Non-psychotic mental disorders in the perinatal period

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Mental disorders are among the most common morbidities of pregnancy and the postnatal period, and can have adverse effects on the mother, her child, and family. This Series paper summarises the evidence about epidemiology, risk factors, identification, and interventions for non-psychotic mental disorders. Although the phenomenology and risk factors for perinatal mental disorders are largely similar to those for the disorders at other times, treatment considerations differ during pregnancy and breastfeeding. Most randomised controlled trials have examined psychosocial and psychological interventions for postnatal depression, with evidence for effectiveness in treating and preventing the disorder. Few high-quality studies exist on the effectiveness or safety of pharmacological treatments in the perinatal period, despite quite high prescription rates. General principles of prescribing of drugs in the perinatal period are provided, but individual risk–benefit analyses are needed for decisions about treatment.

Introduction

Non-psychotic mental disorders are among the commonest morbidities of pregnancy and the post-partum period (the perinatal period). Research about perinatal mental disorders so far has largely focused on depression, particularly postnatal depression. However, increasing evidence shows substantial morbidity from other disorders. In this Series paper, we also review the available evidence base for the epidemiology and treatment of anxiety disorders, post-traumatic stress disorder (PTSD), eating disorders, and personality disorders.

Epidemiology

Depressive disorders

Depressive disorders are common during pregnancy and in the post-partum period and generally have the same phenomenology as non-childbearing depressive disorders (panel 1). Somatic symptoms can result from normal physiological changes in pregnancy and the early post-partum period, so therefore need to be assessed with care. However, these symptoms are more common in women with depression than in women who do not have depression in the perinatal period (with the exception of appetite change), suggesting that they might be valid markers of the disorder. Somatic symptoms are particularly frequent presentations of depression (and anxiety) in non-perinatal periods in women in low-income and middle-income countries (LMICs). In an Ethiopian cohort, there was a moderately high correlation between perinatal total somatic symptoms and depression or anxiety scores, supporting the importance of somatisation of mental distress in the perinatal period.

A systematic review of studies, predominantly in high-income countries (HICs), estimated the point prevalence of major depressive disorder to be between 3·1% and 4·9% during pregnancy and 4·7% in the first 3 months post partum. Point prevalence including minor depression (panel 1) was estimated to be up to 11% in pregnancy and 13% in the first 3 months post partum (period prevalence rates are 18·4% and 19·2%, respectively). A higher prevalence of antenatal and postnatal depression (major and minor) is generally reported in women in LMICs than in women in HICs. A meta-analysis of the point prevalence of non-psychotic common mental disorders (including depression, anxiety, adjustment, or somatic disorders) in LMICs reported values of 15·6% during pregnancy and 19·8% post partum, with substantially higher and lower rates in specific countries. Pregnancy was traditionally considered to be a period of “psychosocial immunity” from mental illness, but this is now known to be largely independent of gestation, with evidence that some women are more vulnerable during pregnancy than during the post-partum period, and during both periods there is an increased likelihood of the onset of mental illness. Women who have already experienced mental illness or its symptoms in the past are also at increased risk of developing a mental disorder in the perinatal period. Risk factors for perinatal depression include age, previous or concurrent mental illness, the presence of a partner, and lack of social support. There are also important risk factors for other forms of mental illness in the perinatal period, including childhood trauma, interpersonal violence, and adverse life events.

Key messages

- Health-care professionals need to be aware that when doing psychosocial assessments in the perinatal period, mental disorders across the diagnostic spectrum can occur during pregnancy and post partum
- Psychological and psychosocial interventions are effective treatments for postnatal depression; evidence from low-income and middle-income countries showed that these can be provided effectively by trained non-specialist workers
- Little research exists about the epidemiology or effectiveness of interventions for perinatal non-psychotic mental disorders, other than postnatal depression
- To what extent interventions that are developed and used outside the perinatal period need modification for the perinatal period is unclear; nevertheless, practitioners need to be aware of differences in context when treating women during this time
- Individualised risk benefit analyses are needed when judging use for psychotropic drugs in the perinatal period, accounting for the risk of untreated illness on the mother and fetus or infant
- Evidence for risks of psychotropic drugs is restricted because it is based on observational studies that can only establish associations and not causality; however, absolute risks from meta-analyses are small and residual confounding is likely
viewed as a time when women are protected against depression, but the latest systematic review and a large US epidemiological study do not report a significant difference in the prevalence or incidence of depression between pregnant and non-pregnant women. However, rates of identification and treatment of depression might be lower in pregnant than non-pregnant women, contributing to the perception of reduced prevalence reported. Studies using non-childbearing comparators might also underestimate risks associated with the perinatal period because women who become mothers might be mentally healthier and have a lower baseline vulnerability to depression than those who do not have children.

