CLASS

Balancing emotions: Antidepressant use in pregnancy and breastfeeding

Perinatal depression is common and carries considerable risks, yet patients often receive contradictory information regarding the safety of antidepressant use during pregnancy and breastfeeding. In this article, **Lucy Broughton** sets the record straight and explains how pharmacists can support this important treatment decision

Professional development goals

This CLASStime article supports professional development with respect to:

- Understanding the risks of perinatal depression
- Recognising the benefits and risks of antidepressant treatment during pregnancy and breastfeeding
- Supporting patient decisions surrounding antidepressant use in pregnancy and breastfeeding

As you read, highlight new knowledge or areas where you need to know more. You can also use the Capture button online to keep notes of your thoughts and reflections on this article. This may be useful if you choose to proceed to CLASSact and CLASSmates for this topic.

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- Keeping up to date – go to MyRecert (myrecert.pharmacycouncil.org.nz), select the "Keeping up to date" page of your portfolio, then enter a description of this article
- Reflection on practice
- Towards culturally safe practice

Lucy Broughton is a registered pharmacist undertaking a PhD at the School of Pharmacy, University of Otago, on decision-making around psychotropic drug use in pregnancy; she is also a senior clinical editor at the New Zealand Formulary

CLASStime

Over 10 per cent of people have clinically significant depression during pregnancy. Ethnic minorities are at greater risk. The Growing Up in New Zealand study found the risk of antenatal depression was 1.2 times higher in Māori, 1.9 times higher in Pacific peoples and 2.4 times higher in those of Asian ethnicity, compared with New Zealand Europeans.[1]

Untreated antenatal depression is associated with a multitude of maternal and foetal repercussions, including an increased risk of spontaneous abortion, preterm birth, low birthweight, peripartum complications and stillbirth.[2] These adverse outcomes may be due to a direct effect of stress hormones (eg, cortisol) on the pregnancy, or caused indirectly by behaviours that result from the mood disorder – for example, decreased attendance at antenatal clinics, poor nutrition, and increased risk of smoking and/or other substance abuse (including alcohol).

Antenatal depression also substantially increases the risk of postnatal depression, which is associated with impaired mother–infant bonding and negative neurodevelopmental outcomes in the child.[3] Severe cases of perinatal depression can result in harm to the infant via neglect or infanticide, and maternal harm via self-neglect, self-harm and suicide. Suicide is the greatest cause of maternal death in Aotearoa.[4]

Despite these risks, depression during pregnancy is under treated. A recent study found almost 12 per cent of pregnant people in Aotearoa had clinically significant symptoms of depression but had not received any

Glossary

- **Antenatal depression:** depression occurring during pregnancy (also known as prenatal depression).
- **Postnatal depression:** depression that begins anywhere between the birth of the child up to one year following birth.
- **Perinatal depression:** depression that occurs during pregnancy (antenatal depression) and/or after the baby is born (postnatal depression).

Note: concomitant anxiety is common with perinatal depression and may be the predominant symptom – therefore, it is often referred to as perinatal anxiety and depression. For simplicity, perinatal depression is used in this article.

antidepressant medication during pregnancy. Pacific peoples (23 per cent) and Māori (17 per cent) had a higher risk of unmedicated depression during pregnancy, compared with people of European ethnicity (7.5 per cent).[5]

Two-thirds of patients on antidepressant medication prior to pregnancy discontinue their antidepressant before or during pregnancy, with a higher rate of discontinuation among those of Māori, Pacific or Asian ethnicity than in those of European ethnicity.[6] Discontinuation of antidepressants during pregnancy is associated with high rates of relapse, especially if there is a history of severe or recurrent depression or if medication is stopped suddenly.[7–9]

These findings are concerning, given the higher rates of antenatal depression in non-European groups. Additionally, the risk of maternal suicide is three times higher in Māori than in those of European ethnicity.[4]

Inequities in the diagnosis of depression and anxiety, along with deficits in Pacific and Māori mental health services in Aotearoa, may explain higher rates of untreated depression and discontinuation of antidepressants among pregnant people in these populations. It could also be due to cultural reasons. For example, stigma related to mental illness across Asian cultures may be a deterrent to seeking treatment, or there may be a preference for non-pharmacological treatment options within non-European ethnic groups.[5]

