TECHNICAL COMMENTARY

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Treatments during pregnancy and breastfeeding

Introduction

Antipsychotic use during pregnancy requires careful consideration of the mother's risk of illness relapse, against the risk of harm or complications for the developing infant if medication is to be continued. However, there is currently very little evidence regarding the use of antipsychotics for schizophrenia during pregnancy and the postpartum period.

Method

We have included only systematic reviews (systematic literature search, detailed methodology with inclusion/exclusion criteria) published in full text, in English, from the year 2000 that report results separately for people with a diagnosis of schizophrenia, schizoaffective disorder, schizophreniform disorder or first episode schizophrenia. Reviews were identified by searching the databases MEDLINE, EMBASE, CINAHL, Current Contents, PsycINFO and the Cochrane library. Hand searching reference lists of identified reviews was also conducted. When multiple copies of reviews were found, only the most recent version was included. Reviews with pooled data are prioritised for inclusion.

Review reporting assessment was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist, which describes a preferred way to present a meta-analysis[1]. Reviews rated as having less than 50% of items checked have been excluded from the library. The PRISMA flow diagram is a suggested way of providing information about studies included and excluded with reasons for exclusion. Where no flow diagram has been presented by individual reviews, but identified studies have been described in the text, reviews have been checked for this item. Note that early reviews may have been guided by less stringent reporting checklists than the PRISMA, and that some reviews may have been limited by journal guidelines.

Evidence was graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group approach where high quality evidence such as that gained from randomised controlled trials (RCTs) may be downgraded to moderate or low if review and study quality is limited, if there is inconsistency in results, indirect comparisons, imprecise or sparse data and high probability of reporting bias. It may also be downgraded if risks associated with the intervention or other matter under review are high. Conversely, low quality evidence such as that gained from observational studies may be upgraded if effect sizes are large or if there is a dose dependent response. We have also taken into account sample size and whether results are consistent, precise and direct with low associated risks (see end of table for an explanation of these terms)[2]. The resulting table represents an objective summary of the available evidence, although the conclusions are solely the opinion of staff of NeuRA (Neuroscience Research Australia).

Results

We found six systematic reviews that met inclusion criteria[3-8].

- High quality evidence finds a small, increased risk of gestational diabetes mellitus during pregnancy with antipsychotic use (first or second generation).
- Moderate quality evidence suggests a small increased risk of heart defect or lower birth weight in infants, and a small increased risk of preterm delivery but not stillbirth, with exposure to antipsychotics.
- Moderate to low quality evidence is unsure about risk of termination or spontaneous abortion, and size and malformation in infants with exposure to antipsychotics.

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Coughlin CG, Blackwell KA, Bartley C, Hay M, Yonkers KA, Bloch MH

Obstetric and neonatal outcomes after antipsychotic medication exposure in pregnancy

Obstetrics and gynecology 2015: 125; 1224-35

View review abstract online

Comparison	**Adverse effects of antipsychotic use during pregnancy vs. no antipsychotic use during pregnancy.** **This review included women taking antipsychotics regardless of disorder (e.g. schizophrenia and bipolar disorder).** **Authors report that the studies did not routinely adjust for potential confounding factors, such as other medications.**
Summary of evidence	**Moderate quality evidence (large samples, consistent, imprecise, indirect) suggests a small increased risk of heart defect or lower birth weight in infants, and a small increased risk of preterm delivery, but not stillbirth, with exposure to antipsychotics (first or second generation).** **Lower quality evidence is unsure about risk of termination or spontaneous abortion, and size and malformation in infants with exposure to antipsychotics.**

Prenatal factors

Elective termination

A large, significant effect of increased risk of elective termination in women on antipsychotics;

4 cohort studies, N = 3,788, OR = 5.98, 95%CI 2.94 to 12.14, $p < 0.001$, $I^2 = 73\%$, $p = 0.01$

Spontaneous abortion

No significant difference between groups;

4 cohort studies, N = 3,788, OR = 1.05, 95%CI 0.61 to 1.81, $p = 0.86$, $I^2 = 70\%$, $p = 0.02$

Perinatal factors

Preterm delivery

A small, significant effect of increased risk of preterm delivery in women on antipsychotics;

7 cohort studies, N = 1,534,350, OR = 1.86, 95%CI 1.45 to 2.39, $p < 0.00001$, $I^2 = 46\%$, $p = 0.08$

Stillbirth

No significant differences between groups;