Whether the incidence of depression peaks in the postnatal period has been greatly debated. A low mood is transient. Investigators of longitudinal studies using medical records have noted an increase in incidence of depression during the first 5 months and 9 months post partum by comparison with rates pre-pregnancy, during pregnancy, or at the end of the first post-partum year; however, the estimates are based on the proportion of women newly seeking treatment rather than community-based measurement of incidence. Poor identification and measurement of depression during pregnancy could lead to many women being misclassified with post-partum onset. Results from a US study suggested 33% of postnatal depression begins in pregnancy and 27% in pre-pregnancy. Additionally, some evidence suggests that there might be a higher prevalence of depressive symptoms during pregnancy than in the post-partum period. Women with postnatal depression often recover within a few months from onset, but around 30% of women still have depression beyond the first year after delivery and there is a high risk of around 40% of subsequent postnatal and non-postnatal relapse.

Anxiety disorders

Anxiety disorders in the perinatal period are often overlooked but are common—e.g., a large US population-based study reported a prevalence of 13% in the past year of any anxiety disorder in currently pregnant or post-partum women, comparable with non-pregnant women. Similar rates of anxiety disorders are reported in African countries and there is substantial comorbidity with depressive disorders. Little research has been done into the course of anxiety disorders in the perinatal period; however, some evidence suggests a reduction in the prevalence of generalised anxiety disorder, and anxiety symptoms, during the course of pregnancy and the post-partum period.

A meta-analysis reported a significantly higher risk of obsessive compulsive disorder in pregnant and post-partum women than in non-pregnant women. Ruminations in the post-partum period can include ruminations of harm to the infant, but these are not associated with actual harm (unlike the delusions in a psychotic disorder); therefore, health-care professionals need to distinguish obsessive ruminations from delusions.

PTSD

Increasingly, authors recognise that women can have PTSD in the perinatal period triggered by traumatic experiences during pregnancy or childbirth, or by traumatic events before conception. Estimates of PTSD prevalence after delivery vary but are often estimated to be around 1–2% in HICs with many more women experiencing subthreshold symptoms; a higher prevalence is reported in LMICs (e.g., 5–9% in Nigeria). Most studies underestimate the total prevalence of PTSD in the perinatal period by only examining PTSD related to traumatic childbirth experiences; higher rates are noted in pregnancy when diverse trauma experiences are included (point prevalence 6–8%). Perinatal PTSD is highly comorbid with depression.
Eating disorders

Women with eating disorders have an increased rate of fertility problems, although many still become pregnant, sometimes with fertility treatment. The expectation of weight gain during pregnancy can be considered healthy, and women are sometimes more accepting of their body size at this time. However, symptoms of eating disorders can persist during pregnancy for mothers who have had a recent episode. A Norwegian prospective population study of 41 157 women reported substantial remission rates during pregnancy between 29% and 78% depending on the type of eating disorder; incident cases of eating disorder during pregnancy were rare, other than binge eating disorder (1.1 incident case per 1000 person-weeks) which was associated with low socioeconomic status.

Binge eating can be common. In a Brazilian study, a prevalence of binge eating of 17-3% was reported and associated with anxiety and pre-pregnancy binge eating disorder.

In a large population study, 77 807 women were assessed for eating disorders in the perinatal period; 35–50% rates of remission were recorded at 18 months post partum, suggesting higher remission rates in the community than in clinical samples. Nevertheless, a substantial proportion of women with pre-pregnancy eating disorders have continuation or recurrence of symptoms post partum. The disruption in sleep and mealtimes and the need to adapt to the baby’s routines, especially around feeding, makes it challenging for many mothers to establish and maintain their own eating patterns.