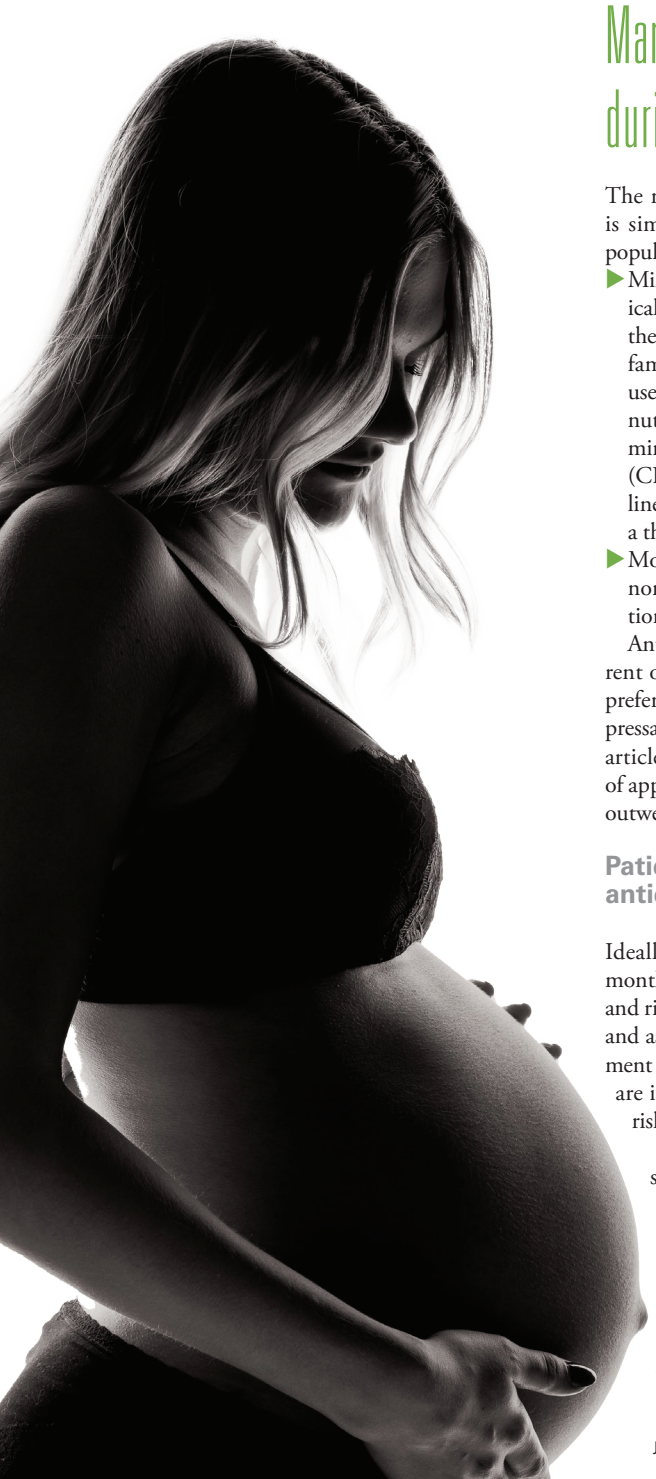
Concerns from both patients and professionals regarding safety of the foetus is a major reason for antidepressant discontinuation during pregnancy.[10] Patients seek safety information from a variety of resources, including friends, family, social media and the internet. However, the information provided from healthcare providers has been shown to be more influential on a patient's decision to stop or continue an antidepressant during pregnancy, compared with other information sources.[11]

To further complicate the decision-making process, pregnancy is a time when patients are likely to engage with several different healthcare providers, including midwives, pharmacists, GPs and specialists. Unfortunately, patients are often given contradictory information from different healthcare providers.[12] This is not surprising – giving medication safety advice to pregnant patients can be challenging and confusing due to the absence of randomised controlled trials in pregnancy, the conflicting nature of the literature, and the amount of misinformation on medication safety during pregnancy.[10]

It is essential that the pregnant patient and their family/whānau are provided with consistent, accurate and balanced information on the benefits and risks of antidepressants in pregnancy to assist them in making an informed decision. Pharmacists, as medication experts, play a pivotal role in providing such information to both the public and other healthcare providers.