3 cohort studies, N = 1,018,795, OR = 1.18, 95%CI 0.88 to 1.57, $p = 0.27$, $I^2 = 0\%$, $p = 0.47$

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Postnatal factors
Small for gestational age at birth *A small, significant effect of increased risk of being small for gestational age at birth in infants exposed to antipsychotics;* 4 cohort studies, N = 1,578,906, OR = 2.44, 95%CI 1.22 to 4.86, p = 0.01, I^2 = 81%, p = 0.001 Large for gestational age at birth; *No significant differences between groups;* 4 cohort studies, N = 1,578,906, OR = 2.50, 95%CI 0.77 to 8.16, p = 0.13, I^2 = 91%, p < 0.001 Low birth weight *A small, significant effect of lower birth weight in infants exposed to antipsychotics;* 3 cohort studies, N = 358,677, WMD = -0.57.89g, 95%CI -103.69 to -12.10, p = 0.01, I^2 = 0%, p = 0.37 Any malformation *A small, significant increased risk of any major malformation in infants exposed to antipsychotics;* 7 cohort studies, N = 1,640,660, OR = 2.12, 95%CI 1.25 to 3.57, p = 0.005, I^2 = 84%, p < 0.001 Meta-regression demonstrated a significant association between increased study quality and increased effect size. Heart defect *A small, significant increased risk of any heart defect in infants exposed to antipsychotics;* 4 cohort studies, N = 1,628,021, OR = 2.09, 95%CI 1.50 to 2.91, p < 0.001, I^2 = 0%, p = 0.48 Authors report no differences in results according to first vs, second generation antipsychotics.

Consistency in results‡	Consistent for heart defect, low birth weight, stillbirth, and preterm delivery. Inconsistent for elective termination, spontaneous abortion, gestational age, and any malformation.
Precision in results§	Imprecise
Directness of results‖	Indirect for schizophrenia (mixed samples).

Gentile S

Clinical utilisation of atypical antipsychotics in pregnancy and lactation

The Annals of Pharmacotherapy 2004; 38: 1265-71

View review abstract online

Treatments during pregnancy and breastfeeding

Comparison	Assessment of antipsychotic drug use during pregnancy and lactation in women with schizophrenia.
Summary of evidence	Moderate to low quality evidence (unclear sample size, unable to assess consistency or precision, direct) is unclear as to any adverse effects of antipsychotic use during pregnancy and lactation.

Olanzapine

1 study (N = 23) reported that rates of spontaneous abortion, stillbirth, and premature delivery in pregnant women taking olanzapine were within the range of normal rates. A further study (N = 96) expanded the previous study sample and also reported similar rates to the general population; however, there was a higher rate of malformations compared to the general population (8% vs. 4%).

In 2 studies (N = 21), 5 infants reported adverse effects (jaundice, sedation, cardiac effects, shaking, movement effects and gastrointestinal upset), following breastfeeding in women taking olanzapine, but these could not be specifically linked to the medication.

1 study (N = 12) found the milk/plasma ratio of olanzapine in mothers ranged from 0.10 to 0.84, and the relative infant dose was 0.22-2.5% of the weight-adjusted maternal dose. All infants experienced no adverse reactions.

Quetiapine

3 case-studies report no complications or adverse events following quetiapine administration to three women during pregnancy.

There were no studies reporting the secretion of quetiapine in breast milk.

Risperidone

1 study (N = 7684) included 10 pregnancies in which the women continued to take risperidone and reported no adverse effects. 2 case-studies similarly reported normal development at 12 months in infants exposed to risperidone during pregnancy. One case-study reported agenesis of the corpus callosum in an infant exposed to risperidone during pregnancy.

2 studies (N = 11) suggest rates of spontaneous abortion in offspring of pregnant women taking risperidone were within the range of normal rates; however there was a higher rate of malformations compared to the general population (9% vs. 4%).

1 study (N = 4) found the milk/plasma ratio of risperidone in mothers ranged from 0.10 to 0.42, and the relative infant dose was 0.42% of the weight-adjusted maternal dose. Two case-studies also found no trace of risperidone or metabolites in infants breastfed while mothers were taking risperidone, and no adverse effects were reported.

Clozapine

2 studies (N = 188) suggest rates of spontaneous abortion in offspring of pregnant women taking risperidone were within the range of normal rates; however there was a higher rate of malformations in this study compared to the general population (10% vs. 4%).

3 case-studies suggest no association between clozapine exposure during pregnancy and congenital anomalies.

5 case-studies suggest metabolic complications in pregnant women taking clozapine.

