Antipsychotic drugs in pregnancy: a review of their maternal and fetal effects

Ther Adv Drug Saf
2014, Vol. 5(2) 100–109
DOI: 10.1177/2042098614522682

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***Abstract*:** Understanding the risks of antipsychotic medication use in pregnancy is becoming an important clinical concern given the evidence of their increasing rate of prescription in the general population for a range of disorders. Despite antipsychotics being amongst the earliest of psychotropic medications to be introduced, the evidence for their effects secondary to pregnancy exposure is extremely limited. While this review does not identify clear evidence for a risk of malformation, there is evidence for risks associated with pregnancy and neonatal outcomes. Studies identified found risks that included prematurity, low and high birth weight, and gestational diabetes. There have also been studies that suggest neonatal withdrawal and abnormal muscles movements. The longer term neurodevelopmental outcomes for children exposed *in utero* remain unclear with only four studies identified: two of first generation antipsychotics and two of second generation antipsychotics. When considering the risk of these medications in pregnancy, the risk of untreated maternal illness (particularly schizophrenia and bipolar disorder) on both maternal and child outcomes is relevant. Future research needs to focus on prospective, longitudinal studies with adequate measures of key confounding variables including maternal mental illness, other exposures (such as smoking, alcohol and illicit drug use) and adequate length of follow up where accurate child developmental measures are obtained.

Keywords: antipsychotics, bipolar disorder, pregnancy, schizophrenia

Introduction

There has been a significant increase in the prescription of antipsychotic medication in the community. While this increase is not specific to pregnancy it includes prescription to women across the fertile years. A study of Australian prescribing between 2000 and 2011 found a 217.7% increase in the prescription of atypical antipsychotics, which makes it now the third most commonly prescribed psychotropic [Stephenson *et al.* 2013]. Alexander and colleagues, in a study of the use of antipsychotics in the US, also found an increase that was not accounted for by use in psychotic illnesses [Alexander *et al.* 2011]. Both sets of authors postulated that much of the increase seen is for off-label use and for wider indications than psychosis alone. The lifetime prevalence for schizophrenia is approximately 1% and bipolar disorder is approximately 2%, making these conditions in pregnancy relatively low prevalence. The trend in wider utilization of antipsychotics in the community makes understanding the risk profile in pregnancy essential for clinicians managing women in their fertile years. This is particularly relevant when consideration is given to the nearly 49% rate of unplanned pregnancies in the community [Finer and Henshaw, 2006].

At present, any comfort we may have in prescribing antipsychotics during pregnancy comes mainly from the absence of negative data rather than the presence of positive data. It has been estimated that at least 500 cases are needed for each individual medication to determine differences in occurrence of major malformation and larger numbers are required to adequately control for other variables [Meador *et al.* 2008]. To date, none of the first generation antipsychotics (FGAs) or second generation antipsychotics (SGAs) has been adequately investigated in this regard. The issue is further complicated by the fact that the majority of studies that aim to evaluate and clarify teratogenic risk associated with antenatal exposure to psychotropic medications were not

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designed to control for possible teratogenic effects of the underlying psychiatric disorder. We await further clarity from prospective registry studies that include a nontreatment control group.

When consideration is given to the risk benefit profile of pharmacological treatment in pregnancy, the consideration of risks of not treating is usually factored into the equation. With off-label use and indications where the evidence for efficacy is limited this is challenging. However, when focusing on the two mental disorders with clear indications for these medications, i.e. schizophrenia and bipolar disorder, the risks of untreated illness are significant. Both schizophrenia and bipolar disorder have been associated with an increased risk of pregnancy complications such as placental abnormalities, antepartum hemorrhage, prematurity, pre-eclampsia, low birth-weight, intrauterine growth retardation, fetal distress, neonatal hypoglycemia, low Apgar score, stillbirth and congenital defects, as well as the potential for adverse neurodevelopmental outcomes independent of any risk associated with exposure to antipsychotic medication [Jablensky *et al.* 2005; Boden *et al.* 2012; Abel and Howard, 2014]. A study of Western Australian women with schizophrenia showed an increased risk of placental abruption; this study also showed women with either schizophrenia and bipolar had an increased risk of antepartum hemorrhage compared with controls even after controlling for a range of confounding variables [respectively: odds ratio (OR) 2.75, 95% confidence interval (CI) 1.32–5.74; OR 1.65, 95% CI 1.02–2.69; OR 1.66, 95% CI 1.15–2.39) [Jablensky *et al.* 2005]. In addition to pregnancy complications associated with serious mental illness, there are also longer term concerns about parenting and child development if a women becomes or remains unwell due to the cessation or undertreatment of her illness.

