

Perinatal mental health: a review of progress and challenges

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Perinatal mental health has become a significant focus of interest in recent years, with investment in new specialist mental health services in some high-income countries, and inpatient psychiatric mother and baby units in diverse settings. In this paper, we summarize and critically examine the epidemiology and impact of perinatal mental disorders, including emerging evidence of an increase of their prevalence in young pregnant women. Perinatal mental disorders are among the commonest morbidities of pregnancy, and make an important contribution to maternal mortality, as well as to adverse neonatal, infant and child outcomes. We then review the current evidence base on interventions, including individual level and public health ones, as well as service delivery models. Randomized controlled trials provide evidence on the effectiveness of psychological and psychosocial interventions at the individual level, though it is not yet clear which women with perinatal mental disorders also need additional support for parenting. The evidence base on psychotropic use in pregnancy is almost exclusively observational. There is little research on the full range of perinatal mental disorders, on how to improve access to treatment for women with psychosocial difficulties, and on the effectiveness of different service delivery models. We conclude with research and clinical implications, which, we argue, highlight the need for an extension of generic psychiatric services to include preconception care, and further investment into public health interventions, in addition to perinatal mental health services, potentially for women and men, to reduce maternal and child morbidity and mortality.

Key words: Pregnancy, postpartum, perinatal mental disorders, maternal mortality, suicide, child outcomes, psychological interventions, antidepressants, preconception interventions, public health interventions, service delivery

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Perinatal mental ill-health has been a focus of interest for centuries, but until recently this interest has mainly centered around postpartum psychosis and depression, with relatively little funding for research into individual level treatments as well as for investment in specialist services and public health interventions. This is, however, changing.

In January 2016, the UK Prime Minister announced a strategic >£290 million investment into new specialist perinatal mental health services (services for women with mental disorders in pregnancy and the first year postpartum)¹. Since then, additional funds have been promised, with the aim of ensuring that women in all parts of the UK have access to specialist community services and psychiatric inpatient mother and baby units, and extending service provision up to two years postpartum. The ambition is to provide care concordant with the Antenatal and Postnatal Mental Health Guidelines produced by the National Institute for Health and Care Excellence (NICE)² to all women needing it. In other countries, there have also been investments in specialist outpatient and/or community perinatal mental health services and/or in mother and baby units^{3,4}.

Perinatal mental disorders are common – indeed, the commonest complication of child-bearing – and are associated with considerable maternal and foetal/infant morbidity and mortality^{5–7}. In addition, there is a huge cost burden, particularly to health and social care, estimated in the UK to be £75,728 and £34,840 per woman lifetime for perinatal depression and anxiety respectively, with an aggregate cost for the country of £6.6 billion. Around 75% of this economic burden is associated with subsequent childhood morbidity⁸.

While these estimates inevitably are subject to various assumptions, the World Health Organization (WHO) has highlighted the urgent need for “evidence based, cost effective, and human rights oriented mental health and social care services in community-based settings for early identification and management of maternal mental disorders”⁹.

The current classifications of perinatal mental disorders are confusing, which partly reflects the debate on whether these disorders are unique in terms of their causes and psychopathology, or the same as mental disorders at other times of a woman's life. Recent evidence suggests that, even within individual diagnostic constructs such as postpartum depression, there are

different phenotypes, potentially needing different interventions and services¹⁰.

In this paper, we summarize and critically examine the epidemiology of mental disorders in relation to childbirth and their impact on the foetus/infant/child, and then focus on the evidence base for interventions during pregnancy and postpartum, as well as in the preconception period, at the individual and population level. We also review the evidence base on service delivery models and discuss implications for research.

In particular, we explore whether, in view of the current evidence base, investment in services can be expected to make a meaningful and lasting difference for women and their families, how service delivery could be optimized, and what the implications can be for general psychiatric services and research.

PREVALENCE OF MENTAL DISORDERS IN THE PERINATAL PERIOD

The early postnatal period is at high risk for new and recurrent episodes, particularly of severe mental illness^{5,11–13}, with around one to two women in 1,000

requiring admission in the first few months after birth⁵.

A seminal study by Kendell et al¹² (replicated by several groups) found that women were around 22 times more likely to have a psychiatric admission in the month following birth than in the pre-pregnancy period. This increased postnatal admission risk is found amongst women both with and without prior psychiatric illness, but more so among women with a pre-existing severe mood disorder¹¹. A systematic review of 37 studies (including 5,700 deliveries in 4,023 women) found that 20% of women with pre-existing bipolar disorder experience a severe postnatal mental illness (i.e., psychosis, mania and/or hospitalization)¹⁴.

For less severe mental disorders (predominantly mild to moderate depression and anxiety disorders), the evidence for postpartum triggering is less clear^{6,11}. Some studies have found an increased rate of disorders requiring outpatient contact and/or psychotropic treatment in the postnatal period, particularly for depression and obsessive-compulsive disorder (OCD)^{15,16}. This may reflect an under-detection and/or under-treatment of these disorders during pregnancy, as studies find that postpartum depressive and anxiety symptoms frequently begin during or before pregnancy^{17,18}, but women are less likely to receive treatment during pregnancy than postnatally¹¹. Nevertheless, it has been estimated that, for each woman requiring psychiatric admission following birth, 2.5 require outpatient treatment and 12 receive pharmacological treatment in primary care¹¹. Therefore, “common mental disorders” (namely, depression and anxiety) represent a significant component of treatment need in the postnatal period.

A systematic review of 58 studies (N=37,294 previously healthy women) reported an incidence estimate for postnatal depression of 12% (95% CI: 4-20) and a prevalence of 17% (95% CI: 15-20)¹⁹. In general, the prevalence is higher in low-to middle-income countries (LMIC) than in high-income countries (HIC)²⁰.

Recent systematic reviews report a prevalence of 15-20% for antenatal and 10% for postnatal anxiety disorders^{21,22}, with higher rates in LMIC versus HIC settings.

Self-reported anxiety symptoms are very common, and increase across the trimesters of pregnancy (with a mean prevalence of 25% in the third trimester)²¹.

Perinatal eating disorders are relatively rare, but there is a history of an eating disorder in up to 15% of pregnant women, who may therefore need support with re-emerging symptoms precipitated by pregnancy or postpartum²³.