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3 case-studies reported sedation, agranulocytosis, and cardiovascular effects in infants following breastfeeding with mothers taking clozapine. 1 case-study found the milk/plasma ratio of clozapine in mothers ranged from 2.79-4.32, and the relative infant dose was 1.2% of the weight-adjusted maternal dose.	
Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Direct

Gentile S

Infant safety with antipsychotic therapy in breast-feeding: a systematic review

Journal of Clinical Psychiatry 2008; 69: 666-673

View review abstract online

Comparison	**Assessment of first and second generation antipsychotic drug use during lactation.**
Summary of evidence	**Moderate to low quality evidence (unclear sample size, unable to assess consistency or precision) is unclear as to any adverse effects of antipsychotic use during lactation.**

Second-generation antipsychotics

Aripiprazole

1 case-study reported that a woman treated with aripiprazole was unable to successfully lactate. It is unknown whether aripiprazole was secreted in the breast milk.

Clozapine

1 study (N = 4) reported adverse events in two cases, including neurodevelopmental delay (delayed speed acquisition), sedation and agranulocytosis.

1 case-study found high concentrations of clozapine in the breast milk (milk/plasma ratio = 2.79).

Olanzapine

1 study (N = 5) found low levels of olanzapine secreted in breast milk, with infant dose ranging from 0.66 to 2.66% of the weight-adjusted maternal dose.

Quetiapine

1 case-study found low levels of quetiapine secreted in breast milk, with infant dose ranging from 0.09 to 0.43% of the weight-adjusted maternal dose.

1 study (N = 6) found that 2 cases showed signs of mild neurodevelopmental delay, but this was not

specifically attributable to quetiapine. Risperidone 1 case-study found no adverse reactions to risperidone treatment during lactation. 2 case-studies reported relative infant doses were calculated to reach 2.3-4.7% of the weight-adjusted maternal dose. Infants were not reported to show any neurodevelopmental delays or adverse effects.
First-generation antipsychotics Flupenthixol 1 case-study found no adverse reactions to flupenthixol treatment during lactation. Chlorpromazine 4 studies (N = 21) suggested no adverse effects or developmental delays in infants exposed to chlorpromazine through breast milk. 1 study (N = 4) reported 1 case of infant drowsiness with high levels of chlorpromazine secreted in the breast milk. Trifluoperazine 1 study (N = 6) found no adverse reactions to trifluoperazine treatment during lactation.

Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Direct

Gentile S

Antipsychotic therapy during early and late pregnancy: a systematic review

Schizophrenia Bulletin 2010; 36(3): 518-544

View review abstract online

Comparison	**Assessment of antipsychotic drug use during pregnancy in women with schizophrenia.** **Many of these results are confounded by the concomitant use of other neuroleptic or psychoactive medications.**
Summary of evidence	**Moderate to low quality evidence (unclear sample size, unable to assess consistency or precision, direct) is unclear as to the adverse effects of antipsychotic use during pregnancy.**
Second-generation antipsychotics	

Aripiprazole

3 case-studies report 2 healthy cases and one case of neonatal tachycardia following exposure to aripiprazole during pregnancy.

Clozapine

19 studies (N = 221) found cases of major malformations, spontaneous abortion, gestational diabetes, poor pregnancy outcome, and perinatal adverse reactions associated with exposure to clozapine during pregnancy. One report of clozapine overdose was associated with fatal poisoning of the infant.

Olanzapine

22 studies (N = 454) found cases of major malformations, spontaneous abortion, gestational diabetes, neonatal adverse reactions and neurodevelopmental delay associated with exposure to olanzapine during pregnancy.

1 study reported that olanzapine had higher rates of placental transfer compared to other antipsychotics.

Quetiapine

14 studies (N = 227) report few cases of spontaneous abortion, cardiovascular and respiratory complications, but quetiapine during pregnancy was mostly associated with healthy outcomes

Risperidone

12 studies (N = 322) reported multiple instances of major malformations, spontaneous abortions, perinatal post-natal complications, and gestational diabetes following exposure to risperidone during pregnancy.

First-generation antipsychotics

Haloperidol

13 studies (N = 411) found cases of limb and other malformations, spontaneous abortion, perinatal complications, cardiovascular, respiratory and motor complications, gestational diabetes following exposure to haloperidol during pregnancy.

Penfluridol

1 study (N = 27) reported one case of limb malformation following exposure to penfluridol during pregnancy.

