

Editorial

Prescribing in pregnancy[†]

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**Summary**

Psychotropic drugs reduce morbidity and mortality related to maternal mental illness but may also cause harm to the foetus, the nature and magnitude of which is not completely understood. Up-to-date information should be shared as fully as possible with the pregnant woman and a treatment plan agreed jointly.

Declaration of interest

In the past 3 years C.P. has acted as a consultant to companies that market antipsychotic and antidepressant medicines, and has contributed to the development of several National Institute for Health and Clinical Excellence guidelines.

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The background risk of congenital malformations is accepted as being 2–3%¹ and is known to be influenced by fixed maternal risk factors such as increasing age, physical illness and genetics, and modifiable risk factors such as the use of medicines during pregnancy. Medicines are commonly taken by pregnant women; in the UK-based Avon study, where data about the use of medicines were collected prospectively for over 14 000 pregnant women, over 80% reported taking medication other than vitamin supplements and homeopathic remedies during their pregnancy.² Medicines may be taken to alleviate minor self-limiting symptoms associated with pregnancy such as heartburn, nausea and constipation. They may also be taken to treat more serious maternal illness such as hypertension, diabetes, depression and psychosis, all of which, if left untreated, may negatively affect both the woman and her unborn child. With respect to psychotropic drugs, the potential benefits of continuing treatment during pregnancy include improved maternal self-care and therefore foetal well-being, and better obstetric outcome and ultimately child development.

Types of drug-induced harm

Almost all drugs are transferred across the placenta to the developing foetus, with the degree of foetal exposure determined by the molecular size and lipid solubility of the drug. Foetal exposure is possible at all stages of pregnancy, including very early pregnancy when many women will not know that they are pregnant.

Drugs generally cause most harm to the foetus in the first trimester, when the major organs and limbs are being formed. An association between the use of a particular drug and foetal abnormality is not always easy to detect, even when a drug commonly causes an abnormality that is rare in the general population. The most extreme example of this is thalidomide, which caused major limb malformations in a third of those exposed *in utero*, yet many thousands of babies had been born before the association was recognised. Perhaps the most teratogenic drug used in current psychiatric practice is valproate. Around 7% of babies exposed to valproate *in utero* have congenital malformations – up to 1 in 20 has a neural tube defect.³ This has

led to the advice that valproate should be avoided in women of child-bearing age,⁴ yet many clinicians may be unaware of the magnitude of the risk that it poses.⁵

Drugs may also cause intra-uterine growth retardation by reducing placental blood flow and therefore the supply of nutrients to the foetus. Problems during and immediately after delivery are also possible; sedative drugs such as benzodiazepines can cause respiratory depression and drugs with a short half-life can cause withdrawal symptoms in the neonate.

Some agents may also affect the foetus in ways that are not apparent until much later in life. For example, valproate is associated with developmental delay and diethylstilbestrol with adenocarcinoma of the vagina in young women.

In this issue of the *British Journal of Psychiatry*, Newham *et al*⁶ present data that suggest an association between the use of second-generation antipsychotics in pregnancy and neonates that are large for their gestational age (defined as >90th percentile). This association is biologically plausible. Some second-generation antipsychotics are associated with considerable weight gain,⁷ direct effects on insulin secretion⁸ and the development of gestational diabetes.⁴ This association is clinically important as a neonate that is large for its gestational age places the mother and the unborn child at risk of birth complications, and in the longer-term, the child may be at increased risk of obesity and, ultimately, diabetes.

Sources of information about drugs in pregnancy

It is obviously unethical to include pregnant women in randomised controlled trials as this would involve the deliberate exposure of the foetus to a potential teratogen. In clinical practice however, women conceive while taking prescribed medicines and pregnant women develop medical conditions that require treatment. Although information from randomised controlled trials can be used to estimate the beneficial and harmful effects that the prescribed medicine may have on the mother, considerably less robust data from a number of sources are used to estimate potential harm to the unborn child.

Studies in animals may provide some reassurance, but can never guarantee safety in human pregnancy. Once a drug has been marketed, case reports start to appear in the literature; these usually highlight negative outcomes and give no indication of the absolute or relative risk of drug exposure, or even whether the outcome reported was due to the drug at all. Case reports can be used to generate hypotheses that can be tested using prescription database or case-control studies.