The evidence is not consistent concerning the relapse rate of prior depression and bipolar disorder during pregnancy. Around 10-20% of pregnant women with prior depression seem to experience a depressive relapse, but with a broad range of estimates (from <5% to 75%)^{24,25}. For bipolar disorder, a systematic review of 14 mainly small studies (including a total of 2,345 women, but with only two studies with a sample size of >100) suggests that around one in five women experience a relapse during pregnancy²⁴, with a possible predominance of depressive and mixed episodes (in contrast to prominent manic episodes in the postnatal period)^{5,24,25}. However, a recent electronic health record study reported a relapse rate of 10%²⁶, possibly reflecting different populations.

There is some indirect evidence that the prevalence of perinatal mental illness has increased in recent years. A study using UK primary care data has reported that the proportion of children exposed to maternal mental illness increased from 22.2% (95% CI: 21.9-22.4) between 2005 and 2007 to 25.1% (95% CI: 24.8-25.5) between 2015 and 2017²⁷.

This could be due to increase in primary care attendance (due to greater awareness of mental health problems) and/or increased detection, and/or different populations. However, it is likely to reflect at least in part a real increase, as similar findings of an increase of common mental disorders in young women has been found in population surveys²⁸. Moreover, a multi-generational pregnancy cohort²⁹ has reported that depression in pregnancy was on average 51% more common among young mothers in the recent generation than among their mothers' generation 25 years ago. We also recently reported a population prevalence estimate of common mental disorders of 45.1% (95% CI: 23.5-

68.7) in pregnant women less than 25 years of age, compared with 15.5% (95% CI: 12.0-19.8) in women aged 25 years or more (adjusted odds ratio: 5.8, 95% CI: 1.8-18.6)³⁰.

Obviously, young pregnant women are now living in circumstances different from their mothers: some have pointed to the fast pace of modern life, changes in technology (including social media use which may amplify experiences of abuse and bullying through “sexting”), isolation, and insecure employment as potential contributors to this²⁹.

Alcohol is a major teratogen, and a recent high-quality systematic review estimated that globally around one in ten women use alcohol in pregnancy, with one in 67 having a child with foetal alcohol syndrome³¹. In the UK, Confidential Enquiries into Maternal Deaths³² have recently highlighted the increasing prevalence of substance misuse among women who died in the perinatal period and the poor maternity and mental health care they often received.

The historical focus on mothers' perinatal mental health reflects a variety of epidemiological, scientific, service-related and sociological factors. Recently, fathers' mental health has rightly gained greater attention, with epidemiological evidence suggesting an unmet treatment need for paternal depression and anxiety^{33,34}. There is also growing evidence on the adverse effects of untreated paternal mental illness on mothers' mental health³⁵, and its association with adverse child emotional and behavioural outcomes^{36,37} and child maltreatment³⁸, particularly when children are exposed to a combination of parental mental illness, parental substance misuse and inter-parental conflict^{7,36}.

ASSOCIATION BETWEEN PERINATAL MENTAL DISORDERS AND MATERNAL AND CHILD MORBIDITY AND MORTALITY

Maternal mortality, suicide and self-harm

Perinatal mental disorders are associated with deaths from suicide, substance misuse complications and the misattribution

of physical symptoms of life-threatening complications (e.g., pulmonary embolism) to mental illness in women with, for example, anxiety disorders or schizophrenia³². In addition, as mental disorders are associated with poverty, physical health complications, interpersonal violence and other forms of disadvantage, women with mental illness are more likely to experience life-threatening complications (sometimes referred to as “near misses”) than those with no mental illness³². Of note, evidence from the US National Violent Death Reporting System found interpersonal violence among nearly half of the mothers who died by suicide, in addition to deaths from domestic homicide³⁹.

While suicide is a leading cause of death during the perinatal period in HICs (accounting for 5 to 20% of maternal deaths)⁴⁰, it is a modest contributor to deaths in LMICs: in a systematic review and meta-analysis, the pooled prevalence was 1.00% for suicide (95% CI: 0.54-1.57) and 5.06% for injuries (95% CI: 3.72-6.58)⁴¹. Reclassifying the leading suicide methods from injuries to suicide increased the pooled prevalence of pregnancy-related deaths attributed to suicide to 1.68% (95% CI: 1.09-2.37)⁴¹.

The Eastern Mediterranean (3.55%, 95% CI: 0.37-9.37), Americas (3.03%, 95% CI: 1.20-5.49) and Southeast Asia (2.19%, 95% CI: 1.04-3.68) regions have the highest prevalence of suicide in the perinatal period, with the Western Pacific (1.16%, 95% CI: 0.00-4.67) and Africa (0.65%, 95% CI: 0.45-0.88) regions having the lowest⁴¹. However, rates may be underestimated, due to different definitions of maternal mortality (e.g., during pregnancy and up to six weeks after birth, or during pregnancy and up to one year after birth), and because rates are based on whether the death certificate records pregnancy or recent childbirth.

In 2012, the WHO introduced the International Classification of Diseases for Maternal Mortality (ICD-MM), which recommended the significant change of classifying all suicides in pregnancy and up to 12 months postpartum as direct obstetric deaths, in order to reduce under-reporting and improve data collection⁴².

Suicide risk in the perinatal period is drastically increased in women with moderate to severe mental illness as compared with mothers with no psychiatric history⁴³ (mortality rate ratio = 289.42; 95% CI: 144.02-581.62). Suicide risk is related particularly to severe depression^{40,44}. Suicides may occur less commonly in women with other diagnoses, including bipolar disorder, schizophrenia and personality disorder⁴⁴. Deaths more often occur in the second half of the first postpartum year. Recent studies have highlighted that women may not be receiving active psychiatric treatment at the time of their death⁴⁴.

A significant proportion (a quarter in the past three months according to one study)⁴⁴ of women self-harm before suicide, and self-harm in women with first-onset severe mental disorder is a risk factor for later suicide⁴⁵. Self-harm in the perinatal period has only recently been highlighted as a public mental health issue⁴⁶. A systematic review of 39 studies (reporting on 19,191,431 pregnancies)⁴⁷ found that perinatal self-harm is relatively rare (though this may partly reflect detection bias) other than in women with severe mental illness. Indeed, in a study using secondary care electronic health records of women with psychotic mood disorder and schizophrenia, 8% self-harmed during pregnancy⁴⁸.

