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Bipolar illness during pregnancy and postpartum

722 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 7 association between mirtazapine use and major congenital malformations, spontaneous abortion, stillbirth or neonatal death.134 ■ ■First-trimester exposure to bupropion may be associated with a slightly elevated risk of ventricular septal defects.135 Bupropion exposure in utero has been associated with an increased risk of ADHD in young children.136,137 Rather limited data suggest the absence of teratogenic potential with moclobemide138 and reboxetine.139 ■ ■Monamine oxidase inhibitors should be avoided in pregnancy because of a suspected increased risk of congenital malformations and because of the risk of hypertensive crisis.140 ■ ■There is no evidence to suggest that electroconvulsive therapy (ECT) causes harm to either the mother or fetus during pregnancy141 although general anaesthesia is of course not without risks. NICE recommends ECT for pregnant women with severe depression, severe mixed affective states or mania, or catatonia, whose physical health or that of the fetus is at serious risk. Box 7.3 summarises recommendations for treating depression in pregnancy. Bipolar illness during pregnancy and postpartum The risk of relapse during pregnancy if mood-stabilising medication is discontinued is high143 and the risk of relapse after delivery is hugely increased. The mental health of the mother influences fetal well--being, obstetric outcome and child development. The risks of not stabilising mood include harm to the mother through poor self-care, lack of obstetric care, the need for hospital admission and harm to the fetus or neonate (ranging from neglect to infanticide). Box 7.3 Recommendations – depression in pregnancy ■ ■Patients who are already receiving antidepressants and are at high risk of relapse are best maintained on the same antidepressant (assuming it is effective and well tolerated) during and after pregnancy ■ ■Those who develop a moderate to severe or severe depressive illness during pregnancy should be treated with antidepressant drugs. If initiating an antidepressant during pregnancy or for a woman considering pregnancy, previous response to treatment must be taken into account. The antidepressant which has previously proved to be effective should be considered. For previously untreated patients, sertraline may be considered. ACOG recommends selective serotonin reuptake inhibitors (SSRIs) first line (with serotonin–noradrenaline reuptake inhibitors [SNRIs] a reasonable alternative) and if there is no pharmacotherapy history, sertraline or escitalopram is a reasonable first-line medication. COPE

recommends SSRIs first line ■ ■For moderate to severe perinatal depression with onset in the third trimester, ACOG recommends consideration of brexanolone ■ ■Screen for alcohol use and be vigilant for the development of hypertension and pre-eclampsia ■ ■Women who take SSRIs or SNRIs late in pregnancy may be at increased risk of postpartum haemorrhage ■ ■When taken in late pregnancy, SSRIs may increase the risk of persistent pulmonary hypertension of the newborn. The absolute risk is very low ■ ■The neonate may experience poor neonatal adaptation syndrome or discontinuation symptoms ■ ■NICE in the UK142 advises additional monitoring of the newborn of women who have taken an SRRI or SNRI antidepressant during pregnancy

