dropped in the early 2000s after reports of cardiovascular and cancer risks,[135,136] but these findings have since been challenged. Most earlier studies were based on conjugated equine oestrogens (CEE), a mixture of multiple oestrogen compounds that differ in potency, receptor affinity, and central nervous system effects. Current evidence indicates a more nuanced risk profile,[75] with substantial benefits and few risks with oestradiol-based regimens, when initiated for clear indications (Appendix pp 1-2).[116] Menopausal HT remains the most effective treatment for menopause symptoms, improving quality of life, as well as genitourinary, bone, cardiovascular and metabolic health. These benefits need balancing against small increases in thrombotic risk which primarily apply to oral preparations only, and risks of endometrial and breast cancer. The increased breast cancer risk is largely attributable to the progestogen rather than the oestrogenic component of combined HT: oestrogen-only HT is associated with little or no change in the risk of breast cancer,[137–139] and combined regimens with micronised progesterone or dydrogesterone are associated with a lower risk than those containing other progestogens.[139,140] Overall, the risk–benefit profile is most favourable when initiated under 60 and within 10 years of menopause, though individual risk factors should guide treatment decisions.[116]

Compared to raloxifene, HT has shown more consistent benefits in psychosis, being particularly well-studied in premenopausal populations. Yet, one study including women up to age 46 found that benefits were primarily driven by women aged 38-46.[141] The strongest evidence comes from trials which used twice-weekly transdermal oestradiol patches (100-200µg/day), although some small studies have also reported benefits with ethinylestradiol,[142] and CEE.[143] Furthermore, in a Finnish national cohort, HT was associated with a 16% lower risk of psychosis hospitalisation compared with non-use.[144] Benefits were greatest when initiated at ages 40-55, but absent at ages 56-62, supporting the therapeutic window hypothesis.[133,134] No differences were found between oestrogen-only and combined therapies, suggesting no added effect of the progestogenic component.

Despite robust evidence supporting HT in women with psychosis overall, RCTs in postmenopausal populations are lacking, even though this group may benefit most. Besides potential improvement of psychosis, HT may reduce risks of comorbidities commonly associated with psychosis and its treatment (Appendix pp3-4),[101] preventing the need for multiple treatments for separate health problems and offering particular benefit for women with psychosis.

Hormonal contraception

Women with psychosis face higher rates of unplanned pregnancy and termination,[145] underscoring the need for proactive contraceptive counselling. A first step is to establish whether a wish for pregnancy exists, which should form an essential part of routine care. When contraception is preferred, method choice requires balancing effectiveness, convenience, and effects on endogenous hormones. Available options include both hormonal and non-hormonal methods, with hormonal contraception comprising combined oestrogen–progestogen formulations (CHCs), and progestogen-only formulations.

CHCs can be delivered as pills (COC), transdermal patches, or vaginal rings. Compared to COC, rings provide slightly lower and patches slightly higher systemic oestrogen exposure,[146,147] with modest differences in side-effect profiles,[148] though contraindications are shared across methods. Most CHCs contain ethinylestradiol which increases thrombotic, metabolic, and hepatic risks, with venous thromboembolism being most clinically relevant. As risk factors such as smoking and obesity are common in women with psychosis, CHCs are frequently contraindicated. Oestradiol-based formulations, though less widely available, have lower hepatic impact and may pose lower thromboembolic risk.[149] Oestradiol doses in this CHC type are often comparable to oral menopausal HT and may be of particular interest given potential symptom benefits,[132] although their endocrine effects are not directly comparable and require further study.

By suppressing endogenous hormone production, CHCs may stabilise women sensitive to hormonal fluctuations,[150] which has been supported by case reports,[151,152] particularly if used off-licence without a hormone free interval. Compared to COC, transdermal patches and vaginal rings may provide more uniform hormone concentrations.[148] Drospirenone-containing COC preparations may improve premenstrual syndrome and may also reduce perimenstrual symptom exacerbation in psychosis.[153] However, a network meta-analysis found no evidence that any specific formulation is superior,[154] showing that while COCs improved overall symptoms of premenstrual dysphoric disorder, they do not consistently reduce depressive symptoms.

