Risks and benefits of psychotropic medication in pregnancy: cohort studies based on UK electronic primary care health records

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Scientific summary

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Background

The onset of psychoses (schizophrenia and bipolar disorder) in women usually occurs within childbearing age and long-term treatment is often required, including a mixture of psychotropic medication such as antipsychotics, lithium (multiple manufacturers) and anticonvulsant mood stabilisers, for example valproate (multiple manufacturers), lamotrigine (Lamictal®, GlaxoSmithKline) and carbamazepine (multiple manufacturers). Antipsychotics are increasingly being prescribed not just for schizophrenia, but also for bipolar disorder and severe depression and valproate is also commonly prescribed to women of childbearing age.

Although many women treated with psychotropic medication become pregnant or plan pregnancy, no psychotropic medication has been licenced for use in pregnancy. This leaves women and their health-care professionals in a treatment dilemma, as they need to balance the health of the woman with that of the unborn child. Advice on treatment varies across countries. The 2014 National Institute for Health and Care Excellence (NICE) guidelines for antenatal and postnatal mental health [NICE. Antenatal and Postnatal Mental Health: Clinical Management and Service Guidance. London: NICE; 2014] clearly state that valproate should not be offered for acute or long-term treatment of a mental health problem in women of childbearing potential. Likewise, the guidelines suggest that lithium should not be prescribed to women who are planning a pregnancy or who are pregnant, unless there has been a poor response to antipsychotic medication.

In recognition of the lack of evidence on the risks and benefits of psychotropic medication in pregnancy and the difficulties encountered in evaluating this issue using a traditional randomised controlled trial design, the National Institute for Health Research Health Technology Assessment (HTA) programme commissioned research utilising information derived from established databases. The commissioned call was titled ‘What are the risks and benefits of psychotropic drugs in women treated for psychosis who become pregnant?’. The ‘health technology’ to be evaluated was psychotropic medications that included antipsychotics, lithium and anticonvulsant mood stabilisers prescribed to women with psychosis (bipolar disorder or schizophrenia or overlap syndromes) and whose symptoms are controlled on treatment and who become pregnant.

The focus of our investigations was to compare the relative benefits and harms of these different drugs on the mother and the child, both when prescribed during pregnancy and when discontinued.

Objectives

- Provide a descriptive account of psychotropic medication prescribed before pregnancy, during pregnancy and up to 15 months after delivery in UK primary care from 1995 to 2012.
- Identify risk factors predictive of discontinuation and restarting of lithium, anticonvulsant mood stabilisers and antipsychotic medication.
- Examine the extent to which pregnancy is a determinant for discontinuation of psychotropic medication.
- Examine prevalence of records suggestive of adverse mental health, deterioration or relapse 18 months before and during the course of pregnancy and up to 15 months after delivery.
- Estimate absolute and relative risks of adverse maternal and child outcomes of psychotropic treatment in pregnancy.
Methods

Data source
We used data from The Health Improvement Network (THIN) and the Clinical Practice Research Datalink (CPRD), two large primary care databases that provide continuous anonymised longitudinal general practice data on the patients’ clinical and prescribing records and include data from >10% of the UK population.

We created a cohort of pregnant women using data from THIN for the period 1 January 1995–31 December 2012. We subsequently linked the pregnant women’s clinical records to that of their children. In order to increase the sample for our last objective we combined records from THIN and the CPRD and removed duplicated records from THIN.

Target population and study participants
The target population was women with psychosis (bipolar disorder, schizophrenia or overlap syndromes) who were in receipt of antipsychotics, lithium and anticonvulsant mood stabilisers, and who became pregnant. Some women receive psychotropic medication prior to formal diagnoses and others may never have a diagnosis of psychosis recorded in their electronic primary care health records. For antipsychotics and lithium, we therefore opted for the most sensitive approach and included all women who were treated with these medications prior to pregnancy in our studies, irrespective of whether or not they had a record of psychosis in their electronic health records. On the other hand, anticonvulsant mood stabilisers are prescribed for various indications. We therefore identified all women prescribed an anticonvulsant mood stabiliser, but for some analyses then limited our analyses to those with a history of psychosis (including bipolar disorder) or a recent record of depression.

Intervention
The intervention comprised (1) antipsychotics (atypical and typical), (2) lithium or (3) anticonvulsant mood stabilisers (lamotrigine, valproate and carbamazepine).

Studies
The project was divided into two parts: a descriptive section and an analytic section.