### Panel 1: DSM-5 and ICD-10 diagnostic criteria for depression

**DSM-5**

Major depression

At least five symptoms present for at least 2 weeks, for most of nearly every day

A symptom must be:

- Depressed mood
- Markedly diminished interest or pleasure in all or most activities

Other symptoms:

- Substantial weight loss when not dieting or weight gain, or increase or decrease in appetite
- Insomnia or hypersomnia
- Psychomotor agitation or retardation
- Fatigue or loss of energy
- Feelings of worthlessness or excessive or inappropriate guilt
- Diminished ability to think or concentrate or indecisiveness
- Recurrent thoughts of death or suicidal ideation (with or without a specific plan)

Symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functionality

Symptoms not due to direct physiological effects of a substance or another medical condition

The occurrence of a major depressive episode is not better explained by schizoaffective disorder or other psychotic disorders and there has never been a manic or hypomanic episode

Depressive episode with insufficient symptoms

Depressed affect and at least one other of the above symptoms associated with clinically significant distress or impairment persisting for at least 2 weeks

With peripartum onset†

Onset of mood symptoms happens during pregnancy or in the 4 weeks after delivery

**ICD-10**

Severe depression

At least seven symptoms, usually present for at least 2 weeks, experienced with severe intensity for most of every day

All three key symptoms associated should be present:

- Persistent sadness or low mood
- Loss of interests or pleasure
- Fatigue or low energy

At least four associated symptoms should be present:

- Disturbed sleep
- Poor concentration or indecisiveness
- Low self-confidence
- Poor or increased appetite
- Suicidal thoughts or acts
- Agitation or slowing of movements
- Guilt or self-blame
- Individual unable to continue with social, work or domestic activities, except to a very restricted extent

Moderate depression

At least two key symptoms and three associated symptoms should be present

Minor depression

At least two key symptoms and two associated symptoms should be present, with no symptoms present to an intense degree

With postpartum onset

Disorder commencing within 6 weeks of delivery

ICD=international classification of diseases (published by WHO). DSM=diagnostic and statistical manual of mental disorders. *Changed from minor depression in DSM-4 (two to four depressive symptoms experienced for at least 2 weeks, one symptom should be depressed mood or loss of pleasure). †Changed from with postpartum onset in DSM-4 (onset of mood symptoms within first 4 weeks after delivery).
Personality disorders

To our knowledge, only one epidemiological study has been done of personality disorders in the perinatal period. The prevalence of personality disorders in pregnancy, based on a self-report measure in a Swedish study was 6%, but the prevalence of specific personality disorders was not reported.34 Personality disorders in the perinatal period are often comorbid with other non-psychotic disorders, such as depression, and emerging evidence suggests that they are associated with an increased risk of adverse outcomes and poor response to treatment.35

Risk factors

Despite substantial research into risk factors for perinatal disorders, particularly depressive disorders, there are few systematic reviews and a paucity of research using diagnostic measures, longitudinal approaches, and comparison groups. Studies often exclude women with a history of mental illness or particular groups of women, such as those who are infected with HIV or are chronically ill, which restricts our understanding of overlapping risks and comorbidities. However, a history of any psychopathology and psychosocial adversities, including the spectrum of low social support and abuse, are predictors of mental disorders during and after pregnancy with little diagnostic specificity and should inform prevention, identification, and treatment. Figure 1 shows a summary of systematic review evidence of risk factors for antenatal and postnatal depression,8,20,36–43 which have a substantial body of evidence.

In addition, PTSD after childbirth has been associated with obstetric complications, particularly with severe morbidity, preterm birth, high subjective distress, and infant complications, although the evidence is inconsistent and quality of studies is moderate-to-low.46,47 Psychopathology (particularly depression and anxiety) during pregnancy is strongly associated with an increased

Figure 1: Risk factors for antenatal and postnatal depression: systematic review evidence

Risk factors for antenatal and postnatal depression are categorized by strength of risk in HICs and LMICs. Extent of risk indicated for HIC and LIC. HIC=high-income countries. LMIC=low-income and middle-income countries. PTSD=post-traumatic stress disorder. *Evidence only available from one setting.
risk of postnatal PTSD and might increase a woman’s distress during labour. Additional risk factors identified include previous traumatic experiences and low support during childbirth.

**Identification**

**Depressive disorders**

Because perinatal mental disorders can have serious consequences in terms of maternal morbidity and mortality and adverse infant outcomes, there is much interest in improvement of identification of disorders to increase treatment rates. Most research and debate has focused on the identification of postnatal depression, whether or not to use screening instruments routinely in the post-partum period, and which methods to use. The most frequently used screening method is the Edinburgh postnatal depression scale (EPDS), which is a self-report ten item questionnaire (including one on self-harm; panel 2), validated for both antenatal and postnatal use. Although the positive predictive value for postnatal major depression can range between 9% and 64% (cutoff between 9 and 10) or 17% and 100% (cutoff between 12 and 13) and for antenatal major depression between 60% and 80% (cutoff between 14 and 15), this range depends on the population, prevalence, translation, and cutoff point, and the diagnostic performance of the EPDS seems quite good in most studies.

