Published in final edited form as:

Obstet Gynecol. 2015 May ; 125(5): 1224–1235. doi:10.1097/AOG.0000000000000759.

Obstetric and Neonatal Outcomes After Antipsychotic Medication Exposure in Pregnancy

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Abstract

Objective—Antipsychotic medications are used by increasing numbers of women of reproductive age. The safety of these medications during pregnancy has not been well-described. We undertook a systematic review and meta-analysis of the adverse obstetric and neonatal outcomes associated with exposure to antipsychotics during pregnancy.

Data Sources—PubMed, Reprotox, and ClinicalTrials.gov were searched to identify potential studies for inclusion.

Methods of Study Selection—Case-control or cohort studies estimating adverse birth outcomes associated with antipsychotic exposure during pregnancy were included. Pooled odds ratios (OR) were used for dichotomous outcomes and weighted mean differences (WMD) were used for infant birth weight and gestational age. Thirteen cohort studies, including 6,289 antipsychotic-exposed and 1,618,039 unexposed pregnancies were included.

Tabulation, Integration, and Results—Antipsychotic exposure was associated with an increased risk of major malformations (Absolute Risk Difference = 0.03, 95% confidence interval [CI] 0.00 – 0.05, $p=0.04$, $Z = 2.06$), heart defects (Absolute Risk Difference = 0.01, 95% CI 0.00 – 0.01, $p<0.001$, $Z = 3.44$), preterm delivery (Absolute Risk Difference = 0.05, 95% CI 0.03 – 0.08, $p<0.001$, $Z = 4.10$), small-for-gestational-age births (Absolute Risk Difference = 0.05, 95% CI 0.02 – 0.09, $p = 0.006$, $Z = 2.74$), elective termination (Absolute Risk Difference = 0.09, 95% CI 0.05 – 0.13, $p<0.001$, $Z = 4.69$) and decreased birth weight (WMD=–57.89g, 95% CI –103.69g – –12.10g, $p=0.01$). There was no significant difference in the risk of major malformations (test for subgroup differences: $\chi^2 = 0.07$, $df = 1$, $p = 0.79$) between typical (OR = 1.55, 95% CI 1.21 – 1.99, $p = 0.006$) and atypical (OR = 1.39, 95% CI 0.66 – 2.93, $p = 0.38$) antipsychotic medications. Antipsychotic exposure was not associated with risk of large for gestational age births, stillbirth, and spontaneous abortion. Although antipsychotic exposure during pregnancy was associated with

increased risk of adverse obstetric and neonatal outcomes, this association does not necessarily imply causation. This analysis was limited by the small number of included studies and limited adjustment in studies for possible confounders.

Conclusion—Women requiring antipsychotic treatment during pregnancy appear at higher risk of adverse birth outcomes, regardless of causation, and may benefit from close monitoring and minimization of other potential risk factors during pregnancy.

Introduction

Antipsychotic medications, which are first-line treatments for psychotic and bipolar manic episodes, are frequently used by women during child-bearing years.(1, 2) Over half of women with severe mental illness become pregnant,(1, 3, 4) wherein offspring are often exposed to antipsychotics while in-utero.(5) Medication, especially atypical antipsychotic, use is on the rise in pregnant women with bipolar disorder, schizophrenia, and unipolar depression, as well as other psychiatric disorders.(6) However, only limited reproductive safety data are available on antipsychotic medications.

Typical and atypical antipsychotics are lipophilic agents that can cross the placenta.(7) In utero exposure to these agents has been associated with adverse pregnancy and neonatal outcomes.(2, 8) A 1996 meta-analysis suggested that low-dose phenothiazine medications, second-line treatment for hyperemesis gravidarum and include typical antipsychotics, were associated with increased risk of congenital malformations.(9) A systematic review and treatment guidelines for management of psychosis have been published recently.(2, 10, 11) However, meta-analytic reviews that may provide a global estimate of risk for antipsychotics use in pregnancy are notably absent.(12) This meta-analysis synthesizes the data on birth outcomes associated with antipsychotic use during pregnancy. We specifically examine cohort studies of women taking antipsychotic agents in pregnancy compared with unexposed women reporting rates of fetal demise, congenital malformations, preterm birth, birth weight, and maternal outcomes. The aim of this analysis is to better understand the risk of adverse events after exposure to antipsychotics during pregnancy such that evidence-based practice guidelines can be designed and to inform future research.

Sources

This review was completed using PRISMA guidelines. The protocol described was not published prior to conducting this systematic review.