Progestin-only pills, implants, injections, and levonorgestrel-releasing intrauterine devices (LNG-IUD) provide effective contraception but can suppress endogenous oestrogen to varying degrees without compensatory replacement.[155] Suppression is most pronounced with depot medroxyprogesterone acetate, whereas other methods may allow partial oestrogen production and continued ovulation in some users. While direct evidence in psychosis is lacking, observational studies suggest a dose-dependent association between LNG-IUD use and mood disorder diagnoses or antidepressant use, with higher levonorgestrel doses linked to greater risk.[156,157] Although these findings suggest an adverse association between progestogen-only contraception and depression, observational studies are subject to potential sources of bias and causality cannot be inferred.[158]

Some women are particularly sensitive to progestogens, which can provoke anxiety or depressive symptoms.[159] This sensitivity varies between individuals and progestogen types, creating clinical challenges for prescribing CHC and HT, often necessitating individualisation of type, dose, and route.

How to prescribe oestrogen-based treatments for women with psychosis

Oestrogen-based treatments are not a standard component of care for women with psychosis, but such treatments may offer benefits, particularly when standard antipsychotic treatment falls short. The recommendations outlined here draw on existing guidelines on menopause management and hormonal contraception use, position and consensus statements, recent toolkit papers on these topics,[138,153,160–167] research evidence published subsequent to these source documents, and our combined clinical experience. Clinicians should in addition refer to their relevant national guidelines and seek up to date guidance. While prescribing will typically be undertaken within primary care or gynaecology, an understanding of indications and contraindications is valuable for the psychiatrist.

For all women with psychosis, careful assessment of the potential role of hormonal fluctuations in past and present symptom expression provides an important basis for understanding how hormonal transitions may shape illness course and overall wellbeing. A thorough hormonal history and assessment of current hormonal status are essential (Box 2), and tracking symptoms across cycles may uncover cyclical patterns, as seen in other disorders.[168] Menopausal status can be defined using the algorithm from Davis and colleagues,[160] though antipsychotic-induced hyperprolactinemia may complicate this, requiring prolactin normalisation first.

Oestrogen-based interventions may be considered in psychosis in three main scenarios: when there is evidence for oestrogen deficiency such as oligo/amenorrhoea or natural/medical/surgical menopause; when there is perimenstrual exacerbation of psychotic symptoms; or when there is worsening of psychotic symptoms during the perimenopausal period (Figure 2). Antipsychotic-induced hyperprolactinaemia should be managed first. If it cannot be resolved, oestrogen-based interventions may still be cautiously considered in the presence of hypogonadism to address short- and long-term consequences of hormone deficiency.[105] In each scenario, oestrogen-based treatments should be approached as a personalised, iterative intervention, guided by medical history, symptom response, tolerability, and patient preference rather than a fixed protocol.[62]

CHCs may be considered in premenopausal women under 50 without contraindications. Omitting the hormone-free interval can be considered to maintain more stable hormone levels.[165] While ethinylestradiol-based preparations remain first-line, oestradiol-based COCs may also be considered given their more favourable side-effect profile particularly in terms of thrombosis risk,[149] and their potential relevance for treating psychosis. Drospirenone-containing contraceptives may be preferred when perimenstrual worsening is prominent or when progestin-associated dysphoria has occurred, despite mixed evidence on its superiority compared to other formulations. If CHCs are contraindicated, poorly tolerated, or when perimenopausal symptoms are present, HT may be considered. The choice between sequential and continuous regimens depends on menopausal status. Sequential HT consist of a fixed daily dose of oestrogen combined with a progestogen for 12–14 days each cycle to induce withdrawal bleeding, whereas continuous HT consists of fixed daily doses of both components.