As there is an increasing fertility rate within this population of women with psychotic illnesses – due in part to both the success of modern treatments which includes the availability of prolactin sparing options and the tendency to manifest during the reproductive years – all clinicians will at some time need to consider the inherent risks of treatment and nontreatment in the perinatal setting [Galbally *et al.* 2010; Gentile, 2010]. Ideally, this is discussed with a woman prior to pregnancy. When consideration is made to continue treatment in pregnancy, often a history of response to a particular medication is relevant to this decision given the risks to maternal mental health of changing to a medication which is then found not to be effective for an individual.

There remains a lack of clarity regarding the natural course of psychotic illnesses during pregnancy. It has been proposed that this altered physiological and psychological state may exert a favorable effect on the course of illness [Grof *et al.* 2000]; however, more recent studies suggest an elevated recurrence rate [Viguera *et al.* 2011]. A 1995 literature review reported that patients with schizophrenia who stop taking antipsychotic medication have a cumulative relapse rate of 53% over a 10-month period compared with 16% among patients who continue treatment [Gilbert *et al.* 1995]. Rapid withdrawal that frequently accompanies the diagnosis of pregnancy, early onset of illness, younger age, high antipsychotic dose requirement and recent psychiatric hospitalization have all been found to be predictors of relapse [Baldessarini and Viguera, 1995]. Similarly, in a prospective study that examined the effects of mood stabilizer cessation during pregnancy, those women with bipolar disorder were more than twice as likely to relapse in pregnancy (85.5% *versus* 37%) compared with women who continued treatment [Viguera *et al.* 2007]. Thus, pregnancy needs to be considered to be a high-risk period for relapse, particularly in the setting of discontinuation of maintenance treatment.

The uses of antipsychotic medications have increasingly extended beyond their use in schizophrenia and bipolar disorder, and are frequently being prescribed for mood and anxiety disorders, self-harming behaviors, trauma-related conditions and even insomnia. Thus, it is essential that an adequate risk benefit analysis be performed whenever any medication is being prescribed in the perinatal setting, or if there is a potential for pregnancy, and a process of obtaining informed consent adhered to. Consideration needs to be given to the risks of teratogenesis, obstetric complications, impairment of neonatal adaption and negative neurodevelopmental outcome. Once decisions are made and enacted a comprehensive plan for obstetric, pediatric and psychiatric monitoring needs to be put in place [Galbally *et al.* 2010].

Risk of structural teratogenicity

All antipsychotics cross the placenta [Newport *et al.* 2007] and, as such, consideration needs to

be given to their potential to cause structural or functional dysgenesis of fetal organs and/or skeletal structures when exposure occurs in first trimester. It is generally considered that the baseline population rate for malformation in the general population is 1–3%.

Most of the FGAs have been available for around four decades and share the action of D_2 receptor blockade throughout the brain, in particular the mesolimbic system. A comprehensive literature review was unable to identify any teratogenic risk associated with the use of promethazine, chlorpromazine, prochlorperazine, haloperidol, perphenazine, trifluoperazine, loxapine, thioridazine, flupenthixol or fluphenazine [Einarson and Boskovic, 2009]. However, the authors warned that less rigorous research standards and flawed methodologies limit our ability to accept these findings without question. The SGAs are newer agents that share a mechanism of action that involves a relatively potent blockade of 5-HT(2A) receptors coupled with transient occupation of the D_2 receptor. The same review examined all available data regarding fetal exposure to clozapine, risperidone, olanzapine, quetiapine, ziprasidone and aripiprazole [Einarson and Boskovic, 2009], and no clear association with any specific malformation has emerged. However, no single agent has begun to approximate the 500 recorded and examined exposures required to determine differences in the occurrence of malformation.

A Swedish Medical Birth Register study found that maternal use of antipsychotic medication (grouping both FGAs and SGAs) was associated with a small, but statistically significant increased risk of major malformation (mainly atrium or ventricular septum defects) [OR 1.52 (1.05–2.19) with 95% CI adjusted for year of birth, maternal age, parity, smoking and previous miscarriages] [Reis and Kallen, 2008] None of these findings were specific to an individual drug. A further systematic review of antipsychotic therapy during early and late pregnancy concluded that, at present, we are unable to advise adequately regarding malformation risk secondary to *in utero* exposure to SGAs [Gentile, 2010].