Prescribing in pregnancy and breastfeeding CHAPTER 7 Mood stabilisers (non-antipsychotics) ■ ■Lithium completely equilibrates across the placenta.144 Lithium exposure during pregnancy has been associated with an increased risk of congenital anomalies.145 The risk is higher in the first trimester146 and may be greater at higher doses.145 Although the overall risk of major malformations in infants exposed in utero has probably been overestimated in the past, lithium should be avoided in pregnancy if possible. However, if lithium is the best drug for the woman and the drug most likely to keep her well, she should be advised of the increased risk but supported to stay on lithium. If discontinuation is planned, slow discontinuation before conception is the preferred course of action31,147 because abrupt discontinuation worsens the risk of relapse. The relapse rate postpartum may be as high as 70% in women who discontinued lithium before conception.148 ■ ■Lithium use during pregnancy has a well-known association with the cardiac malformation Ebstein’s anomaly. However, more recent data suggest that the magnitude of the effect is much smaller than previously estimated.149,150 Furthermore, a large surveillance study of 5.6 million births found an association of Ebstein’s anomaly with maternal mental health problems generally rather than specifically with lithium.151 The period of maximum risk to the fetus is 2–6 weeks after conception,152 before many women know that they are pregnant. The risk of atrial and ventricular septal defects may also be increased.28 If lithium is continued during pregnancy, high- resolution ultrasound and echocardiography should be performed in liaison with fetal medicine obstetric services. ■ ■In the third trimester, the use of lithium may be problematic because of changing pharmacokinetics. An increasing dose of lithium is required to maintain the lithium level during pregnancy as total body water increases, but the requirements return abruptly to pre-pregnancy levels immediately after delivery.153 Women taking lithium should deliver in hospital where fluid balance can be monitored and maintained. ■ ■Lithium use in pregnancy has been associated with an increased risk of spontaneous preterm birth and large for gestational age neonates.154 However, a large cohort study reported that lithium was not associated with placenta-mediated complications or preterm birth.155 Lithium use may increase the risk of neonatal readmission within 4 weeks postpartum,146 although a later study failed to replicate this finding.156 Neonatal goitre, hypotonia, lethargy, cardiac arrhythmia, respiratory symptoms157 and low Apgar scores158 have been reported. ■ ■Lithium probably does not affect neonatal brain development.159 ■ ■Most data relating to carbamazepine, valproate and lamotrigine come from studies in epilepsy, a condition associated with increased neonatal malformation. These data may not be precisely relevant to use in mental illness. Both carbamazepine and valproate have a clear causal link with increased risk of a variety of fetal abnormalities, particularly neural tube defects including spina bifida.160 Both drugs should be avoided, and an antipsychotic prescribed instead. Valproate confers a higher risk (around 10% for major malformations) than carbamazapine161–163 and should not be used in women of child-bearing age except where all other treatment has failed and when there is a long-term effective contraception plan. There is no evidence that folate

protects against anticonvulsant-induced neural tube defects if given during pregnancy,164 but it may do so if given prior to conception (the neural tube is essentially

724 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 7 formed by 8 weeks of pregnancy165 before many women realise they are pregnant). However, folate supplementation may be beneficial with regard to early neurodevelopment and so should always be offered.164 Valproate monotherapy has also been associated with an increased relative risk of atrial septal defects, cleft palate, hypospadias, polydactyly and craniosynostosis, although absolute risks are low.166 Valproate is also associated with a reduced head circumference in the neonate.167 ■ ■There appears to be a clear causal association between valproate use in pregnancy and motor and neurodevelopmental problems in exposed children. A review of studies by the European Medicines Agency showed that up to 40% of pre-school children exposed to valproate in utero experienced some form of developmental delay, including delayed walking and talking, memory problems, difficulty with speech and language and a lower intellectual ability. Poorer outcomes have been shown in language functioning, attention, memory, executive functioning and adaptive behaviour compared with carbamazepine and lamotrigine exposure. Lower IQs and an increased diagnosis rate of ASD are also reported.168,169 Processing, working memory and learning deficits appear to be dose-related.170 Decreased school performance has been associated with valproate use compared with children unexposed to anticonvulsants and with children exposed to lamotrigine.171 ■ ■Valproate use may increase risk of pre-eclampsia.172 ■ ■Where continued use of carbamazepine is deemed essential, low-dose (but effective) monotherapy is strongly recommended as the teratogenic effect is probably dose related.173,174 Use of carbamazepine in the third trimester may necessitate maternal vitamin K. ■ ■There is growing evidence that lamotrigine is safer in pregnancy than carbamazepine or valproate across a range of outcomes.164,168,175–177 The risk of major malformations appears to be in the range reported for children not exposed to anticonvulsants.178 Clearance of lamotrigine seems to increase radically during pregnancy179,180 and then reduces postpartum181 so frequent lamotrigine levels are necessary. ■ ■Behaviour problems have been reported by parents of children exposed to lamotrigine in pregnancy.182 Lamotrigine may be associated with an increased risk of autism.183 However, available data suggest the effect of lamotrigine on neurodevelopment appears to not be significant.184 ■ ■Lower Apgar scores at birth have been reported with carbamazepine, valproate and topiramate. If an association exists, the absolute risk is low.185 ■ ■Major malformations,186 specifically orofacial clefts, have been reported with topiramate.187 The risk of oral clefts may be higher in women with epilepsy who use higher doses of the drug.188 A large population study reported an increased risk of neurodevelopmental disorders, small for gestational age and congenital malformations189 with prenatal topiramate exposure. Topiramate should not be used in pregnant women, and women of child-bearing age should take precautions to avoid getting pregnant.190 ■ ■The data for oxcarbazepine are not clear. A 2022 meta-analysis reported a small but not statistically significant increased risk of malformations in children exposed to oxcarbazepine.191 Three studies in the same analysis reported an association with fetal/perinatal deaths. Because of some notable limitations in the studies incuded in this analysis, it is difficult to draw firm conclusions. ■ ■Similarly, data for pregabalin are not clear.192 However, based on a Nordic study193 that showed a small increased risk of major malformations (compared with