The preferred HT formulation is oestradiol combined with micronised progesterone if needed, as this combination offers the most favourable safety profile. Transdermal oestradiol is preferred to oral administration, again owing to a more favourable safety profile, and is specifically recommended for women at increased risk of venous thromboembolism or cardiovascular disease, including those with BMI ≥30 kg/m².[166]Transdermal

administration also allows for direct systemic absorption and helps maintain higher bioavailable oestradiol, resulting in an estrone:oestradiol ratio closer to premenopausal physiology.[62] Micronised progesterone follows the same metabolic pathway as endogenous progesterone, with metabolites exerting modulatory effects on GABA-A receptors.[169]

Importantly, dose and formulation requirements vary substantially between women, and small adjustments in route, regimen or progestogen type may determine tolerability and efficacy.[62] If treatment is ineffective or poorly tolerated, the oestradiol dose or progestogen type can be adjusted, with BMS providing guidance on common side-effects and their management.[170] Dydrogesterone is a good alternative given its favourable cardiovascular and metabolic profile. Another alternative is combining oestradiol with the LNG-IUD, especially when contraception is desired (Box S1). A further option that also provides contraception is to combine sequential combined HT with a progestogen-only pill (preferably desogestrel or drospirenone), which is endorsed as an off-licence strategy.[171]

For women after age 60 or more than 10 years after menopause, continuous HT may still be appropriate but should be initiated cautiously as the risk-benefit profile may be less favourable. Raloxifene (off-licence) may be an alternative if HT or CHC are contraindicated for reasons other than venous thromboembolism or when ineffective or poorly tolerated, but its use must be balanced against possible adverse effects, including vasomotor symptoms, headache, musculoskeletal pain, and risk of venous thromboembolism.[172]

We recognise that the level of prescribing expertise varies between countries and healthcare settings, and that thresholds for specialist input differ. Specialist consultation is advised when contraindications exist or when therapy is ineffective or poorly tolerated (see standard 11 of the BMS practice standard for further guidance[173]).

Treatment should be reviewed at 6-12 weeks to assess efficacy and tolerability and make dose and regimen adjustments when appropriate. Once stable, reviews every 6-12 months are generally sufficient, unless earlier review is clinically indicated.[160,174] Reviews should include side-effect monitoring, blood pressure and weight checks, and a risk-benefit discussion. Discontinuing HT or raloxifene may cause return of menopausal symptoms, and accelerated bone loss (even after age 60).[175] Ongoing individualised risk–benefit assessment should therefore guide treatment duration rather than a fixed endpoint.

Conclusion

For women with schizophrenia, hormonal fluctuations and transitions can importantly shape disease onset, symptom patterns, treatment response, and long-term outcomes. Oestrogen plays a protective role, and its loss–whether due to natural decline or antipsychotic-induced disruption–can affect both mental and physical health. Yet these factors are rarely considered in routine care. Incorporating a hormone-informed approach through careful history taking, sex-specific prescribing, and judicious use of oestrogen-based treatments offers a pragmatic and evidence-based way to improve outcomes. As our understanding of sex-specific mechanisms grows, translating this knowledge into clinical practice should become a core part of caring for women with psychosis.

Search strategy and selection criteria

This narrative review addressed questions that could not be synthesised by systematic review. Online databases (Google Scholar and PubMed) were searched many times between October 1, 2024 and August 1, 2025, for articles relating to the interplay between ovarian hormones and the disease course and treatment of schizophrenia, and the role and impact of oestrogen-based treatments for schizophrenia. Articles were reviewed and included if they were of relevance to the topic of the review. In addition, clinical guidelines were consulted to ensure inclusion of relevant recommendations and consensus statements.

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Contributions

BAB conceptualised the initial outline, wrote the original draft. BAB and RAM produced the figures. All authors commented on, reviewed, and edited the manuscript.

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The funding source had no role in the conception, writing, or content of the manuscript, nor in the decision to submit it for publication. The authors were not precluded from accessing the relevant literature and accept full responsibility for the decision to submit this work. The authors have not received payment from a pharmaceutical company or any other agency for writing this article.

Declaration of interests

RAM has received speaker or consultancy fees from Boehringer Ingelheim, Janssen, Karuna, Lundbeck, Newron, Otsuka, and Viatris, and co-directs a company that designs digital resources to support treatment of mental ill health. All other authors declare no competing interests.

