

66 - Substance misuse in pregnancy

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554 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 4 Substance misuse in pregnancy Substance misuse in pregnancy has a wide range of adverse obstetric and fetal outcomes (Table 4.27). The overall quality of evidence is poor and based on small-scale observational studies. In the UK, the two main sources of information are the UK Teratology Information Service¹ and NICE guidance for pregnancy and complex social factors.² Outside the UK, WHO guidelines are available.³

Table 4.27 Risks and management of various drugs in pregnancy. Substance Associated risks Management Alcohol Alcohol is a teratogen, even 1–2 units can increase the risk of having a preterm, low birthweight or small for gestational age baby.⁴ In utero exposure can cause fetal alcohol spectrum disorders (FASDs) which include neurodevelopmental impairment, facial dysmorphism, congenital abnormalities and poor growth. These are dependent on dose, pattern timing, duration of exposure, fetal and maternal genetics, maternal nutrition, concurrent substance use and epigenetic response.⁵ Neonates can experience withdrawal symptoms, including hyperactivity, crying, irritability, poor sucking, tremors, seizures, poor sleeping pattern hyperphagia and diaphoresis.⁶ Breastfeeding Pregnant patients should be encouraged to cease alcohol consumption. Medically assisted withdrawal ■ ■ Those who experience withdrawal symptoms should have benzodiazepine-assisted withdrawal.³ ■ ■ The timing of detoxification in relation to the trimester of pregnancy should be risk-assessed against continued alcohol consumption and risks to the fetus.⁷ ■ ■ Benzodiazepines are not known to be major teratogens and the duration of their use in medically assisted alcohol withdrawal is short. Diazepam and chlorthalidone are the benzodiazepines of choice.⁸ ■ ■ Specialist advice should usually be sought. Relapse prevention medications ■ ■ No relapse prevention medications are advised in pregnancy, owing to the lack of safety data. However, given the teratogenicity of alcohol, there is debate over whether the benefit might outweigh the risk in certain circumstances.⁹ ■ ■ Acamprosate – fetal malformation and increased stillbirth are observed in animal studies with greater doses than in human therapy. One retrospective cohort study did not find an increased rate of congenital malformation, preterm delivery, low birthweight or neonatal complications. A small

sample (n = 32) of unpublished data has observed congenital malformations, miscarriage and neurodevelopmental impacts; the results are confounded by maternal alcohol use and therefore cannot be reliably interpreted.¹ ■ ■ Naltrexone – in animal studies it was not found to be teratogenic, however increased early fetal loss was observed at higher than recommended therapeutic doses. Clinical data relate to naltrexone use in opioid use disorder (OUD), and therefore are difficult to apply to alcohol use disorder. One study identified increased rates of pregnancy and labour complications for those with a naltrexone implant, compared with women without OUD, although this may be related to their OUD.⁹ ■ ■ Disulfiram – very limited data. There are concerns over the autonomic instability caused by the disulfiram-alcohol reaction.¹ Animal studies have not demonstrated the safety of disulfiram in pregnancy.⁹ ■ ■ Alcohol is excreted in breast milk in similar concentrations to those in maternal blood. Alcohol is at its highest concentration in breast milk 30–60 minutes after ingestion and declines at the same rate as in maternal blood. Therefore, pregnant patients are advised to wait before breastfeeding. One study demonstrated that alcohol decreased lactation.¹⁰ The safest option is to not drink alcohol, but if an individual chooses to drink, then they should drink no more than the recommended weekly intake and spread the drinks across the week.¹¹ (Continued)

Tobacco Miscarriage, low birthweight, prematurity and stillbirth⁷ Patients should be encouraged to cease smoking completely. Pharmacological treatment ■ ■ Nicotine replacement therapy (NRT) probably does not have adverse effects on the fetus or infant.¹² NRT should be offered at the earliest opportunity and provided if desired throughout the pregnancy.¹³ ■ ■ Vaping may be preferred but its effect on the fetus has not been established, with few studies available. There is some evidence that vaping has no impact on birthweight.¹⁴ ■ ■ NRT should be offered alongside behavioural support.¹³ ■ ■ Bupropion and varenicline are not recommended.¹³ Bupropion, when used to treat depression, may be continued after a risk-benefit analysis. Available human pregnancy exposure data have not indicated an increased risk of miscarriage, major congenital malformations, intrauterine death, impaired fetal growth or preterm delivery for bupropion or varenicline. One single case-control study of bupropion has suggested possible associations with cardiac malformations, but this has not been replicated.¹ Opioids Heroin dependence: sixfold increase in maternal obstetric complications and increased risk of neonatal complications including low birthweight, neonatal abstinence syndrome (NAS) and sudden infant death syndrome.¹⁵ Dependence on other opioids: low birthweight, toxemia, third trimester bleeding, malpresentation, puerperal morbidity, fetal distress, meconium aspiration, NAS, postnatal growth deficiency, microcephaly, neurobiological problems, increased neonatal mortality, increased sudden infant death syndrome (74-fold increase).¹⁵ Treatment should take place within a multidisciplinary team (including obstetric team, anaesthetists, neonatologists and addiction specialists) delivering a holistic package of care. Opioid substitution treatment (OST) ■ ■ It is advised that methadone/buprenorphine (OST) be commenced or continued in pregnancy. It carries a significantly lower risk than continued illicit use despite the known risks of these medications.³ ■ ■ Buprenorphine is associated with a lower risk of NAS than methadone.¹⁶ ■ ■ Buprenorphine and methadone increase the risk of preterm delivery, small for gestational age and low birthweight. Buprenorphine carries a relatively lower risk of these.¹⁶ ■ ■ Buprenorphine has been associated with a lower risk of congenital malformations than methadone.¹⁷ ■ ■ Buprenorphine and methadone have the same rates of severe maternal complications and caesarean sections.¹⁶ ■ ■ Methadone-exposed babies have a higher rate of mortality in the first 2 years when compared with buprenorphine and naltrexone exposed babies.¹⁸ ■ ■ A Cochrane review found no difference