Part 1 of the project included five studies that examined (1) the prevalence of psychotropic treatment prescribing in and around pregnancy; (2) patterns of recording that indicate worsening of mental health; (3) time trends in prescribing of psychotropic medication; (4) discontinuation and factors associated with discontinuation of psychotropic medication in pregnancy; and (5) restarting and factors associated with restarting of psychotropic medication.

Part 2 of the project included a number of cohort studies. For each class of psychotropic drugs (i.e. antipsychotics, lithium and anticonvulsant mood stabilisers) we performed two studies, one which was based on a pregnancy cohort to examine the maternal outcomes and another which was based on a subset of linked mother–child pairs to examine child outcomes.

Outcome measures
Discontinuation and restarting of treatment; worsening of mental health; acute pre-eclampsia/gestational hypertension; gestational diabetes; caesarean section; perinatal death; major congenital malformations; poor birth outcome (low birthweight, preterm birth, small for gestational age, low Apgar score); transient poor birth outcomes (tremor, agitation, breathing and muscle tone problems); and neurodevelopmental and behavioural disorders.
Results

In total, 495,953 pregnancies were included in the study from 1 January 1995 to 31 December 2012. The general patterns of prescribing of psychotropic medication around pregnancy were similar for the three classes of psychotropic medication; it was relatively constant before pregnancy, decreased sharply in early pregnancy and then increased after delivery to equal or even surpass pre-pregnancy levels.

Entries made for mental health hospital admission or invoking of the Mental Health Act [Great Britain. Mental Health Act 1983. London: The Stationery Office; 1983] more than tripled just after delivery in comparison to the period just before pregnancy [prevalence ratio (PR) 3.16, 95% confidence interval (CI) 1.86 to 5.60] and recording of psychosis, mania and hypomania followed similar patterns with a doubling just after delivery (PR 2.02, 95% CI 1.53 to 2.69). The recording of suicide attempts, overdose or deliberate self-harm declined during pregnancy, but rose after delivery, but only to half of what it was prior to pregnancy (PR 0.55, 95% CI 0.48 to 0.63).

Since 2007, both antipsychotic and anticonvulsant treatment have increased both before and during pregnancy with a shift from typical to atypical antipsychotics. By 2011/12 carbamazepine was superseded by lamotrigine before, during and after pregnancy and valproate was the most commonly prescribed anticonvulsant mood stabiliser before pregnancy. Lithium was rarely prescribed, with annual prescribing after delivery almost halving in the study period.

Pregnancy is a strong determinant for discontinuation of psychotropic medication and overall patterns of discontinuation of psychotropic medication were remarkably similar. By the sixth week of pregnancy only 54% of women continued to receive further atypical antipsychotic prescriptions, 37% anticonvulsant mood stabilisers, 35% typical antipsychotics and 33% lithium. By the start of third trimester, 38% continued to receive atypical antipsychotics, 27% lithium, 19% typical antipsychotics and 14% anticonvulsant mood stabilisers.

Few factors (dose, age and comedication) predicted continuation of psychotropic treatment in pregnancy, but women with a record of epilepsy who were prescribed anticonvulsants were much more likely to continue medication in pregnancy than women with a record of psychosis or depression. In general, few women switched psychotropic medication before or in pregnancy.

Depending on the psychotropic drug prescribed, between 40% and 76% of women who discontinued psychotropic medication before or in early pregnancy had restarted treatment at 15 months after delivery. There were no clear predictors of restarting of treatment within 6 months of delivery.

Women prescribed psychotropic medication in pregnancy were in general slightly older, and a larger proportion were smokers, obese and had records of illicit drug use and alcohol problems.

Women prescribed antipsychotic medication in pregnancy were not at higher risk of giving birth to a child with major congenital malformations [relative risk ratio (RRR) 1.74, 95% CI 0.93 to 3.25], but they were at higher risk of giving birth by caesarean section (RRR 1.36, 95% CI 1.12 to 1.64) and giving birth to a child with poor birth outcomes (RRR 2.44, 95% CI 1.71 to 3.47), transient poor birth outcomes (RRR 2.62, 95% CI 1.52 to 4.52) and neurodevelopmental and behavioural disorders (RRR 1.58, 95% CI 1.04 to 2.40) than women not prescribed antipsychotics. These associations were confounded by health and lifestyle factors and concomitant medication use, and, after adjustment, none were statistically significant.
Women prescribed anticonvulsant mood stabilisers in pregnancy were at higher risk of delivering by caesarean section (adjusted relative risk ratio (RRRadj) 1.14, 95% CI 1.04 to 1.26) and giving birth to a child with major congenital malformations (RRRadj 2.05, 95% CI 1.53 to 2.74), poor birth outcomes (RRRadj 1.33, 95% CI 1.06 to 1.67), transient poor birth outcomes (RRRadj 1.76, 95% CI 1.30 to 2.38) and neurodevelopmental or behavioural disorders (RRRadj 1.73, 95% CI 1.42 to 2.09) than women not treated, but no differences were seen when comparing with women who discontinued treatment before pregnancy.

