

Perinatal mental health 2



Bipolar disorder, affective psychosis, and schizophrenia in pregnancy and the post-partum period

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The perinatal period is associated with an increased risk of severe mental disorders. We summarise the evidence regarding the epidemiology, risk factors, and treatment of severe mental illness in relation to childbirth, focusing on bipolar disorder, affective psychosis, and schizophrenia. We discuss women with ongoing chronic conditions and those with the onset of new episodes of post-partum psychosis. Despite the importance of perinatal episodes, with suicide a leading cause of maternal death, few studies are available to guide the management of women with severe mental disorders in pregnancy and the post-partum period. However, general principles of management are discussed, including the need for an individual risk–benefit analysis for each woman.

Introduction

Pregnancy is a major event in any woman's life. The transition to motherhood involves major challenges in the psychological, social, and biological domains. For a woman with, or who is susceptible to, severe mental illness this transition might prove particularly complex and difficult. Although many forms of psychiatric illness can be severe, in this Series paper severe mental illness refers to schizophrenia, affective psychosis, and bipolar disorder, including psychotic and non-psychotic forms of bipolar disorder. This definition includes both women with pre-existing illness who become pregnant, and those who develop severe post-partum episodes as the first manifestation of psychiatric illness. The acute onset of severe psychiatric episodes following childbirth—post-partum (or puerperal) psychoses—are among the most severe forms of illness seen in psychiatry. Psychiatric disorders in the perinatal period result in significant distress, can disrupt the developing bond between mother and child, and have long-term implications for the wellbeing of the woman, the baby, her family, and wider society. In rare but tragic cases, the illness can lead to suicide, a leading cause of maternal death,¹² and infrequently, infanticide.³

Severe mental illness and pregnancy

Fertility

Women with severe mental illness have consistently been reported to have lower fertility rates than do women in the general population, with women with schizophrenia usually having much lower fertility than do women with bipolar disorder.^{4–7} Although women with psychiatric disorders have high rates of abortion compared with the general population, this does not appear to explain the decrease in fertility.⁵ Prolactin-raising antipsychotics, which reduce fertility, seem to partly explain the reduction in general fertility rate,⁶ with evidence that the general fertility rate among women with schizophrenia has increased modestly over the past 13 years coinciding with the

increasing use of non-prolactin-raising antipsychotics.⁷ However, because schizophrenia in particular can affect a women's ability to make and sustain relationships,⁸ some reduction in fertility is likely to continue. Nevertheless, most women with schizophrenia and bipolar disorder do have children,⁹ although their pregnancies are more likely to be unplanned and unwanted than are those of women in the general population.¹⁰ Of those women with psychotic disorders who do have children, some describe motherhood as central to their existence.¹¹

Epidemiology

The prevalence of severe mental disorders in pregnancy has rarely been studied, although a US epidemiological study showed no difference in the prevalence of psychotic (0·4%) and broadly defined bipolar disorder (2·8%) in past-year pregnant women compared with non-pregnant women.¹² Few studies have examined the incidence of severe mental illness in pregnancy, but a Danish registry-based study reported a reduced risk in pregnancy for first psychiatric admissions with both schizophrenia

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Key messages

- Severe mental illness in the perinatal period occurs as a continuation of chronic psychotic illness or a new onset, often shortly after childbirth (post-partum psychosis), and these episodes can result in substantial distress and have long-term implications for the wellbeing of the woman, her family, and wider society
- Childbirth is a powerful trigger of mania and psychosis, and episodes at this time cause substantial morbidity and mortality, with suicide a leading cause of maternal death
- Pregnancy should be an important consideration in the treatment of all women with severe mental illness in their reproductive years, and careful counselling of the woman and her partner to acknowledge the many areas of uncertainty is crucial to optimal care
- Individualised risk–benefit analyses are needed when psychotropic drugs are regarded for use in the perinatal period, and the risk of untreated illness for the mother and fetus or infant should be taken into account
- Further research is essential to help understand more about the triggering of psychotic episodes by pregnancy and childbirth, enable better prediction of women at risk, and develop improved treatments for women who become unwell at this time

Search strategy and selection criteria

We searched PubMed, Embase, PsycINFO, and the Cochrane Library without language restrictions. Original searches were done for systematic reviews (past 20 years) and epidemiological or experimental studies (past 3 years) with the following search terms: "pregnancy" or "prenatal" or "antenatal" or "postnatal" or "postpartum" or "perinatal" or "puerperal" or "breastfeeding" or "birth" or "weaning" or "childbirth" or "trimester" or "peripartum" or "lactation" or "ante-natal" or "post-natal" or "post-partum" and "psychosis" (exploded MeSH term) or "mood disorder" (exploded MeSH term) or "schizophrenia" (exploded MeSH term) or "psychosis" or "mania".