Pimozide

2 studies (N = 6) found no cases of malformation or complications following exposure to pimozide, but one case of premature birth.

Flupenthixol

1 study (N = 98) found cardiac and visceral malformations in 3 infants exposed to flupenthixol treatment during pregnancy, as well as one case of gestational diabetes.

Chlorprothixene

1 study (N = 5) found no adverse following exposure to chlorprothixene during pregnancy.

Zuclopenthixol

1 study (N = 75) found cardiac and visceral malformations in 9 infants following exposure to

zuclopenthixol during pregnancy, as well as 5 cases of gestational diabetes. Penothiazines 7 studies (N = 4,052) found 341 cases of cardiac, limb or visceral malformations, plus 180 cases of spontaneous abortion, stillbirth and 4 premature deliveries. Chlorpromazine 20 studies (N = 288) found 5 cases of limb malformation, and 17 cases of perinatal complications, 1 spontaneous abortion, 1 still birth, 1 small birth weight, and 8 motor complications following chlorpromazine exposure during gestation. Prochlorperazine 6 studies (N = 306) found 17 cases of limb or visceral malformation and one case of neonatal death. Trifluoperazine 8 studies (N = 1030) reported 19 cases of major limb or visceral malformations, 14 spontaneous abortions, and 5 stillbirths. Fluphenazine 3 studies (N = 262) reported 6 cases of malformations, 6 stillbirths, 19 spontaneous abortions, and 1 case of gestational diabetes. Thioridazine 4 studies (N = 58) found 1 case of malformation and 1 case of hypertonia. Thiethylperazine 2 studies (N = 34) found 1 case of neurological malformation and 26 cases of cleft palate. Promethazine 1 study (N = 165) reported 7 cases of unspecified malformations following promethazine during pregnancy. Perphenazine 2 studies (N = 92) found 4 cases of malformations (neurological, visceral) plus one case of gestational diabetes. Levomepromazine 1 study (N = 50) found 2 cases of limb malformation and 1 case of gestational diabetes.	
Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Direct

Uguz F

Second-generation antipsychotics during the lactation period: A

comparative systematic review on infant safety

Journal of Clinical Psychopharmacology 2016; 36(3): 244-52

View review abstract online

Comparison	**Assessment of second generation antipsychotic drug use during lactation.**
Summary of evidence	**Moderate to low quality evidence (unclear sample size, unable to assess consistency or precision, direct) is unclear as to any adverse effects of antipsychotic use during lactation.**

Relative infant dose (RID); the amount of antipsychotics excreted into breast milk (weight-adjusted for the infant), or milk-to-plasma ratio (M/P ratio); an estimate of transfer of the antipsychotics from the maternal plasma to milk.

37 studies report on 206 infants exposed to olanzapine (k = 170), quetiapine (k = 14), risperidone/paliperidone (k = 8), clozapine (k = 6), aripiprazole (k = 4), ziprasidone (k = 2) or amisulpride (k = 2).

Authors report reasonable confidence that olanzapine has low RID values and limited confidence that quetiapine and ziprasidone also have low RID values. There are moderate RID values for risperidone/paliperidone and aripiprazole, and high RID values for amisulpride.

Antipsychotic levels were undetectable in the plasma of most of the exposed infants.

Risks	No clear pattern of adverse effects was established.
Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Direct

Wang Z, Wong ICK, Man KKC, Alfageh BH, Mongkhon P, Brauer R

The use of antipsychotic agents during pregnancy and the risk of gestational diabetes mellitus: a systematic review and meta-analysis

Psychological Medicine 2020; Jan: 1-10

View review abstract online

Comparison	**Assessment of antipsychotic use during pregnancy on risk of gestational diabetes mellitus.**
Summary of evidence	**High quality evidence (large sample, consistent, precise, direct) finds a small, increased risk of gestational diabetes mellitus**

	during pregnancy with antipsychotic use.
Gestational diabetes mellitus	
A small, significant effect of increased risk of gestational diabetes mellitus; 6 cohort studies, N = 917,602, RR = 1.24, 95%CI 1.09 to 1.42, $p < 0.05$, $I^2 = 6.7\%$	
Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct

Explanation of acronyms

CI = confidence interval, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), N = number of participants, OR = odds ratio, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), RR = relative risk, vs. = versus, WMD = weighted mean difference

Explanation of technical terms

* Bias has the potential to affect reviews of both RCT and observational studies. Forms of bias include; reporting bias – selective reporting of results; publication bias - trials that are not formally published tend to show less effect than published trials, further if there are statistically significant differences between groups in a trial, these trial results tend to get published before those of trials without significant differences; language bias – only including English language reports; funding bias - source of funding for the primary research with selective reporting of results within primary studies; outcome variable selection bias; database bias - including reports from some databases and not others; citation bias - preferential citation of authors. Trials can also be subject to bias when evaluators are not blind to treatment condition and selection bias of participants if trial samples are small[9].