[†]See pp. 333–350, this issue.

Prescribers also contact specialist centres such as the National Teratology Information Centre (NTIS) for advice. The advantage of NTIS data is that they are collected prospectively – that is, before the outcome of the pregnancy is known. The disadvantages are that it is not known whether the cases that doctors consult NTIS about are representative of women who take the drug in question during pregnancy and that there is no control group that allows assessment of the impact of other important variables such as the illness the drug was prescribed to treat or lifestyle.

The problems associated with interpreting NTIS data are highlighted by the literature pertaining to the safety of selective serotonin reuptake inhibitors (SSRIs) in pregnancy. A study based on these data suggested an association between paroxetine and cardiac septal defects:⁹ of 330 paroxetine-exposed infants, 5 had septal defects. This finding was not replicated by Alwan *et al*¹⁰ in a case-control study based on 1931 infants with septal heart defects; however, in a further case-control study¹¹ based on 1161 children with septal defects, sertraline has been implicated. In this issue of the *Journal*, Ramos *et al*¹² report on a case-control study that included data only for women who had received a diagnosis of a mood or anxiety disorder and had been prescribed antidepressant drugs in the year prior to conception. This allowed the prevalence of antidepressant use during pregnancy by the mothers of infants with and without congenital malformations to be compared, relatively free of the confounding effects of maternal mental illness. Their data suggest that the effects of maternal mental illness on obstetric outcome may be considerable and the effects of SSRIs negligible. A second study in this issue,¹³ which also controlled for the effects of maternal mental illness, reports that decreased gestational age and birth weight, and increased neonatal respiratory distress, effects that have all previously been linked with SSRIs, were associated with the duration rather than the timing of *in utero* exposure. The severity of maternal illness partially accounted for these outcomes.

Although these studies provide some reassurance regarding the safety of SSRIs in pregnancy, the findings of Newham *et al*⁶ in this issue raise new safety concerns about second-generation antipsychotics, specifically an increased risk of neonates who are large for their gestational age. Their conclusions are in contrast to those of McKenna *et al*,¹⁴ who reported on data from the Canadian and Israeli teratology information services. Outcome data were available for 151 women who took second-generation antipsychotics during pregnancy; babies born to these women had a lower mean birth weight than babies born to controls, despite the mean body mass index of the women taking antipsychotics being higher than that of the controls. The data reported did not suggest an association between second-generation antipsychotics and neonates who were large for their gestational age.

The paper by Newham *et al*⁶ was based on data for 86 women who were exposed to antipsychotics during pregnancy. During the 10-year period that it took to accrue these cases, the average body mass index of the UK population was increasing, as was the use of second-generation antipsychotics – disentangling the weight-gaining effect of medication from the background population effect is impossible in the absence of a control group. Other factors are also important. First- and second-generation antipsychotics are not distinct groups of drugs with clearly delineated receptor affinity or side-effect profiles: grouping drugs in this way to determine an association with something as complex as effects on the foetus is fraught with difficulties. Newham *et al* also acknowledge that there is uncertainty over the accuracy of their data on smoking, an important confounding variable when looking at birth weight as an outcome. Nevertheless, their recommendation that foetal size should be carefully monitored in women who take olanzapine or clozapine during pregnancy is compelling.

Dilemma of prescribing in pregnancy

All standard psychopharmacology texts and evidence-based prescribing guidelines recommend that medicines should be prescribed for pregnant women only if the potential benefits to the mother outweigh the potential risks to the unborn child. Given that neither benefit nor harm are unidirectional and our understanding of the impact of drug treatment in both the short- and long-term is far from complete, the woman and her partner must be as fully involved as possible in the decision-making process. The UK National Institute for Health and Clinical Excellence (NICE) evidence-based guideline on the management of antenatal and postnatal mental health⁴ emphasises the importance of this approach and of acknowledging uncertainty over the nature and magnitude of risk that drug treatment poses to the foetus. Communicating this constantly evolving information in a way that is easy to understand is clearly challenging.

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