The EPDS has been translated and validated in many settings. A systematic review of studies in Africa suggested a pooled sensitivity of 0.94 (95% CI 0.68–0.99) and specificity of 0.77 (0.59–0.88) at a cutoff of more than a score of eight. However, the authors emphasised the low quantity of research into local understandings of perinatal depression syndromes in different African countries. Although two recent studies suggested that very brief screens might be effective in identification of depression or anxiety post partum in HICs and LMICs, additional research is needed.

Only five comparative studies have been published, which together provide low-to-moderate strength of evidence for the clinical efficacy of screening in reduction of morbidity in post-partum women. However, the strongest evidence is for combined identification and treatment programmes, mainly from three cluster...
randomised controlled trials in HICs that reported improvement in maternal mental health for women who received integrated post-partum screening and management strategies by trained health professionals. Although results from cost-effectiveness modelling have suggested that formal identification methods for postnatal depression would not meet willingness-to-pay thresholds, assumptions made in the model might not represent present practice and two large RCTs suggest that systematic identification with enhanced support can be cost effective. Most women and health professionals deem screening acceptable, although small qualitative studies report that women can experience screening as potentially stigmatising and intrusive. Although questions have been raised about the appropriateness of the EPDS for some ethnic groups and the screening context (eg, rural LMIC setting) it is widely used internationally.

Although there is scope for harm through non-identification and thus no access to effective treatment, concerns about other potential harms associated with screening (such as misdiagnosis, labelling, and stigma) are particularly pertinent if a clinical decision about the presence or absence of a mental disorder is made only on the basis of a screening result. However, as international guidelines emphasise, a central principle is that the screening techniques are not designed to diagnose depressive disorders, but aim to identify women for whom further comprehensive psychosocial and clinical assessment is needed. Appropriate training is therefore necessary for health professionals in the skilful interpersonal process for psychosocial assessment with appropriate referral and care pathways for identified risk factors. An evidence gap remains as to whether screening is clinically effective and cost effective during pregnancy, or in LMICs where few effective treatment resources are available.

Other disorders
Many EPDS positive screens that prove false for unipolar depression at diagnostic interview could be indicative of another mental disorder; data from studies suggest around 13% of screen positive women in pregnancy and 23% in the post-partum period have bipolar disorder. At present the evidence about screening instrument accuracy, clinical effectiveness, acceptability, potential harms, and cost-effectiveness of screening for disorders other than depression is inadequate. Nevertheless, there is general agreement about the desirability of training of front-line professionals to identify and treat disorders other than depression in the perinatal period.

Prevention
Depressive disorders
Not much research has investigated the prevention of antenatal depression, whereas a Cochrane systematic review identified 28 RCTs (n=16,000) about psychosocial or psychological preventative interventions for postnatal depression (all but three were undertaken in HICs). Women who received an intervention were significantly less likely to develop postnatal depression than were those who received standard care (relative risk [RR] 0·78, 95% CI 0·66–0·93). Protective interventions included intensive, individualised post-partum home visits provided by health professionals (two RCTs), lay (peer)-based post-partum telephone support (one RCT), and interpersonal psychotherapy (five RCTS), particularly for studies focusing on women at-risk of postnatal depression (RR 0·66, 95% CI 0·50–0·88), and for postnatal interventions compared with interventions in the antenatal period (0·73, 0·59–0·90). However, no significant preventive effect on depressive symptomatology was recorded for psychological structured debriefing (five RCTs, n=3050; RR 0·57, 95% CI 0·31–1·03) or cognitive behavioural therapy (one RCT, n=150; RR 0·74, 0·29–1·88). Additionally, there was no clear evidence to recommend antenatal and post-partum classes, psychoeducation, or sleep strategies (although they might be beneficial for other maternal outcomes). The use of oestrogens and progestins or dietary supplementation with selenium or docosahexaenoic acid has little supportive evidence. Treatment of women with antenatal depression might prevent postnatal depression but this is better conceptualised as treatment rather than prevention.