These search terms were combined with specific terms for the following sections, with date limits based on the amount of recent research output in each area: "prevalence" or "incidence" or "relapse" or "course" (limited to past 5 years); or "fertility" (exploded MeSH term) or "fertility" (limited to past 10 years); "ECT" or "electroconvulsive therapy" or "electro convulsive therapy" (limited to past 10 years); "mother baby unit" or "mother baby units" or "mother and baby unit" or "mother and baby units" or "MBU" or "services" or "safe guarding" or "safeguarding" (limited to past 10 years); "lithium" or "Carbamazepine" or "Sodium Valproate" or "Valproic acid" or "Amisulpride" or "Flupentixol Decanoate" or "Aripiprazole" or "Fluphenazine Decanoate" or "Benperidol" or "Fluspirilene" or "Chlorpromazine" or "Haloperidol" or "Clozapine" or "Pipotiazine Palmitate" or "Cyamemazine" or "Zuclopenthixol Decanoate" or "Droperidol" or "Flupentixol" or "Fluphenazine" or "Haloperidol" or "Levomepromazine" or "Loxapine" or "Olanzapine" or "Oxypertine" or "Paliperidone" or "Pericyazine" or "Perphenazine" or "Pimozide" or "Promazine" or "Quetiapine" or "Remoxipride" or "Risperidone" or "Sertindole" or "Sulpiride" or "Thiopropazate Hydrochloride" or "Trifluoperazine" or "Zotepine" or "Zuclopenthixol Dihydrochloride" or "Ziprasidone" (limited to past 5 years).

and bipolar disorder,¹³ and Kendell's seminal studies¹⁴ of psychiatric admission in Edinburgh did not show the increased rates of admission in pregnancy that were noted in the post-partum period.

Similarly, very few studies have been published that investigate the effect of pregnancy on the relapse of schizophrenia. Initial studies report conflicting findings, probably because of differences in sample selection and outcomes measured. A small prospective study noted that ten of 17 pregnant women with schizophrenia reported worsening mental health,¹⁵ whereas a larger study of 919 women with schizophrenia identified no increased risk of acute relapse, with only three (0.3%) acute episodes occurring in pregnancy (all in the first trimester).¹⁶ Prevalence of prescriptions of antipsychotics in women with schizophrenia might be lower for the second and third trimesters of pregnancy compared with the first,¹⁷ but whether such treatment discontinuation reflects worsening of illness (with consequent worsening of insight affecting adherence with medication), improvement of illness, or merely medication being stopped by women or their clinicians when pregnancy is discovered, is not known.

Recurrence in pregnancy has been assessed more frequently for women with bipolar disorder than schizophrenia, although few prospective studies have been published.¹⁸ Population-based studies suggest that pregnancy is somewhat protective with low rates of both

new onset¹³ and relapse during pregnancy,¹⁹ and a retrospective study in 2013²⁰ noted that only 8% of perinatal episodes in 980 women with bipolar I disorder had their onset in pregnancy. Other clinic-based studies provide conflicting results, with one study²¹ reporting high recurrence rates in pregnancy, particularly in women who discontinue prophylactic medication (53 [85%] of 62 women). A subsequent study²² from the same group in an expanded sample of parous women with bipolar disorder (n=283 BPI and n=338 BPII) noted that 23% had illness episodes during pregnancy compared with 52% with an episode in the post-partum period.

Few data exist for the nature of psychotic relapse during pregnancy although case reports suggest severe psychopathology can occur.^{23,24} Women who are usually maintained on medication to stabilise their condition might stop treatment when they discover that they are pregnant because of fears about potential teratogenicity, and this can lead to a rebound psychosis. Women who are chronically unwell might develop psychotic denial of pregnancy, particularly if they have previously lost custody of a child. This denial can lead to refusal of antenatal care or failure to recognise labour, with consequent unassisted delivery, although this occurrence seems to be rare.²⁵

Severe mental illness in the post-partum period

Severe mental illness can occur in the post-partum period as the continuation of a chronic psychotic condition that began in or before pregnancy, or as an episode of severe mental illness with a rapid onset shortly after childbirth. These later episodes, traditionally labelled as post-partum or puerperal psychosis most commonly take the form of mania, severe psychotic depression, or mixed episodes with features of both high and low mood.²⁶ Despite the current Diagnostic and Statistical Manual of Mental Disorders (DSM) and International Classification of Diseases (ICD) classification systems not recognising the condition (panel 1), the term post-partum or puerperal psychosis has remained in widespread clinical use and some investigators argue that the nosological confusion around severe post-partum episodes has hindered research into this important disorder. Qualitative research has shown that a label of a post-partum mood disorder is favoured by women themselves and by the key user group for women with this condition in the UK, Action on Postpartum Psychosis.¹¹