Risk of adverse obstetric outcome

There is some evidence to suggest that the overall risk for obstetric complications is increased in women with severe mental illness independent of any associated antipsychotic exposure. A Danish study reported an adjusted excess risk of 1.57 (95% CI 1.36–1.82) for low birth weight and 1.34 (95% CI 1.17–1.53) for small-for-gestational-age [Bennedsen *et al.* 1999], and an Australian study of women with schizophrenia or major affective disorder showed a raised risk of placental abnormalities and antepartum hemorrhage [Jablensky *et al.* 2005].

The potential risks associated specifically with antipsychotic use in pregnancy have included gestational diabetes, particularly with the SGAs, some of which are known to increase the risk of diabetes in general adult patients. They have also been associated with prematurity, low and high birth weight; the latter may be associated with gestational diabetes and caesarian delivery.

A large Swedish Medical Birth Register study which examined risks associated with maternal use of antipsychotic medication (grouping both FGAs and SGAs) found these agents were associated with increased risks for gestational diabetes OR 1.78 (1.04–3.01), premature delivery OR 1.73 (1.31–2.29), low birth weight OR 1.67 (1.21–2.29) and caesarian delivery OR 1.43 (1.17–1.74) [Reis *et al.* 2008]. An elevated risk for prematurity OR 2.46 (1.50–4.11), in those receiving FGAs, was also found in a Taiwanese study [Lin *et al.* 2010]. Further studies have found antipsychotic medications to be associated with both low birth weight and large-for-dates babies; the latter mainly associated with exposure to SGAs [McKenna *et al.* 2005; Newham *et al.* 2008].

Unfortunately, to date none of the study designs have been able to adequately control for medication adherence, psychiatric or physical comorbidity, substance and alcohol abuse, smoking and the underlying risks associated with the illness being treated.

Risk to the neonate

It remains unclear to what extent antipsychotics may complicate the neonatal period due to the absence of systematic studies. However, it is reasonable to suspect that there may be an increased risk of neonatal withdrawal, extra-pyramidal symptoms (EPS) and sedation [Gentile, 2010; Galbally *et al.* 2011]. Exposure to antipsychotics is inevitably coupled with exposure to maternal mental illness and associated comorbidity such as physical illnesses, poor nutrition, smoking, substance and

alcohol abuse, and trauma, and it is extremely difficult to separate the specific influence of antipsychotic medication on fetal outcome.

In 2011, the US Food and Drug Administration (FDA) issued a drug safety communication regarding concerns about fetal exposure to any antipsychotic and the association with abnormal muscle movements (EPS) and withdrawal symptoms. This warning was prompted by the FDA's database where 69 cases of neonatal EPS or withdrawal had been identified across both classes of antipsychotics. Symptoms of EPS in neonates have included motor restlessness, tremor, hypertonicity, dystonia and parkinsonism. A study specifically of FGAs found hypertonicity, tremulousness and poor motor maturity in neonates [Auerbach *et al.* 1992]. Duration of symptoms tended to be transient and brief, although one infant exposed to phenothiazines experienced hypertonicity for 10 months that was followed by subsequent normal motor development.

There is an extreme paucity of data relating to neonatal toxicity in newborns exposed to SGAs. It is reasonable to suspect that the potential for a medication to compromise neonatal adaption may relate to its level of placental passage. In an important prospective observational study of 54 pregnant women, Newport and colleagues found the placental passage ratio was highest for olanzapine [mean = 72.1%, standard deviation (SD) = 42.0%], followed by haloperidol (mean = 65.5%, SD = 40.3%), risperidone (mean = 49.2%, SD = 33.9%) and quetiapine (mean = 23.8%, SD = 11.0%) [Newport *et al.* 2007]. There were higher rates of low birth weight (30.8%) and neonatal intensive care unit admission (30.8%) among neonates exposed to olanzapine, though these did not reach statistical significance [Newport *et al.* 2007].

Given the paucity of literature and recommendations for neonatal adaptation or withdrawal following antipsychotic exposure, a literature search was performed to identify all papers reporting on poor neonatal adaptation associated with antipsychotic use in pregnancy. The PUBMED, MEDLINE, EMBASE and PsychINFO databases were searched for papers published in English from 1966 to 2013 using the MeSH/free-text search terms 'poor neonatal adaptation', 'neonatal abstinence', 'neonatal withdrawal', 'neonatal toxicity', 'antipsychotic' and 'psychotropic'. The results are summarised in Table 1.