Anxiety disorders
Much less research has been done in relation to the prevention of perinatal anxiety than depression. Two small trials of group cognitive behavioural therapy (CBT; n=61 pregnant women with subclinically raised stress and anxiety levels; 132 women with mild-to-moderate symptoms or at risk of developing depression or anxiety) had methodological limitations and equivocal results. Another small trial (n=71) suggested that incorporation of CBT-based prevention programme into childbirth education classes for women at risk of developing OCD was associated with significantly lower levels of postnatal obsessions and compulsions compared with women receiving general psychoeducation about anxiety. An antenatal self-guided workbook intervention with weekly telephone support might reduce symptoms of postnatal depression and anxiety, and prenatal parenting education could reduce...
post-partum anxiety and improve marital adjustment. A Cochrane review reported limited evidence for the effectiveness of other interventions (eight trials; n=556) assessing hypnotherapy (one trial), imagery (five trials), autogenic training (one trial), and yoga (one trial) for prevention or treatment of anxiety during pregnancy.

PTSD
Controversy has surrounded postnatal debriefing for the prevention of PTSD. The term debriefing is used to describe a range of provision from the opportunity to discuss childbirth experiences, particularly if they were perceived to be traumatic, to highly structured debriefing interventions. Most trials have shown no evidence that formal structured debriefing is helpful, and one trial showed potential risk of harm.* Women do benefit from the opportunity to discuss the delivery, but formal debriefing interventions are not supported by present evidence.

Eating disorders
No trials have been done on prevention in women at risk of a recurrence of an eating disorder even though guidelines recommend identification of women with a history of an eating disorder. Professionals can help women during pregnancy and the postnatal period to maintain regular eating patterns and optimise nutritional intake for the mother and fetus, and support them in development of realistic goals for body shape.

Psychosocial and psychological treatments

Depressive disorders
Because of maternal treatment preferences and potential concerns about fetal and infant health outcomes, non-pharmacological treatment options are particularly important in the perinatal period. Evidence on the treatment of antenatal depression is limited to small trials (with 36–53 women) of interpersonal therapy, culturally relevant brief interpersonal psychotherapy, and CBT,* and a Cochrane review (six trials, n=406) of other types of non-pharmacological interventions such as massage, acupuncture, bright light, and omega-3 oils reported inconsistent results. More evidence is available for postnatal depression, particularly from HICs, and a Cochrane review found that psychosocial and psychological interventions were effective for reducing depression symptoms within the first year postpartum (RR 0·70; 95% CI 0·60–0·81). Psychosocial interventions, such as peer support and non-directive counselling, show a decrease in depressive symptomatology (five trials, n=506; RR 0·61; 0·39–0·94), confirmed by a recent large cluster trial in which assessment and non-directive or cognitive behavioural counselling were delivered by health visitors compared with standard care. CBT and interpersonal psychotherapy were also beneficial in reducing post-partum depressive symptomatology (six trials, n=602; RR 0·75; 95% CI 0·63–0·88). Insufficient data prevented comparisons between individual-based and group interventions. Two systematic reviews assessing the effectiveness of interventions to improve the mental health of women in the perinatal period in LMICs showed 17 trials (undertaken in predominantly middle-income countries such as China and Chile with only one trial in a low-income country [Uganda]*) that reported a beneficial effect of delivery of a psychosocial or psychological intervention during routine perinatal care (pooled effect sizes: −0·38, 95% CI −0·56 to −0·21; −0·34, −0·53 to −0·16). The reviews show that training is feasible for non-specialist workers, such as community health workers or local women to deliver perinatal mental health interventions including home visits or facilitated group sessions with a focus on parenting, maternal and child health, psychoeducation, social support, or supportive listening adapted to the circumstances the women who are being treated live in. However, interventions should be adapted to the circumstances in which the women being treated live.