Self-harm history is an important marker for perinatal mental disorders^{49,50}, and is associated with adverse obstetric and neonatal outcomes⁴⁷. However, it is not routinely asked about in women during pregnancy and postpartum.

Obstetric and neonatal outcomes

It is well established that women with both common mental disorders and severe mental illness have an increased risk for adverse obstetric and pregnancy outcomes, including preterm births and foetal growth impairments⁵¹⁻⁵⁵. Furthermore, women with severe mental illness also have increased risks of pre-eclampsia, antepartum and postpartum haemorrhage, placental abruption and stillbirths⁵³⁻⁵⁵.

It is also increasingly clear that these risks are elevated regardless of pharmacotherapy during pregnancy^{51,52,56}, suggesting causality beyond medication⁵⁵. This is unsurprising, given the higher prevalence of well-established obstetric risk factors among women with perinatal mental illness, including distal risk factors (such as domestic violence, and poor or delayed antenatal care) and proximal risk factors (such as obesity, gestational diabetes, hypertension and smoking)^{5,6,55,57}.

In general, the risks are greater among women in LMICs than HICs, among those with chronic severe mental illness, and among those with important concomitant conditions such as smoking, substance misuse, poverty and domestic violence.

Infant and child outcomes

There is a large evidence base on associations between perinatal mental disorders and childhood adverse mental health outcomes, particularly for perinatal depression⁵⁸ and antenatal alcohol misuse⁵⁹. The association between prenatal alcohol exposure and childhood cognitive impairment is not only supported by observational data, but also by at least one randomized controlled trial (RCT) and 16 quasi-experimental studies (including nine Mendelian randomization studies and seven “natural experiment” studies)⁶⁰.

Our understanding of the effects of antenatal depression exposure on the offspring is largely reliant on preclinical (animal) research and observational studies (that are problematic due to genetic and environmental confounding and other biases such as recall bias or limited follow-up)^{61,62}. The available evidence suggests that *in utero* exposure to both depression and antidepressants is independently linked to biological changes in the developing foetus, affecting the serotonergic system and the hypothalamic-pituitary-adrenal axis, hypothesized to be related to maternal-placental-foetal stress-related mechanisms, including maternal immune activation^{61,64}. Clinically, exposure to antenatal depression has been associated with childhood cognitive and behavioural problems, attention-

deficit/hyperactivity disorder (ADHD) and autism^{7,61,65}. However, there is limited understanding of protective factors that account for the large proportion of unaffected children, despite exposure to significant antenatal maternal illness.

Antenatal anxiety is associated with a small increase in emotional problems in early and middle childhood. However, in several studies, these associations are attenuated or no longer evident after adjustment for confounders. Moreover, in the studies that included multiple informants, these associations were found using maternal but not teacher-reported child outcomes⁶⁶, suggesting recall bias. Interestingly, women with anxiety disorders in one study perceived themselves to have bonding problems, yet the quality of their observed mother-infant interactions at three months postpartum was similar to the general population⁶⁷.

Conversely, women with personality dysfunctional traits have been found to be less sensitive during observed interactions, but they may not perceive themselves as having problems as measured by the Parental Bonding Questionnaire⁶⁸. Other studies also highlight the importance of personality disorder with respect to adverse outcomes such as higher levels of dysregulated infant behaviour⁶⁹.

There is less consistent evidence on post-traumatic stress disorder (PTSD) impacting on maternal sensitivity and mother-infant interactions⁷⁰. Mothers with eating disorders often have comorbid anxiety and depression, and some studies have found that this comorbidity mediates the association with emotional and conduct problems in their children⁷¹. This reflects a more general finding that at-risk children are generally those whose mothers have a cluster of psychiatric, psychosocial and physical concomitant conditions⁷.

Postnatal mental disorders often begin during or before pregnancy, and it is difficult to disentangle the effects of genetics, prenatal exposure and broader familial/social confounding from the discrete effects of postnatal mental illness. However, a key mechanism for transmission of risk to infants, with substantial theoretical and empirical support, is impaired attachment

related to low maternal sensitivity and “parental mentalization”^{72,73}. Insecure or disorganized attachment is associated with externalizing (and, to a lesser extent, internalizing) childhood problems^{74,75}.

Importantly, impaired attachment is more closely related to mothers’ experience of early trauma (including emotional neglect) than to specific maternal diagnoses⁷², underlining the need for a careful developmental history in perinatal settings. Mental illness in both parents and inter-parental conflict are clearly red flags for adverse child outcomes, but positive parenting by a healthy co-parent (mother or father) can buffer children against the adverse effects of perinatal mental illness^{7,36}.

Research has also highlighted the additional impact of risk factors associated with maternal depression (including young age, low educational level, interpersonal violence, poor social support, substance misuse), which explain a significant proportion of the association between maternal illness and children’s externalizing and internalizing disorders. A study using a large English pregnancy cohort found that exposure to each additional risk factor increased the odds for an internalizing and externalizing disorder⁷⁶, underlining the need for multidisciplinary treatment approaches.

In terms of physical health impact in infancy, a recent systematic review found that postnatal depression was associated with increased mortality and hospitalization among children in the first year of life⁷⁷. In LMIC settings, an association was found between postnatal depression and one of the leading causes of infant mortality, diarrheal illness, but confounders were not adequately addressed in the included studies⁷⁸.

Whilst there are plausible causal mechanisms linking postnatal depression to infant morbidity, including poor maternal care and reduced help-seeking, the evidence for direct causation is limited^{79,80}. Nonetheless, perinatal mental disorders are likely to be a marker for high-risk infants, particularly in LMICs and, for severe mental illness, in HICs.

INTERVENTIONS

Perinatal individual level interventions

Efficacy of psychological and psychosocial interventions

Recent systematic reviews provide robust evidence (>49 RCTs) that psychological and psychosocial interventions for postnatal depression are effective and cost-effective^{81,82}.

Most psychological intervention trials have tested cognitive behavioural therapy (CBT) modified for postnatal depression, but there is also evidence of clinical effectiveness for a range of other interventions, including interpersonal therapy (IPT), listening visits, and exercise. Some uncertainties remain regarding effect sizes, but there is consistent evidence of improvement in depressive symptomatology.