As the name suggests, the core features of psychosis such as delusions and hallucinations are common, and women might also have notable confusion or perplexity.²⁷ Most post-partum psychosis episodes have their onset within 2 weeks of delivery, with more than 50% of symptom onsets occurring on days 1–3 in one retrospective study.²⁸ Sudden onset and rapid deterioration are typical and the clinical picture often changes rapidly, with wide fluctuations in the intensity of symptoms and severe swings of mood.^{27,28} Historically,

other cerebral or systemic conditions such as eclampsia, delirium, thyroid disorders, or infection were important causes of psychosis occurring at this time, and that they are excluded is important because their misattribution to psychiatric disorder has led to several deaths in new mothers.¹

Epidemiology of post-partum psychosis

Several studies have estimated post-partum admission rates to psychiatric hospitals to be about 1–2 per 1000 births in the general population and this figure is often applied to post-partum psychosis.^{13,14,29} However, the true incidence of post-partum psychosis might be higher or lower because at least some women with post-partum psychosis are likely to be treated at home (especially if facilities for admission with the baby are not available); and several women admitted in the post-partum period will be for disorders other than post-partum psychosis.

If doubt remains about the incidence of post-partum psychosis, the evidence is strong and consistent for a specific association between post-partum psychosis and bipolar disorder. Data from both retrospective and population registry studies suggest that women with bipolar disorder have at least a one in five risk of suffering a severe recurrence following delivery^{19,20,30} and an even higher risk (approaching one in two) of experiencing any mood episode in the post-partum period, including non-psychotic major depression.²⁰ Women with a history of a previous post-partum psychosis are at very high risk after subsequent pregnancies, with more than one in two deliveries affected,³¹ and investigators have also suggested that for women with bipolar disorder, a family history of post-partum psychosis gives a similarly high risk in the post-partum period.^{32,33} However, 50% or more of women who develop post-partum psychosis have no history that suggests they should be considered at high-risk.³⁴

Despite the weight of recent genetic evidence suggesting shared causal factors across both the psychosis (schizophrenia and bipolar disorder) and mood disorder (bipolar and unipolar) spectrums,³⁵ susceptibility to childbirth-triggered episodes seems to be one area which differentiates bipolar disorder from these other disorders. For example, in studies of the Danish registries, Munk-Olsen and colleagues reported a substantially higher risk of both the first onset and recurrence of a bipolar episode than was noted for episodes of schizophrenia or major depression.^{13,19}

Post-partum psychosis: risk factors and pathophysiology

As discussed, the strongest and best-established risk factor for susceptibility to post-partum psychosis is a history of bipolar disorder or previous severe post-partum episodes, although several other potential risk factors have been investigated.

Panel 1: Classification of severe post-partum episodes

The commonly used classification systems, International Classification of Diseases (ICD) and Diagnostic and Statistical Manual of Mental Disorders (DSM), do not recognise post-partum psychosis as a separate nosological entity and treat episodes occurring in the perinatal period in different ways. Despite these issues, the term post-partum psychosis has remained in common clinical use, including among women themselves (eg, the user group Action on Postpartum Psychosis).

The Diagnostic and Statistical Manual of Mental Disorders (DSM 5)

Episodes of bipolar disorder, depressive disorders and brief psychotic disorders with onset in pregnancy or within 4 weeks of delivery can be flagged with a peripartum-onset specifier (termed postpartum-onset specifier for brief psychotic disorders).

The International Classification of Diseases (ICD-10)

A category of mental and behavioural disorders associated with the puerperium, not elsewhere classified for episodes with onset within 6 weeks of delivery, but the instruction is that this diagnosis should only be used when episodes do not meet the criteria for other diagnoses. ICD-11 is in development and whether any changes will be made to the classification of perinatal episodes is not known.

Obstetric risk factors

Several obstetric factors have been examined in relation to risk of post-partum psychosis (including pregnancy and delivery complications, caesarean section, sex of baby, and gestation period) but the only consistent finding is a strong association with primiparity.^{36–39} The reason for the excessive risk in primiparous women is not clear. An important bias is that women with a severe post-partum episode might be less likely to go on to have further children, but this suggestion has not been shown to account for the association in studies that have controlled for this confounder.^{14,39,40} First pregnancies and the transition to new motherhood might lead to a greater psychological stress than subsequent deliveries, although hormonal, immunological, and other biological differences between first and subsequent pregnancies should also be considered. The relation of post-partum psychosis to other pregnancy-related disorders that also occur more frequently in first pregnancies, such as pre-eclampsia, is of interest, and the biological and psychosocial differences between first and subsequent pregnancies are a potential area for future study.