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† Different effect measures are reported by different reviews.

Prevalence refers to how many existing cases there are at a particular point in time. Incidence refers to how many new cases there are per population in a specified time period. Incidence is usually reported as the number of new cases per 100,000 people per year. Alternatively some studies present the number of new cases that have accumulated over several years against a person-years denominator. This denominator is the sum of individual units of time that the persons in the population are at risk of becoming a case. It takes into account the size of the underlying population sample and its age structure over the duration of observation.

Reliability and validity refers to how accurate the instrument is. Sensitivity is the proportion of actual positives that are correctly identified (100% sensitivity = correct identification of all actual positives) and specificity is the proportion of negatives that are correctly identified (100% specificity = not identifying anyone as positive if they are truly not).

Weighted mean difference scores refer to mean differences between treatment and comparison groups after treatment (or occasionally pre to post treatment) and in a randomised trial there is an assumption that both groups are comparable on this measure prior to treatment. Standardised mean differences are divided by the pooled standard deviation (or the standard deviation of one group when groups are homogenous) which allows results from different scales to be combined and compared. Each study's mean difference is then given a weighting depending on the size of the sample and the variability in the data. Less than 0.4 represents a small effect, around 0.5 a medium effect, and over 0.8 represents a large effect[9].

Odds ratio (OR) or relative risk (RR) refers to the probability of a reduction (< 1) or an increase (> 1) in a particular outcome in a treatment group, or a group exposed to a risk factor, relative to the comparison group. For example, a RR of 0.75 translates to a reduction in risk of an outcome of 25% relative to those not receiving the treatment or not exposed to the risk factor. Conversely, a RR of 1.25 translates to an increased risk of 25% relative to those not receiving treatment or not having been exposed to a risk factor. A RR or OR of 1.00 means there is no difference between groups. A medium effect is considered if RR > 2 or < 0.5 and a large effect if RR > 5 or < 0.2[10]. lnOR stands for logarithmic OR where a lnOR of 0 shows no difference between groups. Hazard ratios measure the effect of an explanatory variable on the hazard or risk of an event.

Correlation coefficients (eg, r) indicate the strength of association or relationship between variables. They can provide an indirect indication of prediction, but do not confirm causality due to possible and often unforseen confounding variables. An r of 0.10 represents a weak association, 0.25 a medium association and 0.40 and over represents a strong association. Unstandardised (*b*) regression coefficients indicate the average change in the dependent variable associated with a 1 unit change in the independent variable, statistically controlling for the other independent variables. Standardised regression coefficients represent the change being in units of standard deviations to allow comparison across different scales.

‡ Inconsistency refers to differing estimates of effect across studies (i.e. heterogeneity or variability in results) which is not explained by subgroup analyses and therefore reduces confidence in the effect estimate. I^2 is the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) - 0% to 40%: heterogeneity might not be important, 30% to 60%: may represent moderate heterogeneity, 50% to 90%: may represent considerable heterogeneity and over this is considerable heterogeneity. I^2 can be calculated from Q (chi-square) for the test of heterogeneity with the following formula[9];

$$I^2 = \left(\frac{Q - df}{Q}\right) \times 100\%$$

§ Imprecision refers to wide confidence intervals indicating a lack of confidence in the effect estimate. Based on GRADE recommendations, a result for continuous data (standardised mean differences, not weighted mean differences) is considered imprecise if the upper or lower confidence limit crosses an effect size of 0.5 in either direction, and for binary and correlation data, an effect size of 0.25. GRADE also recommends downgrading the evidence when sample size is smaller than 300 (for binary data) and 400 (for continuous data), although for some topics, these criteria should be relaxed[11].

‖ Indirectness of comparison occurs when a comparison of intervention A versus B is not available but A was compared with C and B was compared with C which allows indirect comparisons of the magnitude of effect of A versus B. Indirectness of population, comparator and/or outcome can also occur when the available evidence regarding a particular population, intervention, comparator, or outcome is not available and is therefore inferred from available evidence. These inferred treatment effect sizes are of lower quality than those gained from head-to-head comparisons of A and B.

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