RCTs of interventions using new modalities for delivery, namely online CBT or behavioural activation, for perinatal depression have also demonstrated robust effects in several countries⁸³⁻⁸⁵.

There is a smaller but similar literature on treatment of mental disorders during pregnancy. A systematic review of 29 trials (2,779 patients)⁸⁶, predominantly of depression (28 trials), reported a moderate treatment effect of CBT (seven trials) and to a lesser extent IPT (four trials). This review highlighted the lack of controlled studies for mental disorders other than depression. Recent small trials of guided self-help for antenatal depression provide preliminary evidence of efficacy of low-intensity interventions^{87,88}.

A systematic review of studies of interventions for perinatal anxiety disorders similarly highlighted the limited data (and high levels of heterogeneity), but found evidence of significant reductions in anxiety symptom severity with interventions also used at other times in a woman’s life⁸⁹. There is also some evidence from small trials suggesting that CBT can reduce symptoms in women with blood and injection phobias in pregnancy⁹⁰, PTSD and depression in mothers who have babies on a neonatal intensive care unit^{91,92}, and post-

natal OCD⁹³.

There is a parallel literature examining the impact of transdiagnostic interventions for the intergenerational cycles of developmental trauma often associated with perinatal mental disorders^{73,94}. In addition, some perinatal interventions target depression, anxiety and/or trauma symptoms *and* other risk factors for adverse child outcomes, such as substance misuse, smoking and unsafe infant care practices, with promising results⁹⁵.

Most trials have been conducted in a Western country (usually Australia, US or UK), but some high-quality RCTs have also been carried out in low-resource settings, documenting that CBT-based interventions delivered by trained community mental health workers⁹⁶ or peers⁹⁷ can be effective and cost-effective when compared to enhanced usual care only⁹⁸, though this was not found in all settings⁹⁹.

In addition to the effect on depression in mothers, trials have also examined subsequent impact on infants, though with mixed findings. For example, a systematic review found evidence from 13 studies in LMIC settings that psychosocial interventions for perinatal depression delivered by supervised non-specialists were not only effective at reducing maternal depressive symptoms, but also led to improved infant growth and vaccine uptake as well as reduced diarrheal disease in some studies¹⁰⁰. Some small trials in HICs also suggest that psychological interventions for depression may be associated with improved infant outcomes such as stress reactivity¹⁰¹, but larger RCTs are required to detect clinically meaningful effects.

While women clearly need interventions tailored for pregnancy and subsequent relationships with their infant, there seems to be no reason to assume that treatments which are effective at other times in a woman's life would not be effective in the perinatal period. Many different tailored manuals for perinatal interventions have been developed, but some have argued that the most important aspects of psychological interventions are experience and flexibility of therapists¹⁰².

In summary, there is a reasonably good evidence base on psychological and psychosocial interventions, particularly for

perinatal depression, largely mirroring the evidence on interventions outside the perinatal period.

Efficacy of pharmacological interventions

In the general population, the rate of psychotropic drug use has roughly doubled in the past two decades, with a disproportionate increase among young women, of whom around one in ten are prescribed an antidepressant in HIC settings^{103,104}. There is concern that psychotropics are overused in these young women, particularly those with mild symptoms or with psychosocial risk factors that could be better addressed by non-pharmacological interventions^{105,106}.

To our knowledge, there are no published RCTs of psychotropic drug use during pregnancy, due to concerns regarding the ethics of such trials. The challenge is to reach a consensus among researchers, clinicians and patients on the group of women for whom there is clinical equipoise that would justify such trials. There are, however, ongoing trials evaluating antidepressants in pregnancy, with some focusing on child safety rather than efficacy for the mother as a primary outcome¹⁰⁷.

The much larger observational evidence base on psychotropic drug use in pregnancy has also placed a greater emphasis on safety for the exposed child than on efficacy for the mentally unwell mother⁵⁵. This focus on risk of harm to child is reflected in high rates of psychotropic drug discontinuation during pregnancy in women with bipolar disorder¹⁰⁸⁻¹¹⁰, exceeding discontinuation rates of the same medications for epilepsy¹¹⁰.

The available evidence suggests that there is both an overuse of psychotropic medications among women with milder disorders or for a broader range of conditions than is supported by research^{111,112}, as well as an underuse and inappropriate discontinuation for women with more severe disorders associated with a high relapse risk^{14,113}.

A recent systematic review identified five small studies on lithium continuation and one study on lamotrigine continua-

tion (with a total of 126 women across all six studies), and found that mood stabilizer continuation was associated with up to two-thirds lower risk of relapse during pregnancy²⁴.

There is an even smaller evidence base for antidepressant continuation during pregnancy, with findings from two studies suggesting that these medications may be protective for women with severe depression but not for those with milder depression^{111,113}. There are limited efficacy data for other conditions and medication groups. Confounding is possible: women with stable social situations and insight into their illness may be more likely to remain on prophylactic medication.

There is also reasonable evidence from RCTs for efficacy of antidepressants in the postnatal period, but little data on efficacy of antipsychotics. A recent large cohort study using electronic medical records did not find a beneficial independent effect of prophylactic medication in women with affective or non-affective psychosis in the first three months postpartum¹¹⁴.

Clinical guidance emphasizes the need for individual risk-benefit analyses regarding psychotropic use in pregnancy^{2,55}, reflecting a move towards individualized decisions for antidepressant use in the general population¹¹⁵. As with all finely-balanced clinical decisions, the emphasis is on good-quality counselling, addressing risks of both treated and untreated illness, giving clear information regarding absolute (not relative) risks of adverse outcomes, and enabling women to make informed decisions.

There is some evidence that women often over-estimate medication (including antidepressant) teratogenic risks¹¹⁶, and that evidence-based counselling can enable them to restart medication where needed¹¹⁷. Two recent pilot trials of a decision aid to help women decide whether or not to use antidepressants in pregnancy have reported preliminary evidence of efficacy^{118,119}.

Adverse outcomes

As with other psychotherapy research, the perinatal literature on psychological

and psychosocial interventions rarely reports adverse outcomes, and it is not clear whether this is due to lack of these outcomes or a failure to record them. By contrast, there is an extensive literature on potential risks of antidepressants, mood stabilizers and antipsychotics.