Key points

- Non-pharmacological treatment is first line for mild perinatal depression.
- Moderate to severe depression has significant risks for both the birthing parent and the baby; therefore, benefits of antidepressant treatment during pregnancy and breastfeeding usually outweigh the risks of foetal exposure to medication.
- Where possible, pregnancy should be planned and any changes to the medication regimen should be made before pregnancy.
- Routine discontinuation or switching of antidepressants during pregnancy and breastfeeding is discouraged without consideration and discussion of the specific risks (including the risks of relapse) and benefits for that individual. If the decision is made to discontinue, the antidepressant should be slowly tapered, not stopped abruptly.



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Management of depression during pregnancy

The management of depression during pregnancy is similar to managing depression in the general population:[13]

- Mild depression is treated with non-pharmacological interventions, which can include encouraging the patient to find social support through friends, family/whānau or support groups (see panel on useful resources for patients); regular exercise; good nutrition; avoiding alcohol and drugs; meditation, mindfulness, and/or cognitive behavioural therapy (CBT) or other psychological therapies. Free online CBT is available for those who cannot access a therapist (see panel).
- Moderate to severe depression usually requires non-pharmacological interventions in combination with an antidepressant.

Antidepressant selection primarily depends on current or previous response to treatment and patient preference. Although there are some risks of antidepressant treatment in pregnancy (covered later in this article), patients can be reassured that the benefits of appropriately prescribed antidepressants generally outweigh the risks of foetal exposure to medication.

Patients on pre-existing antidepressants

Ideally, pregnancy should be planned at least six months in advance, so there is time to discuss benefits and risks of treatment and to allow time to adjust to, and assess the outcome of, any changes to the treatment regimen. Depression severity and recurrence risk are important considerations when undertaking a risk versus benefit analysis to aid decision-making.

Consideration can be given to tapering and stopping treatment if the patient is currently well and the risk of relapse is low. Non-pharmacological treatment should always continue.

If ongoing antidepressant treatment is required, consideration could be given to switching an antidepressant *before* pregnancy to one that is deemed lower risk in pregnancy (eg, switching from paroxetine to sertraline); however, this can increase the risk of relapse.

If the risk of relapse is high (eg, history of severe illness, recurrent episodes or treatment resistance), the patient should continue the current *effective* treatment regimen during pregnancy and postpartum.

For *unplanned* pregnancy, if the patient is on a pre-existing effective antidepressant, they should generally continue with the same treatment regimen. This is because switching or tapering antidepressants during a vulnerable time and destabilising the mood disorder is considered a greater risk to both maternal and foetal wellbeing than any risk posed by the antidepressant.[14] Additionally, the foetus would already have been exposed to the current antidepressant by the time pregnancy is discovered, and switching medication would increase the number of medications the foetus is exposed to.[3]

Although some resources recommend decreasing the dose during pregnancy, depression should not be under treated. This can result in the baby being exposed to the risks of both the medication and those associated with uncontrolled depression.[3]

Some resources also suggest tapering the antidepressant in the third trimester to minimise the risk of neonatal adaptation syndrome (NAS; discussed later). However, this practice may not attenuate NAS and can place the patient at increased risk of relapse during a vulnerable time.[10]

If the risks of relapse and untreated depression on a pregnancy have been explained, and the patient still wishes to stop their antidepressant, they should be advised to *not* stop the antidepressant abruptly as this can cause discontinuation symptoms and may result in a potentially severe relapse.[15]

Initiating an antidepressant during pregnancy

If there is any history of antidepressant use, previous response to treatment should be used to guide antidepressant selection. The antidepressant that the patient has responded to in the past should be chosen, and antidepressants that have previously been ineffective or not tolerated should be avoided, irrespective of comparative antidepressant safety in pregnancy.

