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Editorial

Prevention of bipolar episodes with lithium in the perinatal period†

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Summary
Because lithium is now recommended as the initial long-term treatment for bipolar disorder in general and has a lower teratogenic potential than originally reported, it may become more frequently prescribed in childbearing women. The article by Wesseloo *et al* in this issue provides helpful data and guidance for managing lithium dosing in the perinatal period.

Declaration of interest
None.

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Bipolar disorder in the perinatal period

There are few events that have a greater impact on severe mental illness than childbirth. Studies using population databases have found a large increase in the rate of new and repeated psychiatric admissions in the postnatal period with a peak in the first postpartum month.[1] The majority of conditions leading to hospital admissions are postpartum affective psychoses and have a close relationship with bipolar disorder although atypical features can sometimes obscure the overall diagnosis.[1] These illnesses tend to start abruptly within a few days of childbirth, escalate rapidly, fluctuate markedly, and are among the most severe seen in psychiatry. A subgroup of women develop episodes exclusively in the postpartum period and some evidence suggests that this may present a disease entity that is distinct from bipolar disorder.

Irrespective of treatment, about one in three women with a diagnosis of bipolar disorder suffer a relapse after a subsequent delivery and one in five women experience a severe episode.[2] Medication prescribed in pregnancy, with the evidence focused on lithium, is associated with a lower risk of postpartum relapse than no medication (66% *v.* 23%, $P<0.001$).[2]

Current findings are conflicting as to whether the course of bipolar disorder is altered in pregnancy with some population data indicating a reduced rate of hospital admissions.[1] However, the only clinical study that included a non-pregnant control group found that lithium withdrawal within 6 weeks of conception was followed by a similar rate of episodes requiring in-patient or community treatment up to delivery as in non-pregnant patients who had discontinued lithium.[3] In one large retrospective study only 8% of all perinatal episodes in women with bipolar I disorder occurred in pregnancy,[4] whereas another reported that 23% of pregnant women with bipolar disorder attending a perinatal mental health clinic had illness episodes.[5]

Any woman with bipolar disorder who could get pregnant or is in the early stages of pregnancy, should be offered advice about how childbearing might affect her illness, how her illness might affect childbearing and what the likely consequences of different treatment options are for her and her child, including no medication.[6] In many patients medication prophylaxis cannot be avoided.

The use of lithium in pregnancy

Recent UK guidelines for bipolar disorder in general have concluded that lithium should now be considered as the initial long-term monotherapy because it has better evidence for preventing new episodes than other agents, is effective against manic, depressive and mixed episodes, has a more substantial evidence base documenting the risk of prolonged exposure and is associated with a reduced risk of suicide.[7,8] However, the use of lithium in pregnancy has been low in the UK and prescriptions are discontinued in two-thirds of women in early gestation,[9] reflecting concerns about its reproductive safety. A finding of a large increase of the severe cardiovascular anomaly of the Ebstein type, from a general population rate of only 1:20 000 to 2.7 % in children exposed to lithium *in utero*, was reported in the 1970s and has influenced clinical practice in subsequent decades. However, the methodological flaws of the study and the low number of Ebstein cases in subsequent reports lead the authors of a meta-analysis in 2012[10] to conclude that the risk was overestimated. More recently, a European registry-based study covering 5.6 million deliveries reported the largest sample of unexplained Ebstein cases and found that none of the 173 babies had been exposed to lithium *in utero*.[11] Interestingly, there was an association of Ebstein's anomaly with maternal mental illness although this was based on only a small number of cases. Although the study supports the results of the meta-analysis by McKnight *et al*,[10] a small increase of this rare anomaly can still not be ruled out because of a lack of power. In addition, questions still remain about small rises in the overall rate of congenital and other cardiovascular anomalies and suboptimal pregnancy outcomes. A number of neonatal health problems have been described in individuals exposed to lithium in late pregnancy, but systematic data is lacking. Lithium levels in breastmilk tend to be higher than those of most other psychotropic drugs and breastfeeding is not recommended during lithium therapy.