Other disorders
Treatments for other perinatal disorders have been scarcely researched, so management largely relies on extrapolation from the evidence base established for other times in women’s lives such as CBT for eating disorders. The extent to which interventions need modification for the perinatal period is unclear and needs additional research. Restricted evidence from a case series suggests that intensive outpatient CBT that is modified for women with postnatal OCD could reduce symptoms.*

Pharmacological treatment
The mainstay of pharmacological treatment for non-psychotic mental disorders in the perinatal period is antidepressants. Data suggests that in Europe around 3% of pregnant women take an antidepressant at some point in their pregnancy, mostly selective serotonin reuptake inhibitors (SSRIs), with rates of around 10% reported in the USA.* Antidepressants are effective treatments for depression, particularly for severe cases, and meta-analyses have shown that efficacy compared with placebo increases with severity of depression.* Antidepressants are also effective for PTSD, anxiety disorders, and bulimia nervosa.* However, partly because of the difficulties in undertaking RCTs in perinatal women, no trials have been done for perinatal disorders except for postnatal depression. These trials provide evidence of significantly higher response and remission rates for women taking SSRIs than for placebo. A Cochrane systematic review pooled data from three studies comparing SSRIs with placebo and reported significantly higher response (RR 1·43 [95% CI 1·03–2·03]) and remission rate (RR 1·79 [1·08–2·98]) for participants taking SSRIs than in those in the placebo group. However, the evidence-base is restricted because
General principles of prescribing in the perinatal period:

- It should not be assumed that it is always better to avoid psychotropic drugs.
- Use the lowest effective dose.
- Use the drug which is effective for women and has the lowest known risk to mother and fetus.
- Prescribe the least number of drugs as possible.
- Document all decisions.
- Ensure that the mother and partner or family are as involved as possible in all decisions.

In discussions about drugs include:

- Woman's level of distress from untreated symptoms.
- Severity of previous episodes, previous response to treatment and the woman's preference.
- Potential effects of an untreated mental disorder on the fetus or infant (and the need for prompt treatment).
- Risks of relapse or discontinuation symptoms from stopping drug abruptly.
- Background risk of fetal abnormalities for pregnant women without a mental disorder.
- Uncertainty with regards to possible increased risk of harm associated with drug treatments during pregnancy and the postnatal period, including the risk in overdose.
- The possibility that stopping a drug with known risk during pregnancy might not remove the associated risk.
- Absolute and relative risks should be discussed using natural frequencies and common denominators (e.g., 20 in 100 and 25 in 100, not 1 in 5 and 1 in 4).

Where possible, written material (preferably individualized) should be provided to explain the risks.

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**Figure 2: Guidelines to prescribe in the perinatal period**

Adapted from The Maudsley prescribing guidelines (11th edn), by permission of David Taylor.

the three studies were very small, underpowered, and generally focus on women with mild-to-moderate postnatal depression. RCTs have so far not reported evidence of additional improvement with addition of a psychological intervention to antidepressants, nor for addition of sertraline by comparison with placebo for women given a psychotherapeutic intervention for postnatal depression, although the trials were underpowered. An RCT reported significant improvements in EPDS scores in women given 17β-oestradiol skin patches (with dydrogesterone tablets for 12 days per month) compared with women given placebo, but adverse events were reported and there is therefore insufficient evidence to support use of oestrogens for postnatal depression.

Women often stop antidepressants during pregnancy and there is conflicting evidence on whether discontinuation is associated with an increased risk of relapse of depression, probably because of the different levels of severity of depression in the different study populations. However, recurrence after discontinuation consistently seems to be more likely in women with a history of several episodes or a recent episode.

As a general principle, drugs in pregnancy should be minimised, and many women with perinatal mental disorders can be treated with non-pharmacological interventions. However, drugs will be clinically indicated for women with more severe mental disorders in which there are substantial risks to the mother, the pregnancy, and the fetus or infant. Clinicians and women therefore need to assess the benefits and risks of pharmacological interventions in pregnancy using key principles of prescription in the perinatal period (figure 2). Unlike other times in a woman’s life, risks of illness versus risks of drugs do not only affect the women themselves, the fetus and infant can also be affected through exposure to psychotropic drugs across the placenta or through breastfeeding, and side-effects...
potentially affect the mother’s ability to parent (eg, sedative drugs). However, concerns about risks to the fetus or a failure to titrate the dose through the pregnancy (to address the changes in drug concentrations) might lead clinicians to prescribe subtherapeutic doses.109

Risks to the fetus are difficult to assess because of the absence of RCTs and the resultant difficulties in interpretation of the evidence base. Many studies are small, with biased samples, low-quality study design, little adjustment for important confounders (such as smoking), and an almost invariably absence of adjustment for confounding by indication. Initial reports of risks have frequently not been substantiated or are shown to be smaller once larger studies and meta-analyses have been done. For example, despite early reports, a meta-analysis193 did not find an increased risk of spontaneous abortion associated with exposure to antidepressant drugs, and two large population studies111,112 (29 228 and 12 425 SSRI exposures, respectively) have not found associations with antenatal SSRIs and stillbirths or neonatal deaths after adjusting for confounders. Similarly, two meta-analyses113,114 showed paroxetine exposure is associated with only slightly increased risks of cardiac malformations (odds ratio [OR] 1·4) rather than the large ORs initially reported, and residual confounding is possible. Confounding by indication also needs to be considered—a study comparing outcomes in infants of women who stopped SSRIs before pregnancy and women who continued with SSRIs reported a similar increased risk of cardiac malformations in both groups,35 suggesting that the association is due to depression rather than the drug itself.

