Maternal depression: risk factors and treatment options during pregnancy

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Key content:
• Psychiatric illness was identified as the leading cause of indirect death in the fifth and sixth CEMACH reports; the decrease in the rate of suicide in the seventh report may indicate that previous recommendations are having a beneficial effect.
• Half of the women identified in the earlier reports had a history of serious mental illness.
• Depression during pregnancy is complex and difficult to treat.

Learning objectives:
• To learn about the background, diagnosis and management.

Ethical issues:
• How aggressive should any active approach be to reduce the risk of maternal death?
• Can the use of pharmacological agents, which can cause fetal toxicity and neonatal withdrawal problems, be justified?

Keywords antidepressive agents / fetal toxicity / selective serotonin re-uptake inhibitors / suicide / maternal death
Introduction
Although depression is not gender specific, women experience major depression twice as often as men. This increased incidence occurs mainly during the reproductive years and is universal and unrelated to culture, race or class. Approximately 10% of pregnant women will experience clinically significant depressive symptoms during pregnancy. Until recently, it was thought that pregnancy and the postpartum period exerted a protective effect against suicide and that the maternal suicide rate was lower than would be expected. The 1997–1999 and 2000–2002 reports on the Confidential Enquiry into Maternal Deaths changed this perception.

The fifth report described 42 psychiatric deaths, 68% of which resulted from suicide—the leading cause of indirect death and the second leading cause of maternal death overall. Subsequently, the sixth report described similar statistics, with suicide the second leading cause of maternal death after cardiac disease and the leading cause of indirect or late indirect maternal deaths. Both reports revealed that half of women who committed suicide had a previous history of serious mental illness, which was related to their last childbirth in a quarter of cases. In most cases, the risk of recurrence was neither identified nor managed in the index pregnancy.

It is believed that many deaths related to drug and substance misuse, violence, accidents and misadventure were unreported. It is likely that these also include suicide.

It should be noted that the method of suicide in both reports was predominantly violent. Methods included hanging, jumping, throat cutting, self-immolation, drowning and intentional road traffic accidents. The majority of women were aged 30 years or over and white.

These reports have highlighted many recommendations that should be followed in an attempt to reduce these harrowing statistics. The seventh report showed a decrease in the rate of suicide; if this decline is sustained in the next report, this may indicate that previous recommendations are having a beneficial effect. It is advised that all women with a history of serious psychiatric illness, peripartum or otherwise, should be assessed by a psychiatrist in the antenatal period, to ensure that a management plan can be drawn up involving all disciplines relevant to their care.

Depression during pregnancy
Women with a history of major depression are at high risk of recurrent depression during pregnancy, especially if antidepressant therapy has been discontinued. For one-third of women, however, this can be their first episode of major depression. Other risk factors for antenatal depression include:

- lack of psychosocial support
- difficulty coping with changes in body image
- hyperemesis gravidarum
- relationship problems
- unplanned or unwanted pregnancy.

Antenatal depression can be difficult to diagnose as many of the biological symptoms of depression are common in nondepressed pregnant women—for example, sleep disturbance. In addition, certain medical disorders during pregnancy, such as anaemia, gestational diabetes, thyroid dysfunction and even hyperemesis gravidarum, can induce depressive symptoms, complicating the diagnosis.

Cohen et al. recently demonstrated that women who discontinued antidepressant medication during pregnancy relapsed significantly more frequently during their pregnancy than those who continued their medication.

Depression in pregnancy creates several challenges, whether treated or not (Box 1). Maternal depression can itself adversely affect the developing fetus: a number of studies have suggested an association between maternal depression and factors that predict poor neonatal outcome.

These include preterm birth, low birthweight, smaller head circumference and low Apgar scores. Increases in serum cortisol and catecholamine levels, typically observed in women with depression, may possibly induce adverse changes in placental function by altering uterine blood flow and inducing uterine irritability.

Dysregulation of the hypothalamic–pituitary–adrenal axis, which is associated with depression, may also have a direct effect on fetal development. Animal studies suggest that stress during pregnancy is associated with neuronal death and abnormal development of neural structures in the fetal brain, as well as sustained dysfunction of the hypothalamic–pituitary–adrenal axis in the offspring.

The physical condition of the mother can also be affected. Poor attendance for antenatal care, together with poor personal care, diet and decreased weight gain have been associated with negative pregnancy outcomes. In addition, pregnant women with depression are more likely to smoke and to take alcohol or illicit drugs.

Self-harm is also more common in pregnant women with severe depression.
Maternal depression has effects on the rest of the family. Interpersonal relationships are strained and mother–baby bonding can be disrupted, which can be detrimental to the development of the infant.6

Studies have also shown that children born to depressed mothers are more likely to have behavioural problems and/or disruptions in cognitive and emotional development.16,18 Lastly, untreated antenatal depression significantly increases the risk of subsequent postnatal depression.19

Pharmacological treatment

Treatmen of depressed pregnant women requires skilled management by a psychiatrist, working collaboratively with the woman and her obstetric team.20 Medication should be used with caution and only after careful analysis of the associated risks and benefits. Many women are reluctant to take medication during pregnancy and feel the need to make a choice ‘between the drug and the baby’. Every woman is individual and each management plan should reflect this. There are several factors to be taken into account when assessing possible drug treatment of the depressed pregnant woman.18 Potential adverse outcomes include fetal toxicity, intrauterine death and major physical malformations, fetal growth restriction, behavioural teratogenicity and neonatal toxicity, all of which are discussed below by individual drug type. Women should be fully counselled about these risks and informed consent sought.20

Tricyclic antidepressants

Tricyclic antidepressants, such as amitriptyline and imipramine, have lower known risks in pregnancy than other antidepressants.20,21 Recent studies have shown no increase in the incidence of miscarriage or malformation with the use of amitriptyline or imipramine.20,21