Changes in medication

A possible explanation for the increased risk in relation to childbirth is that medication might be stopped because of concerns about teratogenicity. One study that addresses this possibility compared women with bipolar disorder who discontinued mood-stabilising medication because of

pregnancy with women who stopped for other reasons.⁴¹ The study identified similar rates of recurrence during pregnancy or equivalent period, but post-partum recurrences were 2·9 times more frequent than recurrences in non-pregnant women during the equivalent period (70% vs 24%). Therefore, the increased risk of recurrence following childbirth in women with bipolar disorder does not seem to be merely a result of stopping or changing of medication.

Psychosocial factors

In contrast to non-psychotic episodes of post-partum depression (discussed elsewhere in this Series⁴²), the evidence does not suggest that childbirth acts as a general, non-specific psychosocial stressor in the triggering of post-partum psychosis. Four studies have examined high-risk women and are consistent in finding no association between stressful life events and the occurrence of a post-partum psychotic episode,^{40,43-45} although the benefit of a supportive partner in reducing risk has been demonstrated.⁴⁵

Hormonal factors

The role of several hormones (including oestrogen, progesterone, prolactin, follicular stimulating hormone, and luteinising hormone) has been assessed, but the evidence pointing to hormones as a cause of post-partum mood disorders is predominantly circumstantial.⁴⁶ Women with post-partum episodes might not show gross abnormalities in endocrine physiology, but rather the susceptibility to triggering by childbirth could represent an abnormal response to the normal hormonal fluctuations in the perinatal period.⁴⁷

Immunological factors

Pregnancy and the post partum are periods of great immunological challenge, and dysregulation of immune system function has been investigated for its involvement in the causes of post-partum psychosis. Bergink and colleagues reported evidence of dysregulation of the immunoneuroendocrine set point in post-partum psychosis, with a notable overactivation of the monocyte and macrophage arm of the immune system.^{48,49} Further work is needed to explore and replicate immunological abnormalities in post-partum psychosis.

Sleep deprivation

Circadian rhythm disruption such as sleep loss can trigger the onset of mania in susceptible individuals. Although the involvement of sleep deprivation in triggering post-partum episodes is plausible, this hypothesis has not received extensive study and conflicting data arise in the few studies that have been published.^{50,51}

Genetic factors

Evidence from family studies suggests that episodes of post-partum psychosis are a marker for a familial form of bipolar disorder⁵² and that a specific susceptibility to

the puerperal triggering of bipolar disorder is familial.³² Linkage studies have suggested the possible location of a susceptibility gene on chromosome 16³³ and specific candidate genes, such as those involved in serotonergic,^{54,55} hormonal,^{56,57} and inflammatory⁵⁸ pathways, have also been investigated, although no specific genetic variants have been consistently replicated so far.⁵⁹

Factors identified in neuroimaging studies

Despite studies consistently showing that, even at first episode, both affective and non-affective psychoses are associated with abnormalities of brain structure and function,⁶⁰ few imaging studies have assessed post-partum psychosis. A CT study noted that women with post-partum psychosis had larger left ventricular areas, ventricular-brain ratios, and superior cerebellar cistern volumes than did women with psychoses or bipolar disorder unrelated to childbirth, and also healthy controls.⁶¹ A further case study of a discordant monozygotic twin pair employing functional MRI noted that the twin with a history of post-partum psychosis had less activation in the orbitofrontal cortex than did her healthy twin during exposure to emotional film excerpts.⁶² This finding suggests a possible disturbance in the integration of emotionally relevant information, consistent with neuroimaging studies of bipolar disorder and psychoses unrelated to childbirth.

Treatment of severe mental illness in pregnancy and the post-partum period

Several different scenarios ought to be considered regarding the management of the perinatal period. Issues for women with a diagnosis of schizophrenia need to be distinguished from those with bipolar disorder, as do issues that arise before conception from those that arise in pregnancy and later in the post-partum period. Finally, it is important to differentiate women with longstanding psychotic illness from those women with the acute onset of a post-partum psychosis. Moreover, the breadth of treatment options available needs to be considered, from the social and psychological, including child protection, to medication, electroconvulsive therapy (ECT), and services such as mother and baby units.

Preconception care

Guidelines from several countries⁶³⁻⁶⁵ and the Confidential Enquiries into Maternal Deaths¹ emphasise that pregnancy should be a consideration in the management of all women of childbearing age with severe mental illness. Contraception and optimisation of physical and mental health in potential future pregnancies should therefore be discussed at all stages of care, not just when a woman becomes pregnant or wants to start a family. Indeed, the evidence linking valproate exposure in utero in particular to a three-times increase in major malformations and subsequent

cognitive impairment, means that it is best avoided, where possible, in all women in their reproductive years.^{63,66,67}

Provision of structured education about their condition (psychoeducation) to individuals with bipolar disorder and other severe mental illnesses is an approach with a substantial evidence base showing improved outcomes.⁶⁸ Issues around pregnancy and childbirth ought to be included in psychoeducation packages aimed at these conditions. Women can often need information very quickly, (eg, if they unexpectedly find they are pregnant) and therefore online modules specifically addressing issues around pregnancy that can be accessed at any time might be beneficial.