Over the last two decades, there has been an improvement in the quality of observational harm studies, with the use of advanced statistical techniques and more robust methodological approaches that aim to isolate the effect of *in utero* medication exposure. In general, better designed studies have reported smaller or null harm effects compared with earlier, smaller or less well-designed studies^{55,120}. However, the possibility of residual confounding needs to be understood by clinicians and women.

There is clear evidence of teratogenic and neurodevelopmental harm from valproate, mainly from research into treatment of epilepsy in pregnancy, with a recent European regulatory ban on its use in all women of childbearing age, unless use is unavoidable and women are enrolled in a pregnancy prevention programme¹²¹.

For other psychotropics, the evidence suggests less significant harm, but is more challenging to interpret. In general, recent systematic reviews indicate that, once confounders are taken into account, selective serotonin reuptake inhibitors (SSRIs) are not associated with a clinically important increase in the risk of congenital malformations¹²² or growth impairment¹²³. SSRIs and other antidepressants may be associated with a small risk of prematurity, especially when used in the 2nd and 3rd trimesters¹²³⁻¹²⁵, though this could reflect residual confounding by indication.

SSRIs have been linked to an increased risk of a severe respiratory neonatal condition (persistent pulmonary hypertension of the unborn), but with a small absolute risk of around 3 in 1,000 reported in a recent systematic review¹²⁶.

There is considerably less evidence on longer-term neurodevelopmental outcomes, but an emerging consensus that findings from preclinical (animal) studies may not apply to the human population¹²⁷. For example, an initially concerning safety

signal of an association between *in utero* exposure to SSRIs and autism spectrum disorder¹²⁸ is not supported by more recent, better quality evidence that takes into account confounding by underlying illness and familial variables^{125,129}.

Children of women with antenatal depression are at increased risk of autism spectrum disorder, and the risk is similar for siblings with and without *in utero* antidepressant exposure¹²⁹, and following maternal antidepressant use pre-pregnancy as well as during pregnancy¹³⁰, again suggesting the absence of a causal association.

The safety of antipsychotics has been less well studied, but evidence may be prone to even greater confounding by indication and comorbidity. In general, there is no evidence that antipsychotics are major teratogens, but their use may be associated with greater metabolic risks for the mother and growth impairment in infants (including risk of being large for gestational age among babies exposed to second-generation antipsychotics)⁵⁵.

There is a striking lack of evidence on psychotropic use for perinatal mental disorders in LMICs, with one recent systematic review identifying only one RCT that investigated psychiatric medications⁹⁸. This is an important evidence gap, since medications may have a different impact in women at risk for nutritional deficiencies and low body mass index.

Efficacy and safety of other interventions

Electroconvulsive therapy (ECT) may be considered for women with life-threatening complications of perinatal mental disorders (e.g., catatonia, no food or fluid intake, suicide risk), in whom the key consideration is the balance of risks of untreated illness versus ECT risks⁷. Data from case series indicate that ECT is overall safe in these clinical emergencies, but may be associated with pre-term birth.

Other physical treatments, such as transcranial magnetic stimulation, have limited clinical indications¹³¹, may not have sustained benefits beyond a few weeks post-treatment, and have limited pregnancy

safety data¹³², so that further research is warranted.

The novel medication brexanolone, a neurosteroid that acts as a positive neuromodulator at GABA-A receptors^{133,134}, has been developed for postpartum depression and approved by the US Food and Drug Administration for this condition in 2019¹³⁵. Small RCTs (N=246) compared the efficacy and safety of a 60-hr brexanolone infusion vs. placebo infusion, with the primary outcome being the mean Hamilton Depression Rating Scale (HAM-D) score at the end of the infusion period. Lower mean HAM-D scores in the intervention group immediately post-infusion and at 30-day follow-up were reported¹³⁴.

Caution regarding the use of this new medication has been suggested on scientific, clinical and cost-effectiveness grounds¹³⁵, including concerns that findings reflect statistically significant but not clinically meaningful differences.

Limitations of current research into individual level perinatal interventions

Several limitations of current research into individual level perinatal interventions can be pointed out. As with other research¹³⁶, there is limited use of clinically significant patient-defined outcome measures. Moreover, infant care itself can generate symptoms that in some studies are attributed to perinatal mental disorders (e.g., the HAM-D three items on sleep). Evidence of safety is dependent on long-term outcomes, which are rarely collected.

The Edinburgh Postnatal Depression Scale¹³⁷, the most commonly used scale in perinatal RCTs, has been translated into more than thirty languages and has reasonable diagnostic accuracy. However, many studies of this diagnostic accuracy have used methods subject to bias. An individual participant data meta-analysis is underway to address some of these problems¹³⁸. In addition, many translated versions have lower precision in LMICs: in a systematic review of 12 studies, only one study met all criteria for culturally sensi-

tive translations¹³⁹.

Research into the psychometric properties of quality of life measures finds that the Short-Form Six-Dimension (SF-6D) may better capture the effectiveness of perinatal interventions than the more frequently used EuroQol-5D-5L (EQ-5D-5L)¹⁴⁰, though replication is needed to inform future studies of cost-effectiveness.

There has been little research on interventions for women across the diagnostic spectrum and for interventions that target concomitant conditions. When these conditions are identified, there is promising evidence that they may be sensitive to treatment. For example, integrative collaborative care can improve PTSD symptoms¹⁴¹, in addition to the main target of depression; and guided self-help can include modules on smoking and partner abuse, in addition to a focus on depressive symptoms⁸⁷, with reductions found in both symptoms and comorbid problems¹⁴².

Indeed, integrated interventions following comprehensive assessment are essential for holistic perinatal care, but relatively few have been developed. For example, in clinical practice, pregnant or postnatal women with mental disorders and multiple comorbid problems may need to be referred to separate smoking cessation, weight management and substance misuse services.

The development of a core outcome set^{143,144} for perinatal treatment trials across the diagnostic spectrum, and for interventions that target comorbid problems, could facilitate the agreement among researchers on optimal measures and ensure comparability of results in future trials. One such set for perinatal depression is underway¹⁴⁵.

A powerful narrative has argued that intervention in the perinatal period would protect children from long-term adverse developmental outcomes, with significant health and economic gains. However, the direct evidence base for perinatal mental health interventions improving child outcomes is limited, and needs to be considered in the context of concomitant exposure to other familial adversities¹⁴⁶.