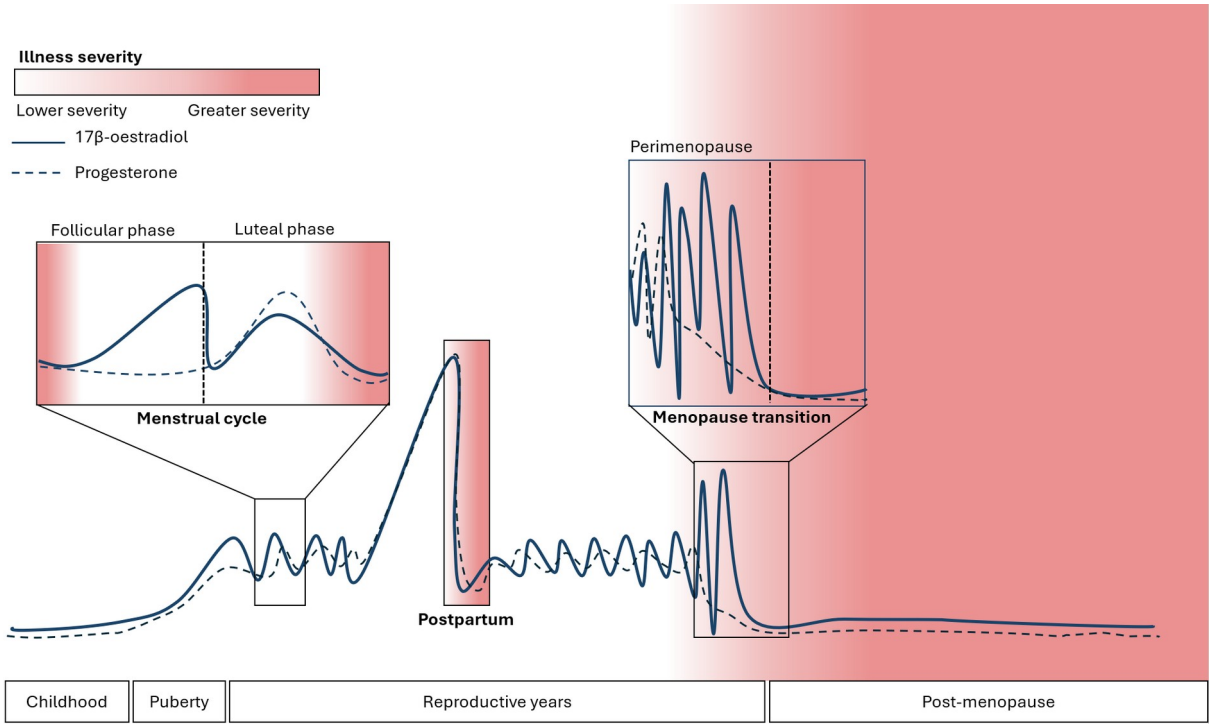


Figure 1: Hormonal fluctuations and psychosis illness severity across the female lifespan. Concentrations of the ovarian hormones 17β-oestradiol (solid line) and progesterone (dashed line) vary across the female lifespan. Insets highlight cyclical changes during the menstrual cycle, the steep decline after childbirth (postpartum), and the marked fluctuations during the perimenopause. Periods of declining hormone levels (shaded red) coincide with increased illness severity and heightened vulnerability to symptoms. Figure inspired by Barth et al.[176]

