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Depression during pregnancy and postpartum54–56

Prescribing in pregnancy and breastfeeding CHAPTER 7 Depression during pregnancy and postpartum54–56 Approximately 10% of pregnant women develop or have a pre-existing depressive illness. Around a third of cases of postpartum depression begin before birth and there is a significant increase in new psychiatric episodes in the first 3 months after delivery. At least 80% of these are mood disorders, particularly severe depression. Women who have had a previous episode of depressive illness (postpartum or not) are at higher risk of further episodes during pregnancy and postpartum. The risk is highest in women with bipolar illness who are also at risk of mania or mixed affective episodes. There is some evidence that depression increases the risk of spontaneous abortion (miscarriage),57 having a low birth weight or small for gestational age baby, or of preterm delivery, although effects are small.3,58,59 The mental health of the mother influences fetal well-being, obstetric outcome and child development. The risks of not treating depression include harm to the mother through poor self-care, lack of obstetric care or self-harm and harm to the fetus or neonate (ranging from neglect to infanticide). Antidepressants Relapse rates are higher in those with a history of depression who discontinue medication compared with those who continue. One study found that 68% of women who were well on antidepressant treatment and stopped during pregnancy relapsed, compared with 26% who continued antidepressants.54 Risk is likely to be highest for women with a history of severe and/or recurrent depression.60 The rate of antidepressant withdrawal will also influence the risk of depressive relapse. Available data do not suggest an association between prenatal antidepressant use and neurodevelopmental disorders (after controlling for maternal illness and other confounders).61 There is also some evidence that successful antidepressant use can be beneficial for child

behavioural outcomes. A Danish study found that adverse outcomes were relatively more likely in depressed women not taking antidepressants.62 However, antidepressant exposure in pregnancy may be an important marker of the need for early screening and intervention. Tricyclic antidepressants ■ ■Fetal exposure to tricyclics (via the umbilicus and amniotic fluid) is high.63,64 ■ ■Tricyclic antidepressants (TCAs) have been widely used throughout pregnancy without apparent detriment to the fetus.65–67 ■ ■A weak association between clomipramine use and cardiovascular defects cannot be excluded68 and the European summary of product characteristics (SPC) for Anafranil states: 'Neonates whose mothers had taken tricyclic antidepressants until delivery have developed dyspnoea, lethargy, colic, irritability, hypotension or hypertension, tremor or spasms, during the first few hours or days. Studies in animals have shown reproductive toxicity. Anafranil (i.e. branded clomipramine) is not recommended during pregnancy and in women of child-bearing potential not using contraception.' The labels for other TCAs also contain a caution about withdrawal effects in neonates. One case of neonatal QT prolongation and torsades de pointes has been reported following maternal clomipramine use69 and one case of Timothy syndrome

 (a disorder characterised by severe QT prolongation) in a newborn whose mother took amitriptyline in early pregnancy.70 ■ ■TCA use during pregnancy is associated with an increased risk of preterm delivery.65,66,71 ■ ■Use of TCAs in the third trimester is well known to produce neonatal withdrawal effects, such as agitation, irritability, seizures, respiratory distress and endocrine and metabolic disturbances.65 These are usually mild and self-limiting. ■ ■Little is known of the early developmental effects of prenatal exposure to tricyclics, although one small study detected no adverse consequences.72 Limited data suggest in utero exposure to tricyclics has no effects on later development.72,73 The authors of a study that reported an association between maternal antidepressant use and an increased risk of affective disorders in offspring74 suggested the observed associations may be attributable to underlying parental psychopathology. There are no convincing data suggesting an association between prenatal antidepressant use and neurodevelopmental disorders61 or ASD diagnoses or traits.75 Selective serotonin reuptake inhibitors (SSRIs) ■ ■SSRIs appear not to be major teratogens.65,67,76–78 An association between prenatal SSRI use and congenital heart defects has been reported, with some studies reporting a higher risk with fluoxetine and paroxetine.79 However, other studies have found no association between any SSRI and an increased risk of cardiac septal defects80–82 nor any other heart defects83–87 and it is suggested that mood disorders alone may be the cause of any increased risk of congenital heart defects.78 ■ ■One database study reported that fetal alcohol disorders were 10 times more common in those exposed to SSRIs in utero than in controls,88 and that alcohol use during pregnancy (which may be used as self-medication for depression) is associated with an increased risk of cardiac defects in the fetus.68 ■ ■Sertraline appears to result in the least placental exposure.89 ■ ■There may be a small increased risk of preterm birth and low birth weight and lower Apgar scores and admission to neonatal intensive care units with SSRIs.78 Maternal depression itself increases these risks.90,91 Poor neonatal adaptation (including withdrawal symptoms) has been reported and risk may be increased with prematurity92 and increasing dose, and may be higher with other SSRIs than sertraline.93 ■ ■SSRIs may increase the risk for persistent pulmonary hypertension of the newborn. The absolute risk appears to be small and more modest than previously estimated.94 The risk may exist only in late pregnancy exposure95 and may be lower with sertraline.96 ■ ■Gestational hypertension, pre-eclampsia, placental abnormalities and postpartum haemorrhage