In addition, some disorders (e.g., perinatal depression) are known to be associated with poorer quality mother-infant inter-

actions (a key mediator of child behavioural outcomes). So, an important research question is whether effective treatment of depression (or other disorders that impact on mother-infant interactions) remove the need for additional support with parenting. To our knowledge, little research directly examined this issue. However, research analyzing outcomes of young children of women treated for depression in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial found that remission of maternal depression after three months of medication treatment was significantly associated with reductions in the children's diagnoses and symptoms¹⁴⁷.

Furthermore, in a trial in which an intervention effectively treating depression was associated to either an additional parenting video-feedback therapy intervention or a control treatment of progressive muscle relaxation, child development outcomes were in the normal range in both treatment groups¹⁴⁸. This trial suggests that additional therapy may not be needed when effective treatment for postnatal depression is available¹⁴⁹. Further research is needed on whether and which women with perinatal mental disorders would benefit from help with parenting, in addition to treatment of the disorder.

Preconception individual level interventions

There is an emerging literature reporting an association between preconception mental health and perinatal depression¹⁸, mother-infant bonding⁵⁰, and infant and child outcomes¹⁵⁰⁻¹⁵². Clinical guidelines and public health professionals are increasingly highlighting the opportunity for improving preconception health when women *plan* a pregnancy.

Traditionally, the focus of preconception interventions has been on optimizing nutrition in early weeks of pregnancy, but more recently this has been extended to include mental health¹⁵³ and other psychosocial factors¹⁵⁴. Perinatal mental health professionals in HIC settings are increasingly offering preconception advice, though with a primary focus on optimizing medication, rather than a broader

spectrum of preconception interventions for nutrition, obesity, interpersonal violence and other relevant factors.

There have been no trials, to our knowledge, that have examined whether preconception mental health interventions improve distal maternal and infant outcomes, but there is a growing literature on what women with mental disorders would like from preconception care. Qualitative studies involving women with psychotic and mood disorders highlight their wish to receive non-judgmental care, better family planning information from generic services, as well as information on adverse effects of medicines on foetal and infant development, on genetic risk to future children, and on risk of relapse if prophylactic treatment were to be stopped¹⁵⁵⁻¹⁵⁹.

Women have also commented on previous traumatic experiences of being told not to get pregnant at all^{155,156}. For most, if not all, women with severe mental illness, the centrality of motherhood in their lives is clear.

Women also expressed dislike of the terminology of "high risk", which they found unhelpful and anxiety provoking¹⁵⁵. Similarly, warnings about preconception health can be potentially damaging, reduce feelings of agency and choice, and at worst push women further into destructive practices. For example, women with eating disorders have described how warnings regarding the impact of their condition on fertility led them to further dietary restriction and purging¹⁶⁰.

Many women with severe mental illness (and in the general population) have unplanned pregnancies, so it is unrealistic to expect more than a small proportion of women to access preconception care even where it is available. We have, therefore, recently suggested that generic adult psychiatric services should include routine preconception discussions within usual care¹⁶¹. Medication reviews, for example, could be an opportunity to discuss physical and mental preconception health, including pregnancy planning, relationships, nutrition, physical exercise, weight management, smoking, substance misuse, and folic acid supplementation.

People with severe mental illness may

not respond to traditional public health campaigns, and therefore targeted interventions may be key. Thinking about pregnancy early could also minimize safeguarding concerns. Indeed, pregnancy planning could be a central part of recovery. Currently, the right to a family and optimizing medication for a future pregnancy may still be often met with discouragement or prohibition^{155,157}.

Public health interventions

The perinatal mental health literature is focused on individual women as the main agent for change. However, social determinants of mental health – poverty, racism, gender disadvantage and other structural inequalities, food insecurity, gender-based violence, poor housing, limited education and social networks – are all of critical importance for women in the perinatal period.

Indeed, interventions often include addressing these determinants at the individual level (e.g., referring to smoking cessation services, writing letters of support for better housing or secure migrant status, referring to local community groups to increase social networks).

Moreover, psychiatrists have an important role in advocating for, and implementing, policies that target social determinants across different sectors¹⁶². These will vary depending on the context, but could include policies involving the criminal justice system (particularly in relation to domestic violence or trafficking), minimum alcohol pricing to reduce foetal alcohol syndrome and family violence, smoking bans, and welfare benefits.

Within a conceptual framework that includes the United Nations Sustainable Development Goals, psychiatrists can also: a) help design policies that attenuate risks of perinatal mental health problems (e.g., provision of targeted support for low-income young families, parenting support including free child care, microfinancing in LMICs); b) carry out research on the effectiveness of interventions that aim to address the social determinants of mental disorders; c) examine the mechanisms by which social determinants affect perinatal

mental disorders; d) examine how best to implement interventions at scale; e) examine cost-effectiveness of universal vs. targeted interventions¹⁶³.

While the focus of this review is on treatment rather than prevention of perinatal mental disorders, we agree with recent arguments in this journal¹⁶⁴ that current prevention programmes for depression do not target the strongest determinants of risk and are not structurally embedded in major social systems. This is also the case for perinatal mental disorders. In addition, the focus on women overlooks the role of fathers' parenting skills, and the impact of family violence on children. There is a risk of "blaming" mothers for the health of future generations¹⁶⁵, when the need for family and system level interventions is clear.

Paternal interventions

In view of the growing recognition that paternal mental health is also a cause of morbidity for the family, and the increasing involvement of fathers in parenting, interventions for expectant and new fathers are seen increasingly as an important focus for research.

The most recent systematic review of paternal interventions¹⁶⁶ identified only 11 studies (including eight RCTs). Most studies evaluated psychosocial programmes (predominantly in the antenatal period), but several of them had significant methodological limitations.

An alternative approach is family interventions. A recent systematic review found two small treatment trials of couple interventions which were associated with improvements in maternal depressive symptoms¹⁶⁷. As with research into maternal interventions, a core outcome set would be useful to improve methodological rigour.

Beyond this literature on paternal-specific interventions, international guidelines on perinatal mental health recommend that services primarily supporting women involve and support their partners and wider families too. While the evidence reviewed in this paper is clear that partners and families have an important influence

on women's perinatal mental health, there is a smaller evidence base on their influence on women's access to care and their own interactions with services.