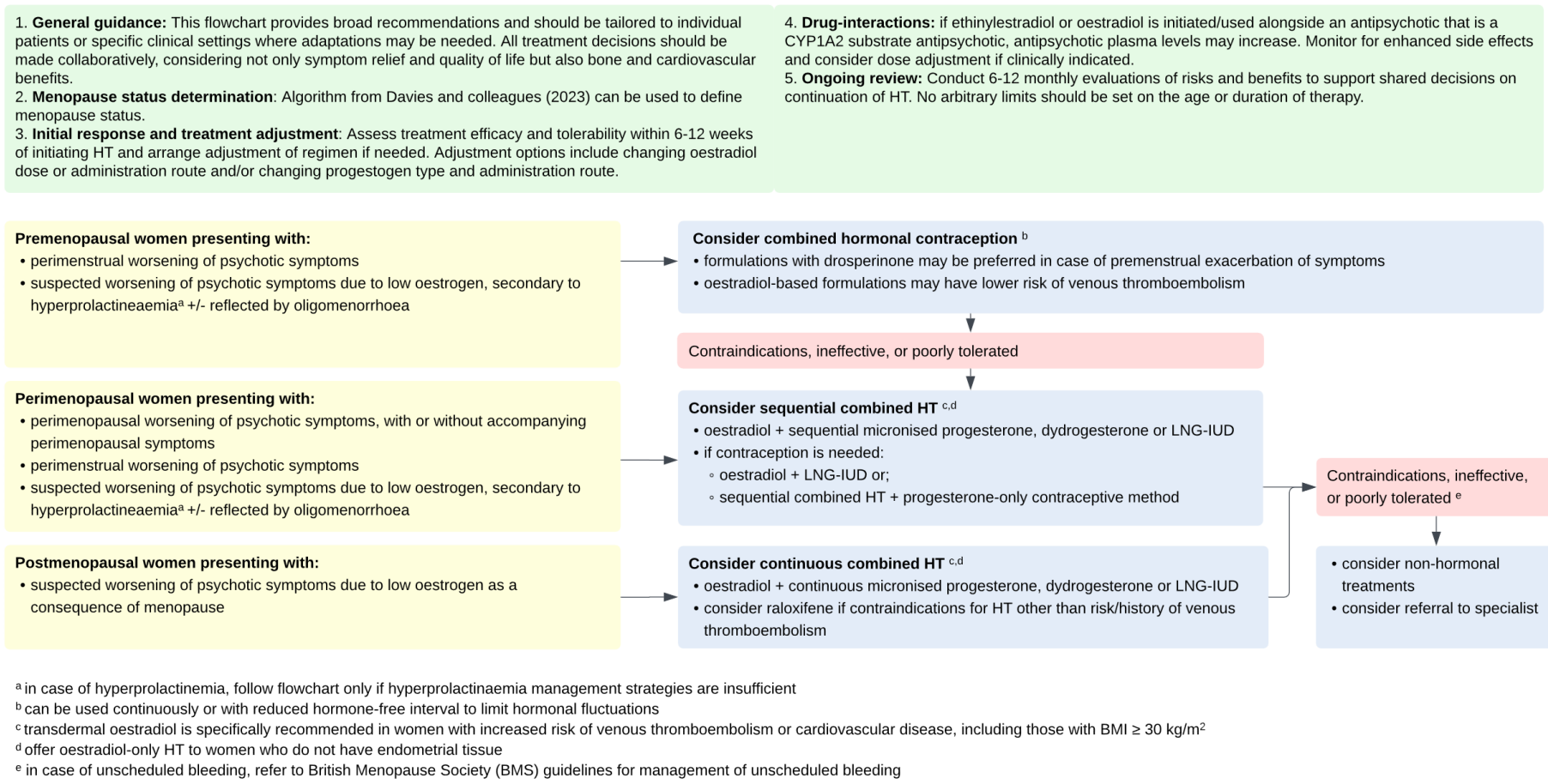


Figure 2: Flowchart for prescribing oestrogen-based treatments.

Abbreviations: CYP1A2 = cytochrome P450 1A2; HT = Hormone Therapy; LNG-IUD = levonorgestrel intrauterine device.

Box 1: Glossary of hormonal treatment terms

Hormone therapy (HT): An umbrella term to describe oestrogen-based treatments used to supplement endogenous hormone levels across the female lifespan, including but not limited to menopausal hormone therapy, used peri- and post-menopause. While the HT can also encompass oncological or anabolic hormone therapies, these are not considered in this article**.** HT does not include hormonal contraceptives, which are prescribed to suppress ovulation rather than to replace deficient hormones.

Menopausal hormone therapy (MHT): Hormone therapy used to treat symptoms associated with the menopause transition and post-menopause. MHT is also commonly referred to as hormone replacement therapy (HRT).

