Fetal antipsychotic exposure in a changing landscape: seeing the future
Kathryn M. Abel

Summary
Pregnant women and their fetuses are increasingly likely to be exposed to antipsychotics. However, safety data remain limited. This editorial suggests that, in future, well-designed observational pharmaco-epidemiology is our best chance of illuminating risk for exposed populations and of informing decision-making for women and clinicians.

Declaration of interest
None.

Pregnant women and their fetuses are more likely than ever to be exposed to antipsychotic medications particularly newer agents, which are increasingly used in women of reproductive age for a range of psychiatric disorders other than schizophrenia. Reproductive safety data remain surprisingly incomplete and guideline recommendations lend limited support to clinical risk–benefit analyses. Randomised controlled trials of antipsychotic medication are considered unethical, and most available observational studies are underpowered, with biased samples unfit for purpose in a rapidly changing prescribing landscape. In a UK population approaching 66 million, 3000–4000 births per year are likely to be exposed to antipsychotics/psychotropic medications. This editorial provides a critical summary of current knowledge about the risks of fetal antipsychotic exposure and proposes specifically how future observational epidemiology might fill crucial gaps in the evidence.

Are we any clearer about exposure risks from first- and second-generation antipsychotics?

Congenital malformations
Pregnancies of women with psychosis were originally shown to be twice as likely to result in congenital malformation or death, irrespective of chlorpromazine use in pregnancy when compared with well population controls. Offspring of women with psychiatric illness are highly likely to be at increased risk of neural tube defects because of higher rates of maternal obesity and reduced serum folate levels related to low dietary vitamin intake. Observational studies support this, but it remains uncertain whether antipsychotics cause any increased risk.

Distinguishing the effects of maternal illness from the effects of medication is challenging. In the past, first-generation antipsychotics (FGAs) were mostly prescribed for morning sickness, not mental illness, using lower, intermittent doses. Meta-analysis of older studies report that infants of well mothers showed excess congenital malformation following exposure to phenothiazines (n = 2591) compared with unexposed infants (n = 71746) (odds ratio (OR) = 1.21, 95% CI 1.01–1.45). However, estimates from recent cohorts may be more reliable because prevalence of outcomes in the reference population change over time. More recent Swedish data report possible excess (mainly cardiovascular) risk of congenital malformation (OR = 1.52, 95% CI 1.05–2.19) compared with well controls.

In the UK, second-generation antipsychotics (SGAs) are now the most commonly prescribed antipsychotics. Manufacturers report no particular concerns for exposure in early pregnancy but manufacturer and spontaneous reporting data are biased by adverse outcomes reporting and often lack pregnancy outcomes. If we only take into account cases from unbiased but smaller samples and if we consider how long many of the compounds have been available, none of the antipsychotics appear to show themselves as clear teratogens. However, limb anomalies cannot be excluded with early exposure to haloperidol/pentfluoridol and there are no/lew reports for aripiprazole, sertindole, amisulpride and zotepine.

Pregnancy outcomes
More common outcomes allow clearer risk estimates in smaller samples, but even in population data, only small effects have been reported. In the largest sample exposed to any antipsychotic (n = 576), prematurity (OR = 1.73, 95% CI 1.31–2.29), birth weight < 2.5 kg (OR = 1.67, 95% CI 1.21–2.29) and small-for-gestational-age (OR = 1.46, 95% CI 0.99–2.15) are all increased. A newer (2005–2009) Swedish cohort found higher risk in pregnancy-exposed infants of small-for-gestational-age (OR = 2.11, 95% CI 1.29–3.47) and gestational diabetes (OR = 2.78, 95% CI 1.64–4.70), which disappears after adjustment for maternal factors such as smoking. Olanzapine or clozapine (grouped n = 169) exposure was also associated with gestational diabetes (OR = 2.39, 95% CI 1.12–5.13) and small-for-gestational-age (OR = 2.42, 95% CI 1.24–4.70), but not large-for-gestational-age. The only study separating risk of drug from risk of illness is Lin et al. compared with the offspring of mothers with schizophrenia who were unexposed to FGAs, the infants of mothers with schizophrenia (n = 242) exposed to FGAs in early pregnancy were more likely to be premature (OR = 2.46, 95% CI 1.50–4.11), but not low birth weight, small- or large-for-gestational-age. However, they did not have information about important potential confounders, i.e. smoking, maternal weight, alcohol and substance use.

Developmental outcomes
There is a remarkable absence of studies of neonatal or developmental outcomes following pregnancy exposure to antipsychotics. Several cases of neonatal extrapyramidal syndrome have been reported with FGA exposure, but there are no other
consistent patterns of adverse effects in the literature. Data are also
limited for neurobehavioural sequelae of antipsychotic exposure;
most data concern high-risk children of parents with psychosis.
Several older studies following FGA-exposed infants suggest that
deficits in infancy and early childhood have poor predictive value
and disappear later in childhood. Older reviews failed to find
differences in behavioural functioning or IQ up to 5 years (for example Altshuler et al).5

Outstanding problems with the evidence base

The cohort effect
For a number of reasons, the applicability of evidence gathered
over a decade ago is questionable. First, the largest Swedish studies
from 1994 to 2004 using midwife-data reported low psychosis
prevalence in pregnant women (<1 in 1000),7 probably because
midwives lacked awareness about psychosis. Contemporary
Second, SGAs are now the most commonly prescribed
antipsychotics in the UK, but earlier studies have limited
SGA-exposure data. Finally, key outcomes such as rates of
stillbirth or prematurity are affected by changing practice, which
alters risk in the background population. Similarly, women
becoming pregnant while on psychotropics are increasingly likely
to be obese8 and, unlike Scandinavia, in the UK they are more
likely to smoke.9 This is important because obesity and smoking
independently increase risk of poor maternal and fetal outcomes.