A meta-synthesis of 20 studies of the experiences of fathers reported that services tend to focus on individual women (and babies), with a marginalization and neglect of women's partners and an unmet need for information by these partners¹⁶⁸. A recent qualitative study, based on separate interviews with women with mental illness and a participant-nominated "significant other", also emphasized the complexity of involving and supporting partners and families, particularly when relationships are poor¹⁶⁹.

SERVICE DELIVERY

Research into the effectiveness of different perinatal mental health service delivery models is in its infancy. The public health and clinical challenge for both general and perinatal psychiatry is to develop services designed to provide personalized medicine with timely assessment and treatment of perinatal mental disorders and comorbid problems, including avoidance of unnecessary medication at the expense of evidence-based psychological therapies, whilst identifying which women with moderate to severe illness would benefit from psychotropic prophylaxis/treatment and/or parenting support.

Furthermore, in light of the high prevalence of the experiences of trauma in pregnant women with mental disorders, trauma-informed interventions in the perinatal period need systematic evaluation⁹⁴. If a key aim of perinatal mental health services is to minimize intergenerational psychopathology, then a family-focused, rather than a mother-focused individual approach, is likely to better meet this aim³⁶.

Preconception care

Preconception advice is highly valued by women with severe mental illness¹⁵⁵. The relative effectiveness of provision of preconception interventions in generic vs. specialist care is not known, but in

general it is perinatal psychiatrists who offer preconception advice, and research is underway to explore its effectiveness in the UK.

Initial evaluations of innovative case management interventions for women with repeated custody loss also show promising results¹⁷⁰.

Case identification in universal/primary care services

Early identification of perinatal mental disorders necessitates detection in universal services, which vary by country but can include primary care, midwives/obstetricians and home visiting nurses/paediatricians. Mental health care is accessed by only a small proportion of women with mental disorders¹⁷¹, and there have been many debates on screening, with divergence in national recommendations¹⁷²⁻¹⁷⁵. Further systematic reviews are underway¹⁷⁶. However, case identification by trained staff (who can be supported by use of screening tools) is good clinical practice, and the evidence suggests that it would be cost-effective in HIC settings where there are services to provide treatment.

There is less clarity on whether use of screening tools by health practitioners who are not experienced/trained/skilled in talking about mental health is helpful or potentially harmful, and whether it is cost-effective. Some would also argue that identification of the extent of psychological morbidity in pregnant and postnatal women, even where services are limited, is an important public health first step in leverage for efficient stepped perinatal mental health care¹⁷⁷.

Routine enquiry into mental health may require careful consideration of how to prepare the maternity environment, particularly for mental health task-shifting initiatives in LMICs¹⁷⁸. In HICs, most women welcome the opportunity to talk about mental health¹⁷⁹, and there are no differences in acceptability of different modes of screening tool (e.g., paper vs. iPad)^{179,180}, as long as women are given the opportunity to talk and are referred appropriately¹⁷⁹.

Some women, however, particularly those with mental health problems or histories of trauma, find disclosure difficult and routine enquiry less acceptable^{179,180}. In LMICs, there may be additional cultural barriers and stigma^{181,182}.

Case identification of perinatal depression is often facilitated in universal services by tools such as the self-administered Edinburgh Postnatal Depression Scale, the Patient Health Questionnaire-9, or the two depression screening questions (the Whooley questions)¹⁸³. However, there is a high prevalence of other mental disorders in the perinatal period, which, in addition to perinatal depression, are also associated with considerable morbidity. So, some have suggested the use of other tools to detect these disorders.

There is very limited evidence to support this. A recent study on the diagnostic accuracy of the Generalized Anxiety Disorder 2-items (GAD-2) suggests that its use would be unhelpful, due to the high number of false positives generated³⁰. This is likely to be even more of a problem for less common disorders. However, depression screening tools can also detect other psychopathology¹⁸⁴.

Assessment and treatment of women in mental health services

Once mental health problems are detected, clear referral pathways should facilitate prompt treatment. The Antenatal and Postnatal Mental Health Guidelines produced by the NICE² recommended comprehensive psychosocial assessment by mental health services within two weeks, and treatment within six weeks.

These are challenging targets and mean that generic mental health services would need to fast-track perinatal women and/or specialist perinatal mental health services to be sufficiently resourced to treat women quickly.

The above guidelines also recommend that assessment should include the relationship with the baby, but it is not clear which tool could be used by mental health practitioners to identify women (and partners) needing extra help with this relation-

ship.

Barriers to access

Some groups may need additional outreach to facilitate assessment and treatment. Teenagers and young women under 25 are at particularly high risk of having perinatal mental disorders, particularly anxiety disorders and PTSD³⁰, yet are groups that may not access timely antenatal care or mental health services. In secondary care, early intervention services have been specifically designed to facilitate access by young people with psychosis, but perinatal mental health services have not yet been designed with a focus on outreach for young people.

Barriers to access for other groups have also been identified across the care pathway – for example, ethnic and socio-economic differences in initial identification by universal services¹⁸⁵, and socio-economic differences in access to inpatient mother and baby units¹⁸⁶. Qualitative research finds that different professional groups use different languages to communicate risk and have different perspectives of mental illness severity. Organizational barriers to access include unclear thresholds for escalating care and poor infrastructure for sharing information¹⁸⁷.

Qualitative meta-syntheses of studies in women with mental illness report several additional barriers for effective identification and intervention: fear of stigma, fear of custody loss, and anxiety about being prescribed psychotropic medications due to concerns about exposure in the unborn child^{157,188}.

Community and outpatient perinatal mental health care

Little is known currently about which community service models would best support women with the full range of diagnoses and complex needs. Qualitative research has found that, while women generally appreciate the tailoring of care to their perinatal specific needs, they also highlight that care from specialist teams

can mean disruption of continuity in community care¹⁸⁹.

Trials in US obstetric settings report a significantly greater improvement in depression in pregnancy and postpartum, compared to usual care, where integrative collaborative care includes an engagement session, assessment by a care manager, choice of support with antidepressant medication or a psychotherapy, and outreach for missed appointments^{141,190}.

Models of collaborative care in psychiatric settings liaising between maternity, primary care, generic community psychiatric care and specialist perinatal mental health care need to be developed and evaluated for women with perinatal mental disorders.