Lithium dosing in pregnancy

Apart from reproductive safety considerations, managing lithium levels is challenging in the perinatal period because of the dynamic physiological changes in renal perfusion and glomerular filtration.

†See pp. 31–36, this issue.

The article by Wesseloo and colleagues in this month's issue of the *British Journal of Psychiatry* on lithium dosing strategies during pregnancy and the postpartum period addresses this neglected issue. Since lithium readily equilibrates across the placenta it is important to avoid blood levels higher than necessary to maintain mood stability. On the other hand, subtherapeutic levels should equally be avoided. In the study, serial lithium and creatinine blood levels were measured in a large sample of 85 women with 113 pregnancies, from 25 weeks before conception through to 25 weeks postnatal. The lithium blood levels, standardised to a given daily dose of 1000 mg, significantly dropped as early as in the first trimester. In the second trimester levels were one-third less than before conception with the lowest values occurring around 17 weeks of pregnancy. There was a gradual return towards preconception levels in the third trimester and the early postpartum period. Creatinine and lithium levels showed a similar longitudinal pattern. That renal function begins to normalise in the last trimester is perhaps not generally known and has important consequences for lithium dosing.

Although the mean daily dose increased in pregnancy, the proportion of subtherapeutic lithium levels rose from 15% preconception to 62% in the first and second trimester, dropped to 39% in the third trimester and fell below the preconception value after delivery. The authors do not state in what proportion of women levels were subtherapeutic, but it is interesting to note that three of the five patients who relapsed during pregnancy had low levels and one had discontinued her medication. Eight women had supratherapeutic levels and in seven this occurred in the week before or following delivery. In 3/7 women the cause was iatrogenic and 4/7 women had pre-eclampsia with impaired renal function.

Implications for clinical practice

The authors recommend an increased frequency of lithium estimations during pregnancy and particularly towards delivery, in line with the National Institute for Health and Clinical Excellence (NICE) guidelines for antenatal and postnatal mental health.[6] They also make the useful suggestion to combine measurements of lithium and creatinine in each blood sample so that non-adherence can be distinguished from rising renal function. Some clinicians advocate stopping lithium or reducing its dose before birth to avoid unpredictable intoxication at delivery. However, this comes at the expense of therapeutic efficacy at the most critical time and the data by Wesseloo and colleagues suggest that this precaution is not necessary. The authors argue that lithium dosing in the immediate postpartum period should aim for levels in the acute treatment, rather than prophylactic, range to maximize efficacy. It should be added that psychiatrists should routinely warn obstetricians about the risk of toxic lithium levels in women who develop pre-eclampsia or other conditions with renal impairment and that this requires intensive monitoring and proactive management jointly by psychiatrist and obstetrician.

With their article, Wesseloo *et al* make a contribution to safer and more effective prescribing of lithium in the perinatal period. Should this mood stabiliser be used more often in women with bipolar disorder who plan to conceive or are pregnant? The choice of medication is restricted in this patient group, in particular in respect of anti-manic agents. This is because the severe and widespread fetotoxic effects of valproate prohibit its use as an alternative and carbamazepine should also not be offered because of its teratogenic potential.[6] In recent years, the reproductive safety of antipsychotics that are effective in the prophylaxis of bipolar episodes such as olanzapine and quetiapine has been more extensively researched than that of lithium. The overall evidence, as it stands at present, suggests that they are not major teratogens and that their effect on developing children is less uncertain than that of lithium. The NICE guidance for antenatal and postnatal mental health recommends that lithium should only be offered if antipsychotic therapy has been ineffective.[6] However, the complexities of individual patient histories, treatment responses and preferences do not always result in clear choices. In the difficult process of weighing the risks and benefits of treatment options in childbearing women with bipolar disorder, recent findings, including those by Wesseloo *et al* in this issue, have made the case for using lithium in this patient group a little stronger.

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