The issues are likely to differ depending on the woman's individual history and particular diagnosis. For women with bipolar disorder, the very high risk of a severe post-partum episode will be an important consideration, while for women with severely impairing and chronic forms of psychosis, issues of parenting could be a significant concern. For all women with severe mental illness, discussions around medication in pregnancy are likely to be prominent, but interventions for other risk factors for adverse fetal outcomes, such as smoking, nutritional deficiencies, and obesity can also be optimally addressed before conception.^{69,70} The potential risks and benefits of all medication options should be considered and will include continuing the current regimen, coming off some or all medication, and switching to drugs with greater evidence of safety in pregnancy. The particular issues with the use of valproate in pregnancy discussed previously should weigh heavily in the risk–benefit analysis for women taking this medication. Women with a history of bipolar disorder or previous post-partum psychosis are at high risk of relapse post partum, but whether starting prophylaxis after delivery is an appropriate strategy or whether medication should also be taken during pregnancy is unclear. A study⁷¹ from the Netherlands suggests that the answer might differ dependent on whether previous episodes have occurred outside of the perinatal period. Women with a history of previous illness restricted to the post-partum period were at high risk in the post-partum period but did not become ill in pregnancy. By contrast, for women who also had a history of bipolar episodes not related to childbirth, pregnancy was also a period of high risk.

Care of women with severe mental illness in pregnancy

Up to now, little research has been done into interventions for psychotic disorders in pregnancy and in particular, few studies have been done into use of antipsychotic medication.⁷² Extrapolation from studies outside the perinatal period is therefore needed when caring for women with schizophrenia in pregnancy.

The relapse of schizophrenia at other times in a woman's life suggests that rehospitalisation and relapse rates are significantly increased after discontinuation of antipsychotic medication.⁷³ Direct evidence shows the effect of treatment discontinuation on women with bipolar disorder, with a prospective cohort study reporting a doubling of risk of relapse and shorter time to relapse in women with bipolar disorder who discontinued prophylactic mood stabilisers in pregnancy, even after adjustment for confounders such as illness severity.²¹ Women with severe mental illness who are stable on prophylactic medication are therefore likely to be at increased risk of relapse in pregnancy if they discontinue medication and a very careful discussion will be needed to weigh up risks and benefits of medication (panel 2).

For the online modules specifically addressing issues around pregnancy see <http://www.ncmh.info/tools>

Panel 2: Preconception advice for women with severe mental illness

All women with a severe mental illness in their reproductive years should be able to access advice with regard to pregnancy and parenting, ideally, from a perinatal specialist. A checklist of issues to consider would include the following criteria:

Planning for motherhood

A large proportion are unplanned and discussion of plans for a family and advice with regards to contraception should be routine with all women of childbearing potential.

Potential effects on illness

For each woman, her individual risk of a relapse or recurrence should be discussed. This discussion will include the severity and nature of previous episodes, severity of current episode or time since last episode, and family history of episodes in relation to childbirth.

Optimisation of physical and mental health

Preconception is an ideal time to address a range of issues key to a healthy pregnancy. These issues will include smoking, obesity, diet, drug and alcohol use, domestic violence, folate and vitamins, and physical exercise. In addition, optimisation of management of mental health is needed to ensure women enter pregnancy as well as possible. In pregnancy, specific tests are required such as assessment of gestational diabetes and consideration should be given to referral for specialised ultrasound.

Medication

The risks and benefits of all options should be discussed, including continuation of current medication regime, stopping of one or all drugs, and switching of medication. Issues to consider in the risk–benefit analysis include evidence of efficacy in this woman for each drug; previous response to change in medications or dose reduction; what alternative treatment options have been explored; and past history of teratogenicity (eg, neural tube defects). Options for restarting of medication later in pregnancy or in the post partum can be discussed.

Genetic risk

Women and their partners might have concerns about passing a susceptibility to severe mental illness to their children and these concerns can be addressed or the woman referred for further genetic counselling.

Liaison with other services

All professionals involved in looking after a woman through pregnancy and the post-partum should be informed about the history of severe mental illness. Professionals include—obstetricians, midwives, mental health services, social services, general practitioners, and health visitors.

With regard to other treatment approaches, weak evidence from a small study of 20 women with schizophrenia treated with antipsychotics suggests that additional non-drug-related support, such as liaison with maternity care staff and consent for partners to carry out child care, contributed to improvements in mental state.⁷⁴

Present guidelines recommend a perinatal care plan for women with current or past severe mental illness and women in this group should be monitored for psychopathology throughout pregnancy and the post-partum period. Antenatal services should therefore identify women with histories that would put them at increased risk of a severe episode in the perinatal period, even if they are currently well and not in contact with psychiatric services. Other avoidable factors that are known to increase risk outside of the perinatal period might also need to be addressed, such as decreasing general levels of stress and paying attention to sleep in late pregnancy and the early post-partum weeks. Support with parenting post partum should also be planned during pregnancy, and evidence-based interventions for comorbid problems such as smoking cessation interventions,⁶⁹ domestic violence advocacy,⁷⁵ and weight management interventions⁷⁶ can also be addressed.