Women who were prescribed valproate in pregnancy were about three times as likely to give birth to a child with major congenital malformations (RRRadj 3.15, 95% CI 1.98 to 5.13) or to give birth to a child who later had records of neurodevelopmental or behavioural disorders (RRRadj 2.83, 95% CI 2.11 to 3.81) in comparison with women not prescribed anticonvulsant mood stabilisers. Comparing the women who continued valproate in pregnancy with those who discontinued treatment prior to pregnancy attenuated these risks somewhat, whereas comparing them with women prescribed other anticonvulsant mood stabilisers in pregnancy attenuated the risks further. However, a significant difference in risk remained, with those who continued valproate treatment being around twice as likely to give birth to a child with major congenital malformations (RRRadj 1.85, 95% CI 1.01 to 3.39) or to give birth to a child who later had records of neurodevelopmental or behavioural disorders (RRRadj 2.10, 95% CI 1.43 to 3.08) as women who were prescribed other anticonvulsant mood stabilisers in pregnancy.

Limiting the analyses on anticonvulsants to women with a record of psychosis or depression, the risk of giving birth to a child with poor birth outcomes was twofold higher in women who continued treatment in pregnancy than in those not prescribed anticonvulsant mood stabilisers (RRRadj 2.38, 95% CI 1.27 to 4.47), but in comparison with those who discontinued treatment before pregnancy there was no significant difference after adjustment.

Conclusion

The use of psychotropic drugs around pregnancy has increased with an increasing number of women using atypical antipsychotics, lamotrigine and, the potentially teratogenic drug, valproate. However, our findings indicate that many women discontinue treatment before or during early pregnancy and then restart again in late pregnancy or after delivery. Lithium continues to be prescribed around pregnancy but its use is decreasing.

Our results support previous findings of associations between valproate prescribed in pregnancy and major congenital malformations as well as neurodevelopmental or behavioural disorders. In contrast, our results suggest the increased risk of adverse pregnancy outcomes in women who continue antipsychotic treatment in pregnancy may be associated with health and lifestyle factors (obesity, smoking, alcohol abuse, concomitant medication and illicit drug use) rather than specific drug effects. It was not possible to investigate the risk associated with lithium use or anticonvulsant use specifically for psychoses owing to the small numbers of women in these groups.

Implications for health care

The results of our study highlight the relationship between general health and lifestyle factors and risks of adverse maternal and child outcomes in women who are prescribed psychotropic medication in pregnancy. Health-care providers should be alerted to the fact that many of the women prescribed psychotropic medication may be at a heightened risk of giving birth to a child with major congenital malformations and other adverse outcomes, perhaps because of obesity, alcohol abuse, illicit drug use and concomitant use of anticonvulsants.
Recommendations for future research

Future research should focus on (1) describing the utilisation and curtailing the use of valproate in women of childbearing potential; (2) quantifying the potential benefits of psychotropic treatment in pregnancy; (3) investigating the risks associated with alcohol abuse, illicit drug use, obesity, smoking and other lifestyle choices that are more prevalent among women using psychotropic medication in pregnancy.

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Criteria for inclusion in the Health Technology Assessment journal

Reports are published in Health Technology Assessment (HTA) if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the reviewers and editors.

Reviews in Health Technology Assessment are termed ‘systematic’ when the account of the search appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

HTA programme

The HTA programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. ‘Health technologies’ are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

The journal is indexed in NHS Evidence via its abstracts included in MEDLINE and its Technology Assessment Reports inform National Institute for Health and Care Excellence (NICE) guidance. HTA research is also an important source of evidence for National Screening Committee (NSC) policy decisions.

For more information about the HTA programme please visit the website: http://www.nets.nihr.ac.uk/programmes/hta

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