Sequential HT: A regimen in which oestrogen is administered continuously and a progestogen is added for part of the cycle, usually resulting in scheduled withdrawal bleeding and transient cyclical progestogen exposure.

Continuous HT: A regimen in which oestrogen and a progestogen are administered continuously, typically prescribed for postmenopausal women.

Oestradiol-based HT: Hormone therapy containing body-identical oestradiol, administered orally or via transdermal routes (patches, gels, or sprays). Transdermal delivery avoids hepatic first-pass metabolism and has lower effects on coagulation and lipid metabolism than oral administration.

Conjugated equine oestrogens (CEE): A mixture of oestrogenic compounds derived from equine sources, historically used in menopausal hormone therapy and differing from oestradiol in pharmacokinetics and receptor binding profiles.

Progestogen: An umbrella term for progesterone (which can be endogenous or manufactured) and progestins, which are synthetic. Progestogens differ in receptor affinity and metabolic, vascular, and breast tissue effects.

Micronised progesterone: A body-identical form of progesterone that is generally associated with more neutral effects on lipid metabolism and coagulation parameters compared with androgenic synthetic progestins.

Dydrogesterone: A synthetic progestogen with selective progesterone receptor activity, characterised by minimal androgenic, glucocorticoid, or mineralocorticoid effects and relatively neutral effects on lipid metabolism and glucose–insulin regulation.

Combined hormonal contraceptives (CHCs): Hormonal contraceptive preparations containing an oestrogen and a progestin (a synthetic progestogen), including combined oral contraceptives, vaginal rings, and transdermal patches.

Combined oral contraceptives (COCs): Oral CHC preparations that differ in oestrogen type and dose and in progestin subtype, influencing their metabolic and vascular profiles.

Progesterone-only contraceptives: Hormonal contraceptive methods that rely solely on a progestin without a oestrogen component, including the progestogen-only pill, the levonorgestrel intrauterine device (LNG-IUD), subdermal progestogen implant, and progestogen-only injectable contraception.

Levonorgestrel intrauterine device (LNG-IUD): An intrauterine system releasing the progestogen levonorgestrel locally, providing endometrial protection and contraception with limited systemic progestogen exposure.

Selective oestrogen receptor modulator (SERM): A class of compounds that exert tissue-specific oestrogen agonist or antagonist effects. Raloxifene is a SERM with oestrogenic effects on bone and the central nervous system and anti-oestrogenic effects on breast and uterine tissue.

Box 2: How to take a hormonal history and assess current hormonal health

The following domains should be explored when assessing hormonal health in women with psychosis. Relevant investigations should be guided by clinical indication and availability.

- **Menstrual history:** include age at menarche, cycle length and regularity, duration and amount of menstrual flow, associated symptoms, date of last menstrual period, presence of intermenstrual/postcoital bleeding, and history of amenorrhoea or oligomenorrhoea.
- **Menopausal history**: age at menopause, presence and severity of perimenopausal symptoms, and any postmenopausal bleeding.
- **Perinatal history**: specifically, development or worsening of perinatal mental disorders, including postpartum psychosis and depression
- **Drug and alcohol history**: particularly substance misuse related to menstrual cycle
- **History and current use of exogenous hormones:** current and previous use of hormonal contraception, hormone replacement therapy, or other hormone-modulating treatments and any associated psychological symptoms
- **Hormone-related symptoms**: assess for cyclical, hormone-related, or menopausal exacerbation of psychotic symptoms. Where relevant, retrospective assessment may be supported by prospective symptom tracking across 2–3 menstrual cycles using tools such as the Daily Record of Severity of Problems (DRSP)[177] although this does not specifically track psychotic symptoms.
- **Past medical and surgical history:** conditions that affect hormone levels or choice of hormonal treatment (e.g., PCOS, thyroid disorders), history of oophorectomy, hysterectomy, risk of VTE, cancer, cardiovascular risk, BMI, migraines with aura, liver problems
- **Family history**: include potentially hormone-sensitive cancers (breast, ovarian), age at menopause in mother and/or sisters, and familial risk of thromboembolic disease
- **Lifestyle factors**: smoking, alcohol, caffeine, physical activity, and stress levels.

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