Medication in pregnancy

A key aspect of the care plan should be an individualised risk–benefit analysis around medication.^{63,64} This plan should include the likelihood of relapse in pregnancy and post partum based on diagnosis, illness severity, and recency of acute episodes. The evidence of response to particular medications or combinations for that individual woman, along with the possible need for increased doses of medication for an acute episode compared with maintenance treatment are also important considerations. Ideally, pregnancy will have been planned and decisions about medication will have been made before conception. For women on medication presenting with an unplanned pregnancy, however, some exposure of the fetus will have already happened, and abrupt discontinuation might not be the best option as a relapse in pregnancy can have devastating consequences.

Little research has been published on adverse outcomes associated with antipsychotics in pregnancy, but a systematic review⁷⁷ and the largest cohort study to date (561 women exposed to second-generation antipsychotics and 284 women exposed to first-generation antipsychotics)⁷⁸ have not implicated any antipsychotic as a major teratogen. However, as more data become available, consideration of the evidence for the reproductive safety of each antipsychotic individually will be important, as these groups differ substantially in their pharmacokinetic and pharmacodynamic characteristics. To what extent other adverse outcomes reported in small studies (such as gestational diabetes, low birthweight, and developmental outcomes) are caused by confounders is not known; one of

the few large studies in this area, for example, noted that bipolar disorder was associated with an increased risk of adverse pregnancy outcomes, whether women were taking medication or not.⁷⁹

With regard to antiepileptic medications that are used as mood stabilisers, the reproductive safety data predominantly comes from studies on women with epilepsy rather than psychiatric disorders, but highlights teratogenicity and adverse cognitive outcomes with valproate use in pregnancy.^{63,64,66,67} The risks from other antiepileptic drugs used as mood stabilisers might be less than is noted with valproate, but increased rates of malformations have also been reported for carbamazepine and lamotrigine, although the risks associated with the latter drug might be lower than initially thought.⁸⁰ More data are clearly required on the reproductive safety of these medications when used in the management of psychiatric conditions.

The safety of lithium in pregnancy is a particular area of controversy. Although the use of lithium in psychiatric disorders was first described in 1949, few data are available on its reproductive safety. Retrospective data from the lithium baby registry reported 25 malformations from a total of 225 exposed babies (11%), with 18 (8%) cardiovascular defects, six of which were Ebstein's anomaly.⁸¹ Retrospective studies, however, are subject to major issues of bias and subsequent prospective studies have recorded much lower rates of malformations. A review of the prospective data (that included 105 unpublished cases from the Israeli Teratogen Information Service) identified 296 lithium-exposed infants, eight of whom had malformations (3%), a rate consistent with that noted in controls.⁸² However, two infants exposed to lithium had Ebstein's anomaly while none of the 43 infants with malformations among 1354 controls (3%) had this cardiac anomaly.

More recently, a systematic review and meta-analysis of lithium toxicity identified 62 studies of the teratogenic potential of lithium: seven cohort studies, seven case-control studies, and 48 case reports.⁸³ It concluded that the evidence that exposure to lithium is teratogenic is weak and the risk has been overestimated, although the CIs were wide and the upper confidence limit was consistent with a clinically significant increase in risk of congenital malformations.

Despite more than 50 years of lithium use in clinical practice, it is still difficult to come to firm conclusions about its safety in pregnancy. Early retrospective studies reporting a 400-times increased risk of Ebstein's anomaly⁸⁴ were influential in blanket recommendations to avoid lithium in pregnancy, but a more reasonable approach might be to explain the uncertainty around risk to women and to consider the balance between harm to the baby and risk of worsening maternal mood instability. When lithium is used in pregnancy, lithium levels need to be checked more frequently because of the changes in blood volume, and particularly closely in women who

develop pre-eclampsia. Some uncertainty surrounds when to stop lithium around the time of labour. However, once labour has begun, lithium should not be taken until after delivery when plasma levels and electrolyte balance can be checked and lithium reinitiated.