Antidepressant exposure in pregnancy is significantly associated with gestational age at birth (pooled mean difference in weeks, −0·45, 95% CI −0·64 to −0·25), preterm delivery (<37 or <36 weeks depending on the individual studies included; pooled OR 1·55, 95% CI 1·38–1·74), and Apgar score at 1 min (mean difference of −0·18 points), and 5 min (mean difference of −0·45, 95% CI −0·64 to −0·25), although some might be of restricted clinical significance.109 Meta-analyses have previously reported associations with birthweight, but no significant association with reduced birthweight was reported in the 2013 meta-analysis when the comparison group was limited to depressed mothers without antidepressant exposure.110

A consistent significant association exists between exposure to antidepressants during pregnancy and occurrence of poor neonatal adaptation syndrome (PNAS; OR 5·07, 95% CI 3·25–7·90), and individual clinical signs (respiratory distress, OR 2·20, 1·81–2·66; tremors, 7·89, 3·33–18·73).106 The use of observational study designs means causality cannot be inferred; the results could suggest measurement bias, selection bias, and confounding, but since abrupt discontinuation of antidepressants in adults is associated with withdrawal symptoms, infants might be at risk after birth. Whether the symptoms reflect withdrawal or toxicity is under debate. Symptoms noted are usually mild and self-limiting, but one study reported that infants who developed PNAS were at an increased risk of social-behavioural abnormalities even though they had normal cognitive ability.107 Whether tapering of antidepressants the week before expected labour would reduce the occurrence of PNAS is unclear; some authors have argued that the balance of evidence suggests that discontinuation of clinically needed antidepressants in women near term is unwarranted because neonatal symptoms only occur in a small number of cases and are self-limited, but the risk to a woman’s mental health will be increased.100 Evidence on how long to observe the neonate for PNAS symptoms is scarce. If no symptoms emerge within the first 72 h after birth, PNAS is unlikely; when PNAS symptoms are present it is advisable to observe the infant until symptoms are resolved in case supportive treatment is needed.100

Some PNAS symptoms can suggest a spectrum of effects with mild respiratory signs potentially showing sub-clinical persistent pulmonary hypertension of the newborn (PPHN). A systematic review and meta-analysis119 reported an increased risk of PPHN associated with late pregnancy SSRI exposure (OR 2·50, 95% CI 1·32–4·73; absolute risk difference 2·9–3·5 per 1000 infants). Although individual studies used different diagnostic criteria and possible moderating variables such as caesarean section, body-mass index, or preterm delivery these could not be included in the meta-analysis. Serotonin has a role in the development and modulation of the lungs and this could be a factor in the development of PPHN. Evidence also shows that prenatal SSRIs are associated with neurobehavioural disturbances in early infancy including stress or pain regulation; the severity of these symptoms seems to be associated with high drug concentrations and pharmacogenetic metabolic factors.120

Fewer data exists for long-term outcomes of infants exposed to antidepressants in utero. However, studies are similarly difficult to interpret because of methodological problems and the known associations between maternal depression, impaired mother–infant interactions, and adverse infant or child outcomes.36 Some studies reported a range of normal neurodevelopmental outcomes including cognitive, behavioural, and emotional outcomes while also noting adverse outcomes (eg, behavioural problems measured by the strengths and difficulties questionnaire120) in children exposed to maternal depression in utero in the comparison groups,121,122 but others have reported small delays in developmental milestones in children exposed to antidepressants in utero. A study123 using Danish National Cohort data reported that 415 children exposed in the second or third trimester in utero to antidepressants at 15–9 days (95% CI 6·8–25·0) and walked 28·9 days (95% CI 15·0–42·7) later than children who were not exposed to antidepressants (although still within the normal range of development); fewer children with
exposure to antidepressants in utero were able to sit without support aged 6 months (OR 2·1, 95% CI 1·23–3·60), and fewer were able to occupy themselves aged 19 months (2·1, 1·09–4·02) than children who were not exposed. A study of 31 infants exposed prenatally to SSRIs scored significantly lower than the 52 non-exposed infants on gross motor (p=0·03), social-emotional (p=0·04), and adaptive behaviour (p=0·05) subscales of the Bayley Scale of Infant Development. Two nested case-control studies have reported an association between antidepressant exposure in pregnancy and autism spectrum disorders, but no significant association was shown in a large cohort study.