Illness v. medication
Maternal (and in some cases paternal) psychotic disorder is
consistently associated with adverse pregnancy outcomes such as
genital malformation, stillbirth, neonatal death, low birth
weight and prematurity.10 However, lifestyle factors associated
with severe illnesses/psychoses (smoking, substance misuse, poor
nutrition and antenatal attendance) are independent risk factors
for many of these outcomes (congenital malformation, premature,
small- and large-for-gestational-age). Studies of the
effect of maternal psychotropic exposure on pregnancy outcome
often sample exposed mothers with a range of mental or other
chronic illness severity that may confound findings. Lin et al10 is
the only study to have analysed unexposed ill women, as well as
unexposed well women. Unfortunately, their control group was
mothers with schizophrenia who were not exposed to
antipsychotics so that although they were able to examine excess
risk of medication over and above illness alone, confounding by
indication means that the ill, unexposed women may have been a
less unwell group with less inherent risk than the ill, exposed group.

Adherence to medication
Evidence of adverse drug effects obviously must take account of
adherence to medication, which is often compromised in severe
mental illness. If an ill mother discovers she is pregnant, she
may be especially likely to discontinue medication. Data-sets
large enough to provide reliable information on pregnancy
psychotropic exposure rarely contain detailed information on
adherence, but recording prescription refills is one way to measure
it. Some national registers, such as those used in the recent studies
by Bodén et al9,12 contain information on all prescription fills,
including drugs dispensed using, amount, formulation and date of
prescribing and dispensing.

Antipsychotic groupings
Prior literature confines analyses to exposure to all/any
antipsychotics or, if numbers allow, to groupings of FGA/typicals
and SGA/atypicals. Drugs in these groups differ in many of their
properties including efficacy, side-effects and pharmacology and
do not form a homogeneous class.13 Heterogeneity in effect and
side-effects suggests that such ‘improper grouping’ may create
confusion in the exposure.

Confounding
Compared with well, unexposed women, evidence suggests that a
higher proportion of women exposed to psychotropics during
pregnancy are immigrants, older, not living with the child’s father,
have more children and are smokers, with a high body mass
index.9,12 These factors may all be independently associated with
both exposure and outcome, acting as potential confounders of
any association between drug and outcome in ill mothers. Few
population studies account for potential confounders, which
are unavailable in most data-sets. In addition, simultaneous
administration of other agents is rarely considered because sample
sizes or statistical complexity do not allow it and/or information
on over-the-counter prescriptions is unavailable.

Missing information
No studies have been able to look separately at clozapine or the
antipsychotics that are now most prescribed in the UK
(olanzapine, quetiapine, risperidone).13 This is important because
recent examination of the placental passage of antipsychotics
(umbilical cord: maternal plasma concentration) suggests
olanzapine has highest passage (mean 72.1%, s.d. = 42.0) and, also,
higher rates of low birth weight and/or perinatal complications
compared with other antipsychotics.14 In data-sets powerful
enough, no studies examine quality of life, drug adherence or time
to, or risk of, relapse in mothers with schizophrenia or related
disorders who discontinue antipsychotic medication in pregnancy.

No long-term cognitive, psychopathological or developmental
effects have been examined epidemiologically. This is particularly
important because so-called ‘high-risk’ literature shows evidence
that offspring of parents with severe mental illness are more likely
to show poorer cognitive, social and clinical outcomes.11 However,
none of this literature accounts for fetal psychotropic exposure.

Animal models are needed to explore the effects of anti-
psychotics on fetal growth and placental function, whereas
multicentre studies might examine human placental handling of
antipsychotics. Meanwhile, observational epidemiology offers far
greater potential.

What should future observational epidemiology
aim to do?

(a) Create cohorts large enough to enable analyses stratified by
trimester of exposure and to examine individual drugs,
including mono- v. polytherapy.

(b) Consider combining data-sets on common exposure and
outcome variables (diagnoses, maternal characteristics,
common obstetric outcomes).

(c) Adjust estimates for important potential confounders.

(d) Examine risk using both well and ill unexposed women as
comparators.

(e) Link information obtained by midwives and self-reported
medication use from antenatal visits, with actual filling of
prescriptions during pregnancy to examine adherence.
(f) Examine groups of drugs by side-effect profile. For example, susceptibility to metabolic side-effects such as maternal weight gain, gestational hypertension and gestational diabetes, and low-potency FGA/typicals should be grouped with -pines; thus, for example the ‘typical’ chlorpromazine grouped with ‘atypical’ olanzapine and clozapine.

(g) Compare outcomes between siblings and generations to account for non-measured family-wide effects.

(h) Examine evidence of longer-term developmental effects.

Kathryn M. Abel, MA, MBBS, MRCP, MRCPsych, PhD, Centre for Women’s Health, 3rd Floor Jean McFarlane Building, University of Manchester, Manchester M13 9PL, UK. Email: kathryn.abel@manchester.ac.uk

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References


Ode to Anxiety

Ankur Sharma

Whine of mangled nerves
Like convoluting steel rails
Conducting trains of worry
Deafeningly.

Blur of contracting sight
Like curtains falling
Leaden lids, shutting down
Hazily.

Anxiety, you are potent
Like cyanide
Choking on contact
Gaspingly.

Leave me, leave me
Like life from a corpse
Stop this galloping pulse
Hurriedly.

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