If the patient has not had antidepressants before, selective serotonin reuptake inhibitors (SSRIs)

PANEL

Useful resources for patients

Support for perinatal anxiety and depression

- **Perinatal Anxiety & Depression Aotearoa** provides screening tools, factsheets on antenatal and postnatal anxiety and depression, and locally available support services and helplines – **pada.nz**
- **Mothers Helpers** offers support for mothers with antenatal and postnatal anxiety and depression, including an online perinatal depression recovery course – **mothershelpers.co.nz**
- **Healthify** has information on perinatal depression and anxiety, how it is treated, and a list of available support services – **tinyurl.com/Healthify-PND**
- **Just a Thought** provides free online cognitive behavioural therapy – **justathought.co.nz**

Patient advice on medication safety

There are currently no publicly available, New Zealand-specific patient information leaflets discussing the risks and benefits of antidepressants in pregnancy and breastfeeding. The following factsheets can be helpful, but some brands may not be available in New Zealand, and any phone numbers or organisations listed do not apply to New Zealand.

- Organization of Teratology Information Specialists (US), MothertoBaby factsheets – **mothertobaby.org/fact-sheets**
- UK Teratology Information Service, Best Use of Medicine in Pregnancy leaflets – **tinyurl.com/BUMPS-leaflets**

are generally recommended for first-line treatment:[13]

- Sertraline is the preferred SSRI in pregnancy. It is thought to have the lowest placental transfer of any SSRI and may have the lowest risk of persistent pulmonary hypertension (discussed in more detail later). Additionally, if breastfeeding is desired, it has low infant exposure via milk.
- Escitalopram or citalopram are also relatively safe in pregnancy and breastfeeding and are reasonable alternatives.
- Fluoxetine, while having a reasonable safety profile during pregnancy, is least preferred during breastfeeding as it has a long half-life and may accumulate in milk.
- Paroxetine may have an increased risk of congenital heart defects, although this has not been conclusively proven (discussed in more detail later). Paroxetine also has an increased risk of NAS compared with other SSRIs. For these reasons, some guidelines recommend avoiding paroxetine during pregnancy, if possible, although it has low infant exposure via milk for those who wish to breastfeed.

Treatment should start at the lower end of the dose range and be slowly titrated upwards until depression and anxiety symptoms become manageable. It is important not to under treat as this can expose the foetus to both the risks of medication and the risks of uncontrolled depression and anxiety.[3]

Risks during pregnancy

Antidepressants, particularly tricyclic antidepressants (TCAs) and SSRIs, are one of the most researched class of medications in relation to safety during pregnancy.[10] Overall, most studies on the risks of antidepressants during pregnancy are reassuring, although they are not completely without risk.

Observational studies (predominately on SSRIs or TCAs) have associated antidepressant use during pregnancy with a variety of adverse outcomes. However, many of these studies have not sufficiently controlled for confounding factors, including risks arising from a direct effect of the underlying mood disorder on a pregnancy, and risks resulting from behaviours associated with the mood disorder (eg, smoking, alcohol intake and other substance abuse, poor nutritional status, and poor antenatal care). Many of the adverse outcomes associated with antidepressant use in pregnancy have disappeared or been attenuated in more recent studies that have controlled adequately for confounding factors.

Some observational studies have found small increased rates of spontaneous abortion, preterm birth and low birthweight among antidepressant-exposed patients. However, depression itself can increase the risk of these outcomes, and not all studies have adequately controlled for the underlying illness.[3,14] One large cohort study found *depression* was associated with preterm birth and low birthweight, but antidepressants were not;[16] another study found a *reduced* risk of preterm birth and low birthweight in women treated with SSRIs, compared with untreated women with psychiatric illness.[17] Overall, the evidence is inconclusive with regard to whether antidepressants increase the risk of spontaneous abortion, preterm birth and low birthweight.[3]

The most common complication of antidepressant exposure in pregnancy is NAS (also referred to as neonatal withdrawal syndrome) – a non-specific syndrome that occurs in approximately one-third of infants exposed to antidepressants (of all classes) in the third trimester. The risk may be highest with paroxetine and venlafaxine.

Newborns with gestational exposure to antidepressants should be monitored for withdrawal symptoms after birth. Symptoms include jitteriness, increased or decreased muscle tone, irritability, colic, changes in sleep patterns, tremors, poor feeding, hypoglycaemia, temperature instability, respiratory distress and seizures (rare).[3]

Although NAS is common, the symptoms are usually mild, do not require special care, and resolve within a few days after birth. Rarely, for more severe symptoms, admission to a special care baby unit may be required for supportive care.