Prescribing in pregnancy and breastfeeding CHAPTER 7 lamotrigine and duloxetine) the UK MHRA194 and the manufacturers of pregabalin advise that women taking pregabalin be made aware of this risk and advised to use effective contraception. ■ ■A large cohort study reported

that anticonvulsant mood stabilisers were not associated with placenta-mediated complications or preterm birth.170 Recommendations for the treatment of bipolar disorder in pregnancy are outlined in Box 7.4. Box 7.4 Recommendations – bipolar disorder in pregnancy ■ ■For women who have had a long period without relapse, the possibility of switching to a safer drug (antipsychotic) or withdrawing treatment completely before conception and for at least the first trimester should be considered ■ ■For women with a severe mental illness, discuss referral to perinatal services for pre-conception advice ■ ■The risk of relapse both pre- and postpartum is very high if medication is discontinued abruptly ■ ■No mood stabiliser is clearly safe. In the UK, NICE recommends the use of mood-stabilising antipsychotics as a preferable alternative to continuation with a mood - stabiliser ■ ■Women with severe illness or who are known to relapse quickly after discontinuation of a mood-stabilising agent should be advised to continue their medication, following discussion of the risks. (This advice does not apply to valproate.) NICE recommends that if a woman taking lithium becomes pregnant, consider stopping lithium gradually over 4 weeks if she is well. Explain to her that there is a risk of relapse, particularly in the postnatal period, if she has bipolar disorder. If a woman taking lithium becomes pregnant and is not well or is at high risk of relapse, consider switching gradually to an antipsychotic or stopping lithium and restarting it in the second trimester (if the woman is not planning to breastfeed and her symptoms have responded better to lithium than to other drugs in the past) or continuing with lithium if she is at high risk of relapse and an antipsychotic is unlikely to be effective. If lithium is considered essential in a woman planning pregnancy, the woman should be informed of the risk of fetal heart malformations when lithium is taken in the first trimester and the risk of toxicity in the baby if lithium is continued during breastfeeding. In the UK, NICE recommends checking the plasma lithium levels every 4 weeks, then weekly from the 36th week, and to adjust the dose to keep plasma lithium levels in the woman’s therapeutic range, ensuring the woman maintains an adequate fluid balance. The woman should give birth in hospital and be monitored by the obstetric team when labour starts, including checking plasma lithium levels and fluid balance because of the risk of dehydration and lithium toxicity. Lithium should be stopped during labour and plasma lithium levels checked 12 hours after the mother’s last dose. ACOG recommends that pregnant patients taking lithium in the first trimester receive a detailed ultrasound examination in the second trimester to evaluate the fetal anatomy with a particular focus on cardiac anatomy. COPE recommends a 13- or 18–20-week ultrasound for women taking lithium or anticonvulsants in the first trimester ■ ■Women prescribed lithium should undergo appropriate monitoring of the fetus in liaison with fetal medicine obstetric services to screen for Ebstein’s anomaly ■ ■NICE, ACOG and COPE strongly advise against the use of valproate in pregnancy. Valproate should be discontinued before a woman becomes pregnant. Women taking valproate who are planning a pregnancy should be strongly advised to gradually stop the drug because of the high risk of fetal malformations and adverse neurodevelopmental outcomes after any exposure in pregnancy. COPE recommends once the decision to conceive is made to stop valproate over 2–4 weeks, while adding in high-dose folic acid (5mg/day), which should continue for the first trimester.52 In the UK, valproate may not be initiated in patients under 55 or continued in women of child-bearing potential unless two specialists agree and document that there is no other effective or tolerated treatment195

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