Longer term risk of adverse neurodevelopmental outcome

A number of published reports have identified the offspring of mothers with psychotic illnesses as being at greater risk of delays in neurological and motor development, generalized cognitive deficits and learning difficulties as well as poorer performance than controls on specific neurocognitive tasks [Abel and Howard, 2014]. However, the potential effects of fetal antipsychotic exposure were not taken into consideration. Schizophrenia has also been associated with poorer maternal sensitivity towards infants with potential to impact on later socioemotional development [Snellen *et al.* 1999; Wan *et al.* 2007; Wan and Green, 2009]. These studies suggest that the mothers with symptomatic illness, potentially from being untreated or undertreated, is associated with poorer mother–child outcomes.

There is an extreme paucity of studies that investigate the neurodevelopmental effects of prenatal exposure to both FGAs and SGAs. There are three studies which have examined FGAs. The first is a case controlled study of long-term behavioral outcomes following exposure to phenothiazine agents (n = 63) [Stika *et al.* 1990] and the second a retrospective study of promethazine exposure (n = 127) [Czeizel *et al.* 1999]. Neither revealed adverse neurocognitive outcomes, although significant methodological and design issues limit our ability to draw conclusions. The third, a larger study described the effects of first trimester exposure to FGAs, found that the intelligence quotients (IQs) at 4 years of age for the 1309 exposed children were similar to the 48,973 nonexposed children [Slone *et al.* 1977].

The two most recent studies have examined SGAs and each followed a prospective case-controlled design. Both found an association between *in utero* exposure to SGAs and early delayed neuromotor performance [Johnson *et al.* 2012; Peng *et al.* 2013]. The more recent study also found delayed cognitive, socioemotional and adaptive behavior scores on the Bayley Scales of Infant Development at 2 months of age, although reassuringly these differences were no longer significant by 12 months [Peng *et al.* 2013]. This finding is encouraging, suggesting that, while there may be a risk of delay, there is not permanent impairment; further studies with longer follow-up periods and more comprehensive assessment of child

Table 1. Neonatal adaptation and exposure to antipsychotic medication in pregnancy.

Study	Study type	Number of subjects	Medication	Outcome
US FDA [2011]	Retrospective review	69 pregnancies reported to Adverse Event Reporting System	Typical and atypical antipsychotics	Motor and behavioral symptoms potentially associated with withdrawal in neonatal period
Coppola *et al.* [2007]	Retrospective and prospective observational data	713 pregnancies, 516 prospective (68 with known outcome), 197 retrospective	Risperidone	37 retrospective reports of perinatal syndrome, 21 with behavior or motor disorders
Newport *et al.* [2007]	Prospective observational study	54	Olanzapine, haloperidol, risperidone, quetiapine	6 NICU admissions, 7 respiratory complications, 12 cardiovascular complications, 2 hypotonia
Auerbach *et al.* [1992]	Prospective case control	29 psychiatrically unwell women, 12 taking antipsychotics	Antipsychotics	Neonates exposed to antipsychotics in utero showed poor neonatal motor functioning compared with controls, speculated to reflect withdrawal syndrome

development are required. Given the higher rate of exposure to other variables that may impact on child development such as smoking, alcohol, illicit drugs, as well as maternal mental illness there needs to be studies which adequately control for this as well. In addition, studies need to follow up children long enough so that rigorous measures with good predictive validity can be undertaken.

Summary

In a literature review published in 2009, Einarson and Boskovic summarised the data available from 1996 to 2008 [Einarson and Boskovic, 2009]. A general paucity of studies examining the safety of antipsychotic medication during pregnancy was found, so while overall no clear evidence of increased risk of birth defects or other adverse outcomes was identified, the authors cautioned any conclusions. A 2004 Cochrane review of antipsychotic medication in pregnancy found no studies met the inclusion criteria and this resulted in 'serious clinical and ethical problems' [Webb *et al.* 2004]. For this current review, the 2009 Einarson and Boskovic review has been augmented by an additional search for all original data assessing the safety of antipsychotic drugs during pregnancy published in English from 2008 to October 2013. The MEDLINE, PUBMED, EMBASE and PsychINFO databases were searched and the results are summarised in Table 2.