There might be concerns about whether antidepressant exposure during pregnancy results in long-term adverse outcomes on behaviour and development. While an increased risk of autism spectrum disorder from antidepressant-exposed pregnancies was reported in earlier studies, this was not confirmed by larger studies or meta-analyses that appropriately controlled for underlying depression. Maternal depression itself is a risk factor for autism spectrum disorder.[18,19]

Breastfeeding has long-term benefits that usually outweigh the risks of antidepressant exposure via milk

There is also some evidence that maternal antidepressant use may be protective for child behavioural outcomes. One study found adverse effects on child behaviour were more likely when pregnant patients with depression were unmedicated, compared with those taking antidepressants.[20]

Another study, which followed children up to the age of six years, found that neither TCA nor fluoxetine exposure during pregnancy adversely affected a child's global IQ, language development or behaviour. IQ was significantly and negatively associated with duration of depression, whereas language development was negatively associated with number of depression episodes after delivery.[21]

Selective serotonin reuptake inhibitors

SSRIs are *not* considered to be major teratogens.

Early observational studies suggested an increased risk of cardiac defects with SSRI exposure in the first trimester (particularly with paroxetine), but this finding has not been replicated across all studies, and there is some evidence that this association may be due to confounders, such as smoking, alcohol or the use of concomitant medications. If there is an increased risk, then the absolute risk is thought to be small. For example, with paroxetine, cardiac defects have been estimated to occur in approximately 1.5–2 per cent of exposed births, compared with approximately 1 per cent in the general population.[13]

Observational studies have shown a small increased risk of postpartum haemorrhage when SSRIs are used during the month up to delivery. This may occur because serotonin has a role in platelet function. The increase in absolute risk of postpartum haemorrhage is small. One observational study estimated one excess case of postpartum haemorrhage for every 80 to 100 people taking these antidepressants close to the time of delivery. The exact amount of blood loss and the clinical consequences have not been reported in the studies.[22]


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SSRIs taken after 20 weeks' gestation have been reported to slightly increase the risk of persistent pulmonary hypertension of the newborn (PPHN); however, the absolute risk is thought to be small. Among the non-depressed population, PPHN occurs in one or two out of 1000 births (0.2 per cent). The absolute risk difference for pregnancies exposed to serotonin and noradrenaline reuptake inhibitors (SNRIs) or SSRIs has been estimated at 0.619 per 1000 births, with a number needed to harm of 1615. The risk of PPHN with sertraline may be lower than with fluoxetine.[19]

Tricyclic antidepressants

TCAs have been widely used throughout pregnancy and most studies have found no association between TCA exposure and congenital malformations; however, clomipramine may be associated with cardiac defects.[14]

Serotonin and noradrenaline reuptake inhibitors

Venlafaxine is currently the only SNRI available in New Zealand. Less data is available on the safety of venlafaxine during pregnancy than for SSRIs or TCAs; nevertheless, data to date is reassuring. A meta-analysis concluded no association between first trimester exposure to venlafaxine and increased risk of major congenital malformations.[23] There is some evidence SNRIs may increase the risk of gestational hypertension, particularly at higher doses, and this should be screened for. The risks of postpartum haemorrhage and PPHN are thought to be similar to SSRIs.[19,22]

Mirtazapine

Data on the safety profile of mirtazapine during pregnancy is limited. While evidence to date is reassuring, with no evidence of congenital malformations, further study is required. NAS in newborns has been reported.[24]

Monoamine oxidase inhibitors (MAOIs)

The safety of MAOIs in pregnancy has not been established. There are concerns regarding the risk of hypertensive crisis in pregnant people, particularly with non-selective MAOIs. If a patient becomes pregnant while taking an MAOI, specialist advice should be sought.

Breastfeeding

Breastfeeding should usually be encouraged for patients taking antidepressants (with some exceptions). For most antidepressants, the long-term benefits of breastfeeding are considered to outweigh the risks of antidepressant exposure via milk. Additionally, exposure via breast milk will be less than what the infant was exposed to during pregnancy. There is also some evidence that breastfeeding may help to mitigate symptoms of NAS.[14]

Although antidepressants with low or minimal excretion into milk are ideal, if an effective antidepressant was taken during pregnancy, it should usually be continued postpartum and not switched as this is a vulnerable time for relapse and development of postpartum depression.