The risks associated with overdose of tricyclic antidepressants remain, however, as does the issue of tolerability. Doxepin is not recommended as first-line treatment in pregnancy. Tricyclic antidepressant usage during pregnancy has been associated with a neonatal withdrawal syndrome.20 If a tricyclic antidepressant is required throughout pregnancy, therefore, consideration should be given to a dose reduction 3–4 weeks prior to delivery.22,23 Tricyclic antidepressants in overdose present their greatest risk when the mother is unconscious. In the absence of severe maternal toxicity, the prognosis for the fetus is thought to be good and the risks no greater than for the general population.22 It must be remembered, though, that in cases of multiple drug overdose, or when alcohol has been taken as well, there can be an adverse synergistic effect.23

Selective serotonin re-uptake inhibitors

Fluoxetine is the best-documented selective serotonin re-uptake inhibitor (SSRI) used in pregnancy. Information on the safety of other SSRIs in pregnancy is limited, but the US Food and Drug Administration issued a warning in December 200524 advising that the use of paroxetine in the first trimester of pregnancy was associated with an increased risk of birth defects, in particular cardiac defects, compared with other SSRIs. Many studies25–28 have shown that the use of fluoxetine in the first trimester of pregnancy is not associated with teratogenic effects. There is increasing recognition, however, of an association between SSRI use in pregnancy and a neonatal withdrawal syndrome characterised by convulsions, irritability and feeding problems.29 It is not fully understood whether the adverse effects observed in newborns are caused by serotonergic overstimulation resulting from SSRI drug exposure in late pregnancy, or neonatal withdrawal following abrupt cessation of exposure postdelivery.27

Laine et al.29 conducted a prospective controlled follow-up study, with 20 mothers taking 20–40 mg/day of either citalopram or fluoxetine for depression or panic disorder, and 20 matched controls not receiving psychotropic medication for confounding obstetric characteristics. Maternal cord blood and infant blood levels of the SSRIs and their metabolites were measured. The newborns underwent a specific assessment of serotonergic symptoms during the first 4 days of life and at 2 weeks and 2 months of age. This study showed a
problems in the newborn.

orofacial clefts.

in the first trimester has been associated with fetal vasoconstriction can also occur.

flow.

an exacerbation of problems with placental blood

Gestational hypertension may worsen and lead to adverse effects on the central nervous system and that the severity of these symptoms is significantly related to cord blood 5-hydroxyindoleacetic acid levels. There is minimal data on the effects of fluoxetine overdose in pregnancy.

A recent study published in The New England Journal of Medicine suggests a link between the use of SSRIs in late pregnancy and persistent pulmonary hypertension of the newborn. This was a case-control study involving 377 women with infants with persistent pulmonary hypertension of the newborn and 836 matched control women and their infants. The results showed that exposure of an infant to an SSRI after the 20th week of gestation was associated with an increased association with persistent pulmonary hypertension of the newborn (adjusted odds ratio 6.1: 95% CI 2.2–16.8). The study concluded that further research in the area was warranted but that the findings needed to be considered when making decisions about using SSRIs in pregnancy.

Monoamine-oxidase inhibitors

Fetal growth restriction and fetal toxicity are the main problems associated with the use of monoamine-oxidase inhibitors in pregnancy.1 Gestational hypertension may worsen and lead to an exacerbation of problems with placental blood flow. Accumulation of serotonin and subsequent fetal vasocostriction can also occur.2 No neonatal effects have been reported. There is limited data available on the use of many newer antidepressants and they are not, therefore, recommended for treatment.

Benzodiazepines

Benzodiazepines are used in pregnancy for the treatment of seizures and other conditions such as anxiety disorders and panic attacks. There is limited data on benzodiazepine use in pregnancy.3 Their use in the first trimester has been associated with oral clefts.4–6 They may also cause adaptation problems in the newborn.8 Lin et al.9 studied infants exposed to clonazepam monotherapy during pregnancy. They did not observe an increase in major birth malformations in exposed infants. Although this study was larger than previous reports, it was still not large enough to have adequate power.

Somatic therapy

There is an absence of evidence on the safety and efficacy of electroconvulsive therapy in pregnancy, although there is no reason to suppose it is any less effective than at other times. The necessity for its use is likely to be extremely rare. Given the theoretical risk of inducing labour by the induction of seizures and the administration of a general anaesthetic, its use should be avoided in late pregnancy. Nonpharmacological, environmental treatments for depression, such as partial sleep deprivation and rapid transcranial magnetic stimulation, have been proposed in the USA. Avoidance of drug exposure may be valued by women and, therefore, other modalities, though novel, may need to be considered.10

Psychotherapy

The recently published National Institute for Health and Clinical Excellence (NICE) guidelines11 suggest that for women developing mild or moderate depressive illness during pregnancy, psychotherapeutic interventions such as brief cognitive behavioural therapy or interpersonal psychotherapy should be considered. Self-help strategies and non-directive counselling delivered at home can also be useful. They suggest that there should be a lower threshold for access to psychological therapies during pregnancy because of the changing risk–benefit ratio for psychotropic medication.

Summary

Psychiatric illness causes serious morbidity and mortality during pregnancy and beyond. The role of obstetricians and their colleagues in midwifery and general practice is to recognise these high-risk women early in the antenatal period. Psychiatric input is recommended for management and follow-up. There are several different management options available and each should be patient-specific. If we follow the recommendations from the 1997–1999 and 2000–2002 Confidential Enquiries into Maternal Deaths, we could further reduce the rate of maternal morbidity and mortality from serious psychiatric illness.

References

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