Other psychopharmacological treatments for bipolar disorder

While this review is limited to antipsychotic treatments in pregnancy, particularly for bipolar disorder, there are other psychopharmacological treatments that are prescribed either alone or in combination with antipsychotic medications. These include antiepileptic drugs such as sodium valproate, carbamazepine and lamotrigine, and also the mood stabilizer lithium carbonate. A systematic review was published in 2010 outlining the risks from pregnancy exposure [Galbally *et al.* 2010]. The literature on antiepileptic drugs (AEDs) is now substantial with comprehensive follow up of children. There is clear evidence of an association between certain AEDs, such as sodium valproate, and malformation risk. There is also an association with sodium valproate, particularly at doses above 1000 g, with lower cognitive outcomes in children exposed [Galbally *et al.* 2010]. The literature on lithium carbonate is far more limited, but there is evidence of an increased risk of Ebstein's anomaly, a cardiac malformation [Galbally *et al.* 2010].

Table 2. Antipsychotic medications and pregnancy outcomes from 2008 to October 2013.

Study	Study design	Number of subjects	Medication	Findings
Brunner *et al.* [2013]	Prospective observational study	610	Olanzapine	No difference in pregnancy and neonatal outcome compared with general population data.
Habermann *et al.* [2013]	Prospective cohort study	1967	Typical antipsychotics (*n* = 284), atypical antipsychotics (*n* = 561), controls (*n* = 1122)	Higher rate of major malformations in neonates exposed to atypical antipsychotics. Higher rates of postnatal disorders in neonates observed in groups exposed to typical and atypical antipsychotics. Preterm birth and low birth weight more common with exposure to typical antipsychotics.
Peng *et al.* [2013]	Prospective case control study	152	Atypical antipsychotics (*n* = 76)	More exposed infants had lower birth weight. Lower scores on Bayley Scales of Infant Development for exposed infants at 2 months, but no significant difference at 12 months.
Boden *et al.* [2012]	Population-based cohort study	358 203	Olanzapine/ clozapine (169), other antipsychotics (338) or none (357,696)	Exposure to antipsychotics increased the risk of gestational diabetes. No increased risk of SGA. Olanzapine/clozapine associated with macrocephaly
Johnson *et al.* [2012]	Prospective case control	309	Exposed to antipsychotics (22), antidepressants (202) or no psychotropics (85)	A history of *in utero* antipsychotic exposure was associated with lower scores on a standardized test of neuromotor performance in 6 month olds compared with antidepressant or no psychotropic exposure.
Babu *et al.* [2010]	Prospective cohort study	70	Olanzapine	Olanzapine may be associated with higher birth weight.
Lin *et al.* [2010]	Birth data	4176	Typical and atypical antipsychotics	Higher risk of preterm birth for mothers prescribed typical antipsychotics. No significant difference in rates of low birth weight, LGA or SGA.
Wichman [2009]	Retrospective case file review	16	Aripiprazole (2), quetiapine (10), risperidone (4), ziprasidone (1)	One major malformation with ventriculomegaly and hydrocephalus in an infant exposed to aripiprazole. Shortened gestational age.

Non-pharmacological management

While pharmacological treatment is often important in both the treatment and prevention of relapse for schizophrenia and bipolar disorder (particularly in pregnancy and the postpartum), ensuring there is adequate support for women and their families cannot be underestimated as part of management. There are no specific psychological interventions for women with schizophrenia and bipolar disorder in pregnancy and in a review of mother–infant interventions for women with schizophrenia none were identified [Wan *et al.* 2008]. Yet limited research suggests that women with schizophrenia do have significant challenges in early mother–infant interactions and the developing relationship [Snellen *et al.* 1999]. Therefore, it is important as part of managing a woman across pregnancy and into the

Box 1. Management recommendations for antipsychotics use in pregnancy.