If the patient is *initiating* an antidepressant postpartum, then antidepressants with lower excretion into breast milk are preferred (eg, sertraline, paroxetine). However, as per the principles of antidepressant prescribing in pregnancy, if there is any history of antidepressant use, previous response to treatment should primarily be used to guide choice.[13,14]

Infants exposed to antidepressants via milk should be monitored for potential adverse effects. Initially, these may be difficult to differentiate from symptoms of NAS that arise from the use of the antidepressant during pregnancy. Extra caution and monitoring are required for neonates and preterm infants as they can have reduced drug clearance.[14]

> If an effective antidepressant was taken during pregnancy, it should usually be continued postpartum

If either parent is on sedating medications (eg, TCAs or mirtazapine), co-sleeping should be strongly discouraged due to the risk of falling asleep and smothering the baby.

Selective serotonin reuptake inhibitors

Although often used uneventfully, if breastfed infants are exposed to an SSRI via milk, particularly fluoxetine, they should be monitored for sleep disturbances, colic, poor feeding, irritability or restlessness.

Sertraline and paroxetine are preferred due to minimal excretion into breast milk and low to undetectable infant serum levels. Escitalopram or citalopram are alternatives – there is some excretion into breast milk, but infant plasma levels are low to undetectable.[14]

Fluoxetine is present in breast milk at higher concentrations than other SSRIs and has a risk of accumulation in breastfed infants because of its long half-life and active metabolite. Adverse effects have been reported in some breastfeeding infants, although there are other reports of the medication being used uneventfully. One study found no long-term effects on development in exposed infants followed up for one year. Although some resources recommend avoiding use in breastfeeding patients, it can be used with caution.[25]

Tricyclic antidepressants

The amount of TCA excreted into breast milk is generally considered to be too small to be harmful, and plasma levels of TCAs in breastfed infants are low to undetectable (except for doxepin, which is unavailable in New Zealand). Sedation and poor feeding have occasionally been reported in infants exposed to amitriptyline via milk, but there are no reports of adverse effects in infants exposed to other available TCAs.[14] If necessary, TCAs can be used during breastfeeding, but infants should be monitored for drowsiness, poor feeding and irritability.

Serotonin and noradrenaline reuptake inhibitors

The New Zealand Data Sheet does not recommend venlafaxine for those who wish to breastfeed. Venlafaxine is excreted in breast milk, and the main metabolite of venlafaxine has been detected in the serum of breastfed infants. However, reports of adverse effects in breastfed infants are rare, and other resources state that it is possible to breastfeed while on venlafaxine. If venlafaxine is used in a breastfeeding patient, the infant should be monitored for sedation, poor feeding, restlessness and sweating.[25]

Mirtazapine

The New Zealand Data Sheet does not recommend mirtazapine for those who wish to breastfeed. However, reported infant plasma levels are low to undetectable and, therefore, would not be expected to cause adverse effects in the infant. Other resources state that it can be used during breastfeeding.[14,25]

Monoamine oxidase inhibitors

Due to limited information on the use of MAOIs in breastfeeding patients, and the potential for serious interactions with food and medications, breastfeeding may need to be avoided and specialist advice should be sought.[25,26]

Summary

Perinatal depression is common and under treated, particularly among ethnic minorities. Patients often receive information from a variety of resources, but the information they receive from healthcare professionals is regarded as being the most influential. Unfortunately, patients often receive conflicting advice, and the risks of antidepressant medication in pregnancy and breastfeeding may be overestimated. This can result in discontinuation of antidepressant medication, thereby placing the patient at risk of relapse during a vulnerable time.

Antidepressants are not risk free. However, given the adverse outcomes associated with uncontrolled depression for both the birthing parent and their baby, most antidepressants have a favourable risk–benefit ratio for moderate to severe depression.

Pharmacists, as experts in medication, are well placed to ensure that balanced information on the benefits and risks of antidepressants in pregnancy and breastfeeding is provided to both patients and other healthcare professionals. PT

▶References for this article are available at pharmacytoday.co.nz under CLASS