Current specialist perinatal mental health service models often exclude certain groups (e.g., women with comorbid substance misuse problems and/or personality disorder or experiences of child removal by social services)¹⁹¹. There has been remarkably little research on how services can best help women with complex mental health needs that are likely to impact on the mother and the child. Women often have themselves a history of developmental trauma, including removal from their own parents who may have been violent and abusive, and other experiences of childhood maltreatment¹⁹².

Similarly, there is relatively little research into services for women with schizophrenia and related disorders, who, despite some evidence of reduced fertility, are likely to be pregnant at some point in their lives^{193,194} and, from a human rights perspective, have the right to family life, with support if needed wherever possible, while ensuring safeguarding of children.

In practice, many countries do not have practitioners trained specifically for the perinatal period. Qualitative studies suggest that receiving interventions within generic services can be experienced as unhelpful by women^{189,195}, partly due to the therapists' failure to understand the potential impact of mental disorders on maternal functioning¹⁹⁵, and poor facilities for infants^{169,195}, though, as RCTs in LMICs demonstrate, task-shifting is possible if staff are suitably trained⁹⁶.

Where specialist community perinatal

mental health services are available, the optimal skill mix of such services is not yet known. In the UK, for example, community multidisciplinary perinatal mental health teams now usually include most if not all of the following: psychiatrists, psychologists, mental health nurses, social workers, nursery nurses, an occupational therapist and a specialist pharmacist. Interventions include psychological therapies, medications, support in the relationship with the infant, and care planning including for women with a history of moderate to severe illnesses who may relapse in the postnatal period. Services have also recently expanded their remit to mental health assessment of partners¹⁹⁶. Research in the effectiveness of these teams is underway. However, as staff in generic services need to address the needs of women of child-bearing age, there is a potential risk of such perinatal mental health services deskilling staff in community and generic care.

Further evidence is needed on whether extension of services to the second year after birth is effective and cost-effective. However, quantitative and qualitative evidence supports the idea that the second year after birth is an important time for intervention. There is evidence of care needs after discharge from inpatient care¹⁹⁷, increased symptoms in the years 1-4 postpartum¹⁹⁸, a continued risk period for suicide beyond the first year after birth⁴⁵, and the importance of the first 1,001 days of the infants' life (from conception to age 2)¹⁹⁹. This evidence also highlights the importance of generic psychiatric care, which needs to "think family" after the first two years postpartum.

Inpatient care

The provision of psychiatric inpatient mother and baby units around the world varies considerably²⁰⁰. However, these units have been established in several European countries, Australia and more recently Sri Lanka, India, the US, and New Zealand.

Mother and baby units provide mental health care for mothers, alongside care of the infant(s), and aim to treat the mother's mental illness and promote the facili-

tation of mother-infant interactions²⁰⁰.

Consensus on the structure and staffing of these units varies internationally, but individual jurisdictions have produced guidance on skill mix and the minimum number of beds needed to retain specialist skills^{201,202}. There are differences also in the nature of care for the infant (which varies from care provided by nurses, families providing care also within the unit, to a lack of facilities to admit infants overnight, so that infants are cared for at home other than for a few hours each day on the unit)²⁰³⁻²⁰⁵.

Before-and-after assessments of the clinical and social care outcomes of patients attending mother and baby units indicate considerable improvements at discharge^{203,205}. The extent of improvement is, however, adversely impacted by key clinical and demographic factors, such as a diagnosis of schizophrenia or personality disorder, low social support and low socio-economic status²⁰⁶.

We have recently completed the first study using a quasi-experimental design to examine the effectiveness and cost-effectiveness of mother and baby units compared with generic acute psychiatric wards or crisis resolution teams (teams available daily providing intensive treatment at home)²⁰⁷. Analysis is underway to examine the effectiveness of mother and baby units in reducing readmission rates and other outcomes, including improving quality of mother-infant interactions one month after discharge.

RESEARCH IMPLICATIONS

Perinatal mental health research is increasingly seen as critical to public mental health, but evidence gaps mean that there is a need for:

- large RCTs on effectiveness and cost-effectiveness of interventions for the full range of disorders, including complex PTSD, eating disorders, anxiety disorders, autism and psychosis, in pregnancy and after birth;
- intervention studies in women with perinatal mental disorders that have adverse obstetric/pregnancy outcomes – obstet-

ric research (e.g., smoking cessation in pregnancy RCTs) should include better measures of perinatal mental health (to investigate whether this affects treatment efficacy and safety), and RCTs of obstetric interventions modified for this population (in particular, complex interventions that address multi-morbidity) should be conducted;

- research into how to support parenting difficulties, including support for women who experience custody loss;
- research on how to improve access to treatment for women with difficulties due to factors such as poverty, racism, stigma, interpersonal violence;
- research into public health interventions to fight stigma and to address the underlying causes of perinatal mental disorders;
- structured approaches in evaluating large-scale implementation programs, addressing not only maintenance of fidelity of interventions, but also how to facilitate system change with local contextual solutions.

Methodological work needed includes:

- improved measurement (adapting use of current instruments and/or developing new instruments, where needed, for the perinatal period, with robust evaluation of their psychometric properties);
- development of one or more core outcome sets, with the participation of women with lived experience of disorders;
- development of methods so that outcomes related to infant physical and mental health can be included in cost-effectiveness analyses of interventions for perinatal mental disorders²⁰⁸;
- more systematic use of tools when designing and evaluating studies in systematic reviews (e.g., ROBINS-I²⁰⁹ for observational studies of medication outcomes in pregnancy; TIDieR²¹⁰ for trials of psychosocial interventions);
- use of individual participant data meta-analysis, wherever possible, to facilitate systematic adjustment for known confounders and increase precision of estimates.

CONCLUSIONS

Generic psychiatric services will always care for women of childbearing age, many of whom will become pregnant, sometimes planned and sometimes unplanned, and have children. Therefore, mental health professionals in generic services need to be trained to “think family”, so that they can deliver care with a life course lens, having pregnancies and families in mind.

Effective co-designed specialist perinatal mental health care, where available, is likely to impact on psychological morbidity in women and their children, but there is remarkably little known about how best to deliver this care.

Preconception and public health strategies may have the greatest impact on population health, but investment into perinatal mental health services, particularly when underpinned by a larger evidence base on interventions, is likely to reduce suffering for women and positively impact on their families.

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