Electroconvulsive therapy (ECT) in pregnancy

Despite remaining a controversial treatment option, ECT can be lifesaving in episodes of severe mood disorder. Evidence for the efficacy and safety of ECT in pregnancy is from case series only. Anderson and Reti⁸⁵ reviewed 57 papers, describing 339 cases of ECT in pregnancy and identified one fetal death, a 3% rate of fetal complications (fetal bradyarrhythmias most common) and a 5% rate of pregnancy complications (premature labour most frequent). ECT could therefore be an appropriate option in pregnant women with psychosis who are acutely suicidal, are in stupor or catatonia, and have life-threatening physical status caused by poor oral fluid intake. Women with a prior history of poor response to medications or good response to ECT might also be referred for ECT to ensure rapid resolution of symptoms.

Care of women in the post-partum period

For women with severe mental illness who stopped medication in pregnancy, re-establishing their prepregnancy medication regimen should be considered. Effectiveness of prophylactic medication in the immediate post-partum period for those women at high risk of post-partum psychosis has been assessed. Although no randomised controlled trials have been done, retrospective and open studies support the use of lithium prophylaxis in women with bipolar disorder in this context,^{86,87} but several practical problems exist with reaching therapeutic levels quickly to cover the period of risk and there are significant concerns around breastfeeding. Some guidelines therefore suggest typical or atypical antipsychotics as alternative options for prophylaxis, although they have only been investigated in small studies.⁸⁸

Treatment of acute post-partum psychosis

An episode of post-partum psychosis is a psychiatric emergency, can quickly become severe, and the presentation can vary substantially from hour to hour. For these reasons admission might be necessary, even for women with the most supportive of families (panel 3).⁸⁹ The severity of episodes of post-partum psychosis also means that medication is required in the acute stage of treatment. Few studies have assessed pharmacological interventions for post-partum psychosis so the choice of drug is based on extrapolation from studies outside the perinatal period, which emphasise several factors, including the individual symptoms, level of disturbance, and previous response to medication. Similarly, few studies of infants exposed to antipsychotic drugs during breastfeeding have been done, and general principles of prescribing for breastfeeding women

Panel 3: Decision making regarding admission in the post-partum period

Many women with severe mental illness in the post-partum period will require admission to hospital. Decisions about the need for admission will depend on several considerations—the following factors should lower the threshold for admission:

- Severe episode with significant impairment
- Suspicion of post-partum psychosis—an acute onset of a new episode in the immediate post partum
- Rapid deterioration or fluctuating picture
- Psychotic symptoms, particularly command hallucinations, passivity phenomenon
- Delusions involving the baby
- Poor social support from partner and other family members
- Previous severe episodes of illness
- Suicidal ideation
- Aggression to others
- Risk of harm to infant including poor infant care and lack of bonding

described in the first paper in this Series⁴² apply here too. Maternal side effects of medication also need to be taken into account because sedation, for example, could affect a mother's ability to care for the child, particularly at night.

Despite limited data on its use in this context, ECT could also be an effective treatment in severe post-partum psychosis, particularly in the presence of high suicidal risk.⁹⁰

Post-partum psychosis responds well to treatment and the short-term prognosis is generally very good, although in a recent retrospective study, 26% of women with post-partum psychosis reported ongoing symptoms a year after delivery.³⁰ On recovery, women need to be counselled about the risk they have of further puerperal and non-puerperal episodes. Women are at a greater than 50% risk of a severe recurrence after further pregnancies but are also at risk of further episodes not related to childbirth. The same study reported that 69% of women with post-partum psychosis had at least one further non-puerperal affective episode.³⁴ Therefore, the risk of non-post-partum episodes should also be discussed with women to ensure that they do not believe that avoiding further pregnancies is a way of guaranteeing no further episodes of illness.

Support for partner and wider family

The needs of a woman's partner and her wider family also need to be considered in the management of the acute illness and beyond. Around 50% of post-partum psychosis episodes are the first expression of severe mental illness, and the acute onset and rapid deterioration that are characteristic of this condition are distressing and perplexing for those close to the patient. Qualitative research has demonstrated that women with post-partum psychosis believe that the needs for

information and support for their partners are not currently being met and addressing these issues is an important aspect of care.¹¹

Psychiatric mother and baby units

The severity of many post-partum episodes requires admission, and guidelines from several countries recommend mothers should be admitted with the baby whenever possible.^{63–65} Until now, no studies have been done into the effectiveness or cost-effectiveness of MBUs, although a National Institute for Health Research (NIHR)-funded study is underway (Howard LM, unpublished). Mother and baby units avoid separation of mothers and babies, encourage breastfeeding, provide specific interventions for parenting, enhance mother–infant bonding, provide support to partners and caregivers, and offer an opportunity for education about the illness and prevention of future episodes.