have been reported with SSRI use. The risks appear to be small and it should be noted that maternal depression itself increases the risk of these outcomes.78 The UK Medicines and Healthcare products Regulatory Agency (MHRA) advises that healthcare professionals need to be aware of the small increased risk of postpartum haemorrhage with SSRI/serotonin–noradrenaline reuptake inhibitor (SNRI) antidepressant use during the month before delivery. ■ ■Data relating to neurodevelopmental outcome of fetal exposure to SSRIs are less than conclusive.72,73,97–100 Depression itself may have more obvious adverse effects on development.72,101 Some studies have reported a small increased risk of ASD.102–104

Prescribing in pregnancy and breastfeeding CHAPTER 7 However, larger studies have either failed to show this association after accounting for maternal illness and other demographic confounders75,105–107 or have found it to be no longer statistically significant.108,109 A large cohort study in 2022 reported that antidepressant use in pregnancy itself does not appear to increase the risk of neurodevelopmental disorders in children.61 There is no reliable evidence indicating an increased risk of ADHD.91 Poorer cognitive and gross motor development110 and problems with speech and language,111–113 behaviour114,115 and fine motor control have been reported116 but it is not clear whether or not this is a result of confounding. Authors of two separate studies, one reporting an association between antidepressant exposure in pregnancy and increased risk in the offspring of affective disorders74 and the other describing higher rates of emotional disorders and antidepressant medication prescriptions,117 have suggested the observed associations may be attributable to underlying parental psychopathology rather than direct exposure in utero. A 2023 study reported changes in brain morphology associated with SSRI exposure during pregnancy, some of which persisted into adolescence. The study did not assess clinical outcomes in the children and as such the significance of these findings is unclear.118 Other antidepressants ■ ■Despite a previous reported association between venlafaxine and increased risk of specific birth defects111 including cardiac defects, anencephaly and cleft palate,119 a 2022 meta-analysis concluded that available data do not indicate any SNRIs to be major teratogens.120 An earlier observational study of 281 venlafaxine-exposed pregnancies did not find conclusive evidence that venlafaxine increased the risk of adverse pregnancy or fetal outcomes.121 However, venlafaxine has been associated with neonatal withdrawal and poor neonatal adaptation syndrome,122 babies being born small for gestational age123 and postpartum haemorrhage.124 The UK MHRA advises that healthcare professionals need to be aware of the small increased risk of postpartum haemorrhage with SSRI/SNRI antidepressant use during the month before delivery. SNRIs may be associated with an increased risk for persistent pulmonary hypertension of the newborn. The absolute risk appears to be low.96 ■ ■A large cohort study using propensity scores and several sensitivity analyses found duloxetine use in pregnancy may be associated with a small increase in the risk of postpartum hemorrhage,124 and a case of suspected withdrawal syndrome in the newborn requiring hospitalisation has been reported.125 However, no specific risks were identified with duloxetine in a study that prospectively followed 233 women through pregnancy and delivery.126 A population-based observational study from Sweden and Denmark did not show an increased risk of major or minor congenital malformations or stillbirth with duloxetine.127 ■ ■Trazodone, bupropion (amfebutamone) and mirtazapine have few data supporting their safety.122,128,129 A 2023 observational study did not find a significant difference in the risk of major congenital anomalies after first-trimester exposure to trazodone compared with SSRI exposure.130 Available data suggest that both bupropion and mirtazapine are not associated with malformations but, like SSRIs, may be linked to an increased rate of spontaneous abortion;131–133 however this might be attri butable to underlying psychiatric disease. A

2022 Danish study did not observe an

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