1. Wherever possible, taking into account the potential for pregnancy, preconception consideration should be given to the most appropriate form of pharmacological treatment.
2. Strive for the minimal effective dose of antipsychotic medication. However, the emphasis needs to be on **effective** rather than **minimal**, and partial treatment should be avoided as this exposes the fetus to **both** the risks of treatment and nontreatment.
3. Optimize the therapeutic alliance and nonpharmacological treatments.
4. Establish a close liaison relationship between all disciplines involved in perinatal care: psychiatry, psychology, obstetrics, pediatrics, midwifery, social work, and maternal and child health nursing.
5. Obtain baseline measures of biological parameters that could be compromised by illness and its treatment.
6. Ensure that a process of obtaining informed consent is followed in which all available information regarding the risks and benefits of treatment and nontreatment in the perinatal setting is detailed.
7. Prescribe 5 mg of folate daily from three months preconception and throughout pregnancy, as there is some evidence to suggest that this may be neuroprotective, as well as multivitamins.
8. Aim for monotherapy wherever possible.
9. Ideally, a treatment team that specializes in high-risk scenarios should undertake obstetric care.
10. Ensure that adequate monitoring throughout pregnancy occurs of fetal development, obstetric physiology and maternal mental state.
11. Ultrasound assessment that focuses on nuchal translucency should be performed at 12 weeks, followed by a high-resolution morphology scan performed at 20 weeks' gestation.
12. Given the potential for increased risk of metabolic syndrome and gestational diabetes with SGAs, glucose tolerance testing rather than glucose challenge testing should be performed early in the second trimester (14–16 weeks) and again at 28 weeks' gestation.
13. Similarly, adequate review of fetal growth (preferably through growth scanning at 28 and 34 weeks and further as indicated) is essential given the increased risk of impaired growth, including low and large birth weight.
14. At delivery, commence observation for evidence of neonatal withdrawal, toxicity, extrapyramidal symptoms, sedation or other adverse effect, and ensure that a careful morphological examination is undertaken.
15. Create and implement a Mental Health Care Plan for the postdelivery maternity setting that encourages a low stimulus environment, sleep preservation, close liaison between all healthcare providers, and allow an extended maternity stay in which observations can be made for any neonatal compromise secondary to exposure to psychotropic medications *in utero*.
16. Establish early warning signs for relapse and pathways to care should this occur.
17. Give clear recommendations and preferences for breastfeeding (either for breastfeeding or not) with ideally, a discussion of risks and benefits for particular medications, prior to delivery. Avoid pharmacological suppression of lactation.

postpartum to ensure that there is adequate support for her and her infant and, where possible, her partner and family.

Management recommendations for antipsychotics use in pregnancy

The recommendations in Box 1 are intended as suggestions only, given that many women with schizophrenia and bipolar disorder and women with other severe mental illnesses that require antipsychotic medications will need to continue their medication well in the perinatal period. Each woman requires an individual management plan derived for her circumstances for pregnancy management. These recommendations were derived as part of a specific antenatal clinic for women with schizophrenia and bipolar disorder at Mercy Hospital for Women (Australia) and were developed as a collaboration with obstetrics, maternal-fetal medicine and psychiatry [Galbally *et al.* 2010].

Postpartum

A clear plan for a woman and her supports (partner and family as appropriate) for postpartum care is important for ongoing monitoring and care. This should include monitoring of maternal

mental health, infant health and wellbeing, and the developing relationship between mother and baby. The crucial role of a woman's supports, whether they be a partner or wider family, cannot be underestimated and, where possible, communication and support of her family is important in ensuring both maternal and infant wellbeing. Clear recommendations about breastfeeding and sleep are also helpful for women and their families. These recommendations will depend on a discussion of the risk and benefits of breastfeeding according to the profile of the specific medication prescribed and the role of sleep in increasing vulnerability to relapse for an individual woman. Given the lack of data regarding longer term outcomes for children exposed to antipsychotic medication in pregnancy, ensuring there is appropriate ongoing monitoring of infant and child development is optimal.

Conclusion

While there is only limited knowledge about the safety of antipsychotic medications in pregnancy, this must be balanced with their important role in keeping women with schizophrenia and bipolar disorder well across this crucial life stage. There is evidence to suggest that maternal mental illness is associated with not only increased morbidity for mother and baby but also maternal mortality [Austin *et al.* 2007]. In addition, mothers who are unwell with these illnesses are less sensitive in their parenting [Snellen *et al.* 1999] and this may increase the risk of abuse and neglect [Niemi *et al.* 2004]. However, this current review has also raised the issue of wider use of antipsychotic medications for indications beyond schizophrenia and bipolar, and given the paucity of data regarding safety of these medications in pregnancy, this is an area of use where a careful risk benefit analysis needs to be made.

Future studies are needed which are well designed, prospective and follow children up for a long enough period to be able to accurately assess development. These studies also need to account adequately for key confounding variables such as maternal illness, illicit drugs, smoking and alcohol, as well as accurate measures of exposure. This has been achieved to a large extent with epilepsy and the anti-epileptic medications [Meador *et al.* 2008; Galbally *et al.* 2010] and is now urgently required for antipsychotic medications.

Acknowledgements

The authors wish to acknowledge Professor Michael Permezel and Professor Sue Walker for their contribution to the guidelines for the management of antipsychotics in pregnancy.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

The authors declare no conflict of interest in preparing this article.

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