Although most studies focus on adverse outcomes with some inconsistent results, there is new evidence, albeit with small samples, that SSRI use in pregnancy could have a positive effect. For example, prenatal antidepressant treatment mitigates the effect of maternal anxiety on P50 sensory gating (associated with increased vulnerability to attentional deficits) and infants exposed to SSRIs in utero show more readiness to interact during a toy session than do a non-SSRI group exposed to high levels of maternal depressive symptoms. Prenatal antidepressant exposure might account for some neurobehavioural outcomes in early childhood, but maternal and infant genetic and environmental factors (including maternal depressive symptoms in pregnancy and the postnatal environment) will also shape childhood behaviours.

Antidepressant exposure in breastfed infants is lower by five to ten times than is exposure in utero. The milk drug concentration can be used to estimate the daily drug dose ingested by the infant, assuming an average milk intake of 150 mL/kg bodyweight per day. The infant dose per kg can be expressed as a percentage of the maternal dose per kg and a relative infant dose of less than 10% is deemed a negligible exposure. A review reported low relative infant doses for fluvoxamine, paroxetine, sertraline, duloxetine, reboxetine, bupropion, and mirtazapine, and an earlier review reported a low relative infant dose for nortriptyline. Relative infant doses around 10%, and in some cases higher than 10% for citalopram, fluoxetine, and venlafaxine, with somewhat lower relative infant dose for escitalopram have been reported. When high concentrations have been reported, infants have been aged younger than 3–4 months, when infants are still developing hepatic function. Metabolic capacity is not well developed in preterm babies and those with genetically determined impairment in antidepressant metabolism via cytochrome P-450 enzymes (CYP2D6 and CYP2C19). Reassuringly, indirect biological evidence shows that serotonin transmitters are not affected because no platelet serotonin effects are noted in infants of breastfeeding mothers treated with sertraline or fluoxetine.

Some adverse but non-specific events in infants exposed to antidepressants via breast milk have been reported in case reports and case series, more often after exposure to fluoxetine (eg, irritability and poor feeding) and citalopram (eg, poor sleep) than after exposure to other drugs. Respiratory depression, hypotonia, and vomiting have been associated with the tricyclic doxepin. No studies have identified an increased risk of adverse long-term outcomes. Most authors conclude that if a mother was successfully treated for depression during her pregnancy, the same drug should usually be used in the post-partum period because discontinuation or switching of an antidepressant treatment could lead to relapse.

Perinatal mental disorders are common and can adversely affect the mother and infant. However, they are treatable and should therefore be identified early to prevent adverse long-term effects. Where possible, non-pharmacological treatments should be used but in more severe cases, effective doses of antidepressants will be needed after a careful collaborative analysis of the risk versus benefit.

Future research directions

Data for the epidemiology and prognosis of perinatal mental disorders excluding postnatal depression, in both high-income and low-income settings are scarce. Similarly, there are few data for emerging risk factors (such as migration and substance misuse), prevention, and how and whether treatments (both psychological and pharmacological) need to be modified in the perinatal period. The effect of antidepressants on the infant exposed in utero and breastfeeding, particularly with respect to long-term outcomes, needs further research. Future assessments of psychosocial interventions should include distance, online self-help interventions and self-help groups (ie, groups not facilitated by a health professional), the potential role of the father, and family-focused interventions. Finally, trials of integrated models of service delivery including identification, prevention, and treatment in high-income and low-income settings could be used to inform development of perinatal mental health services, which are themselves in their infancy. In view of the rates of perinatal disorders, the potential implications for the mother, infant, and family, and that these disorders happen at such an important time in the infant’s life, these research initiatives need to be considered a priority.

Contributors

LMH, AS and JM developed the outline for the Series paper. EM did the literature search. All authors contributed to the writing and editing of the manuscript. LMH prepared the final version of this Series paper, which all authors approved.

Declaration of interests

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