in treatment retention between methadone and buprenorphine during pregnancy.¹⁵ However, a larger systematic review and meta-analysis not focused on pregnancy found greater treatment retention for methadone.¹⁹ ■ ■Pregnant patients are not advised to switch from methadone to buprenorphine because of the risk of withdrawal.³ Table 4.27 (Continued) Substance Associated risks Management

Detoxification Naltrexone Other considerations Breastfeeding ■ ■In the past, guidelines recommended that patients who take buprenorphine-naloxone (e.g. Suboxone) be switched to buprenorphine owing to there being inadequate safety data for the former.²⁰ However, a 2020 systematic review and meta-analysis identified no difference in outcomes for pregnant patients receiving buprenorphine-naloxone and that neonates were less likely to require treatment for NAS.²¹ A 2023 systematic review confirmed that Suboxone was no less safe than buprenorphine alone (or methadone).²² ■ ■Metabolism of methadone is increased in the third trimester so it may be necessary to split the dose to twice daily or increase the dose.⁴ ■ ■Pregnancy increases the metabolism of buprenorphine. Increased frequency of dosing is required to maintain plasma levels, reducing the risk of withdrawals and increasing adherence to treatment.²³ ■ ■Buvidal (long-acting buprenorphine injection) – there are very limited safety data available, and any benefits of use should be balanced with possible risks.²⁴ ■ ■Detoxification is associated with a higher rate of relapse and mortality.³ It should be driven by informed patient choice. If desired, detoxification is safest in the second trimester, as in the first it is associated with spontaneous abortion and in the third with preterm delivery, fetal distress and stillbirth.⁴ ■ ■Detoxification medications should be employed in small, frequent decrements, e.g. 2–3mg of methadone every 3–5 days.⁴ ■ ■Cycling between abstinence, relapse and intoxication results in fluctuating opioid concentrations, which increases the risk of maternal, obstetric, fetal and neonatal complications.²⁵ ■ ■There are limited human data that suggest similar findings with regard to safety as for methadone and buprenorphine.¹⁸ ■ ■It is useful to anticipate potential problems in pain management for pregnant patients prescribed opioids who are likely to require opioid pain relief. Such patients should be managed in specialist antenatal clinics due to the increased associated risks. ■ ■Antenatal assessment by anaesthetists is recommended to anticipate any anaesthetic risks, analgesic requirements and problems with venous access. ■ ■Patients prescribed methadone or buprenorphine should be encouraged to breastfeed even if they continue to use illicit opioids.¹ The level of buprenorphine and methadone in breast milk is low.¹⁸ ■ ■Breastfeeding brings general health benefits to mother and infant, low concentrations of methadone and buprenorphine are transferred to infant, and it reduces admission length and need for intervention in NAS. ■ ■Patients should be advised to discontinue breastfeeding gradually as abrupt cessation can cause a delayed NAS.²⁶ (Continued)

Table 4.27 (Continued) Substance Associated risks Management Cannabis Associations with stillbirth, fetal growth restriction, impaired fetal neurodevelopment, preterm delivery, neonatal intensive care unit admissions and small for gestational age infants, neonatal withdrawal-like syndrome, increased aggressive behaviour and attention deficits.²⁷ Breastfeeding Benzodiazepines No conclusive evidence of congenital defects. Associations have been found with increased risk of spontaneous abortion and preterm labour.²⁸ Prolonged use of benzodiazepines in the near-term period, especially high doses, is associated with a neonatal withdrawal syndrome and ‘floppy baby syndrome’.¹ Breastfeeding Stimulants Increased risk of miscarriage, placental abruption, preterm birth, decreased birthweight, disturbed neurobehaviour at birth, poorer medical/ behavioural/cognitive and motor problems.²⁹ Breastfeeding Abstinence should be

encouraged. CBT, motivational enhancement therapy and abstinence-based incentives can be used. There are no pharmacological treatments currently available.²⁷ ■ ■ There are limited data. Avoid or reduce use during breastfeeding.²⁷ Ideally, benzodiazepines should be discontinued before pregnancy. Abrupt withdrawal of benzodiazepines is not advised because of the possibility of destabilisation, and the risk that it could lead to alcohol being substituted, which could pose a considerable risk to the fetus.¹ The consensus is that those dependent on illicit benzodiazepines should be stabilised on long-acting benzodiazepines (e.g. diazepam) at the lowest dose possible to prevent withdrawal symptoms. The dose should be gradually reduced, as long as it does not result in illicit use.⁴ ■ ■ People taking high doses of benzodiazepines should not breastfeed.⁴ There are no effective pharmacological interventions and detoxification is the primary aim. ■ ■ Breastfeeding is not advised.³

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