Data from mother and baby units in several countries show that the average stay duration is 8–11 weeks and 75–80% of admitted mothers have a good outcome.^{91–94} Data from low-income and middle-income countries is sparse, because of the scarcity of such units in these settings, but a study from India reported an average mother and baby unit stay duration of 4 weeks and most mothers were improved at discharge.⁹⁵

Lack of facilities for conjoint admission can lead to several problems, including separation from infants causing mothers to refuse admission, problems with breastfeeding, difficulties in diagnostic evaluation, lack of dyadic psychotherapy, longer hospital stays, and increasing the responsibility of caring for the baby on the spouse and extended family.⁹⁶

Child protection

The presence of severe mental illness might generate concerns among health and social care professionals about the mother's ability to safely parent. Concern about professionals' judgments of their parenting ability and worry about losing access to their children can be an important deterrent to mothers seeking psychiatric help.⁹⁷ Children can be at risk in various ways, and in addition to situations of frank neglect or abuse, severe mental illness might subtly impair mother–infant interaction (see the third paper in this Series⁹⁸). Several factors affect the risk of child protection issues, including the severity of the mother's psychiatric and personal history, level of functioning, living circumstances, and relationship status. A diagnosis of schizophrenia, personality disorder, and drug and alcohol problems are all associated with increased risk of social services involvement, and diagnosis has been reported as the most important single predictor of parenting outcome.⁹⁹ An assessment of mothers with psychotic episodes (schizophrenia, bipolar disorder, depression) discharged from mother and baby units in the UK reported that schizophrenia was significantly associated with social services supervision at

discharge, with an odds ratio of 25.7.⁹³ In addition, the content of psychotic symptoms is of great importance, especially if the child becomes involved in delusions, hallucinations, or passivity experiences. Nevertheless, many women with schizophrenia are able to parent¹⁰⁰ and a diagnosis alone does not in itself mean child protection concerns or a need for social care referral will exist—the level of functioning and quality of parenting should be assessed by the mental health team involved in her care and a referral made only where appropriate.

The absence of a supportive partner or extended family, financial and housing status, and the presence of stress and adversity such as domestic violence are also all associated with poorer parenting and higher likelihood of social services supervision.^{93,101} Finally, the presence of mental health problems in the father has been identified as a predictor of custody loss.^{101,102}

Conclusions

Childbirth is a powerful trigger of psychiatric episodes, and episodes at this time cause substantial morbidity and mortality, with suicide a leading cause of maternal death. Despite the undoubted importance of severe perinatal mental illness, these disorders are under-researched and there is still a poor evidence base in many areas. Further research is vital to help us understand more about the triggering of episodes by pregnancy and childbirth, enable us to better predict women at risk, and to develop improved treatments for women who become unwell at this time. Genetic studies of post-partum psychosis, for example, might lead to more individualised risk assessments, earlier identification of women at risk, and improved treatments for women who become ill.⁵⁹

Data for the risks and benefits of psychotropic medication in the perinatal period are urgently needed for women and their families, and decision aids to help with risk–benefit analyses could be beneficial in helping women in the transition to motherhood. Pregnancy should be an important consideration in the treatment of all women with severe mental illness in their reproductive years. Careful counselling of the woman and her partner, and sensitively providing understandable information while acknowledging the many areas of uncertainty is critical to optimal care.

Contributors

IJ and LH developed the outline of the review. All authors contributed to the writing and editing of the manuscript. IJ prepared the final version of the review, which all authors approved.

Declaration of interests

LH is Chair of the National Institute for Health and Care Excellence (NICE) (update) guideline on Antenatal and Postnatal Mental Health. She is Chief Investigator of a National Institute for Health Research (NIHR) Programme Grant for Applied Research on the effectiveness of perinatal mental health services (RP-RP-DG-1108–10012) and has funding from an NIHR Research Professorship on maternal mental health, and a grant from Tommy's baby charity (with the support of a corporate social responsibility grant from Johnson and Johnson) on antipsychotics in pregnancy. Her work is also supported by the NIHR Mental Health Biomedical Research Centre at the South London and

Maudsley NHS Foundation Trust and King's College London. The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health. IJ is a member of the Guideline Development Group of the NICE (update) guideline on Antenatal and Postnatal Mental Health. He has received funding for research in bipolar disorder and perinatal mental health from the Wellcome Trust, British Occupational Health Research Foundation, National Institute of Social Care Research and Health Research, NIHR, The Big Lottery, The Medical Research Council (MRC), and The Women's Mental Health Trust. He is Director of the National Centre for Mental Health (NISCHR-funded Biomedical Research Centre). He is Director of the Bipolar Psychoeducation Programme Cymru (BEP-C). Although he has not received honoraria in the last three years he has previously received honoraria from Lilly, GlaxoSmithKline, Lundbeck, Jansen and AstraZeneca to give talks on Psychoeducation and his research on perinatal mood disorders. PD receives funding from National Alliance for Research on Schizophrenia and Depression (NARSAD) and the Medical Research Foundation for research in post-partum psychosis. PC reports grants from the Indian Council of Medical Research and support for educational posters on preconception counselling from Ranbaxy India, however, with no mention of the company name on the posters.

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