PubMed, Reprotox, and ClinicalTrials.gov were searched for eligible articles. PubMed (1954 – June 2013) was searched using medical subject headings (MeSH): (“Antipsychotic Agents”[Mesh] OR “Antipsychotic Agents” [Pharmacological Action]) AND (“Pregnancy” [Mesh] OR “Pregnancy Complications”[Mesh] OR “Congenital Abnormalities”[Mesh] OR “Birth Weight”[Mesh] OR “Infant, Low Birth Weight”[Mesh] OR “Cesarean Section” [Mesh]). The MeSH and pharmacological action categories included all indexed synonyms and medications, respectively. All articles available as of June 10, 2013 were used. The PubMed search results were also limited using the search filter for human studies. The Reprotox database was searched for all FDA approved antipsychotic agents for additional

references. One reference was incidentally identified by PubMed search, as it has not been MeSH indexed.(13) During preparation of the manuscript, ClinicalTrials.gov was searched as follows; Intervention: “Antipsychotic Agents;” Conditions: “Congenital Abnormalities” “Foot Deformities, Congenital” “Infant, Newborn, Diseases” “Neonatal Abstinence Syndrome” “Pregnancy Complications” “Puerperal Disorders.” No relevant studies were identified.

Study Selection

Two reviewers (CC and CB) independently selected and identified studies for this analysis. Inclusion criteria for eligibility were (1) randomized, controlled trials, case-control or cohort studies that included a non-exposed control group, (2) limited to human research; (3) examined pregnancy or birth outcomes, and (4) examined antipsychotic exposure. There were no relevant randomized controlled trials or case-control studies for inclusion. Remaining studies were examined for eligibility based on investigation of outcomes of interest. Trials were included if they reported rates of congenital malformations in offspring, birth weight, gestational age or pregnancy outcomes. Studies were not limited by language or date of publication, duration or timing of antipsychotic exposure, indication for antipsychotic use, or duration of follow-up.

Two reviewers (CC and KB) independently extracted data from included articles using specifically designed Excel spreadsheets. Differences in extracted data were resolved by a third reviewer (MB). Data extracted included antipsychotic type (typical or atypical), design of study (case-control vs. cohort study), number of pregnancies and events of interest in the exposed and unexposed groups, birth weight, and whether studies included adjusted risk estimates. For studies missing specific data, authors were contacted for more information. Typical antipsychotics include chlorpromazine, flupenthixol, fluphenazine, haloperidol, loxapine, perphenazine, pimozide, trifluoperazine, thiothixene and zuclopenthixol, while atypical antipsychotics include risperidone, quetiapine, olanzapine, ziprasidone, paliperidone, aripiprazole and clozapine. Outcomes of interest included congenital malformations, fetal demise, gestational age, and birth weight. We also intended to examine risk of maternal diabetes and weight gain, but there were too few studies reporting these outcomes (e.g. $k < 3$) to make these analyses informative. We also noted the potential confounders reported by the studies, including maternal age, maternal weight, maternal smoking, alcohol and substance use, concomitant medication use, presence and severity of mental illness, education and measures of socioeconomic status. For articles analyzing outcomes from the same population, the study with the largest population for the outcome was used. Additionally, when outcomes were available for specific agents or monotherapy exposures, these were used in secondary analysis.

We conducted meta-analyses in RevMan version 5.2 (Cochrane Collaborative, Copenhagen, Denmark).(14) Outcomes were either dichotomous or continuous. For dichotomous outcomes (congenital malformations, stillbirth, spontaneous abortion, preterm delivery, infant weight for gestational age), our primary outcome measure was pooled odds ratio (OR). For null values, a value of 1 was used. For infant birth weight and gestational age at birth, continuous measures, we utilized weighted mean difference (WMD) as our primary

outcome measure. When there were greater than 3 studies available for each subgroup, we stratified them based on exposure to typical or atypical antipsychotics. We used a random-effects model for meta-analysis, due to methodological and sampling differences between studies, while a fixed-effects model was used for sensitivity analysis. Results were similar between the random-effects and fixed effects models except where noted. Heterogeneity was assessed utilizing the chi-squared test for heterogeneity and the *I-square* statistic. For outcomes with sufficient studies ($K \geq 7$), publication bias was assessed by visual inspection of the funnel plot and using Egger's test (Comprehensive Meta-Analysis, Version 2.2.064, Biostat, Englewood, NJ, USA).⁽¹⁵⁾ Study quality was assessed using Newcastle-Ottawa Scale⁽¹⁶⁾ and analyzed by fixed effects meta-regression using Comprehensive Meta-Analysis. We performed sensitivity analysis for data source (teratology information services vs. other sources) when there were adequate number of studies sampling different types of populations ($K \geq 3$).

Results

Figure 1 depicts our strategy for selection of studies. Thirteen cohort studies, including 6,289 antipsychotic-exposed and 1,618,039 unexposed pregnancies and 6 057 antipsychotic-exposed and 1 641 187 unexposed infants during pregnancy, were eligible for inclusion in this review (Table 1). Three studies were derived from the same population-based cohort^(17–19) and data from one study were subsequently published as a book^(20, 21); therefore, the study reporting the largest population for each outcome was used. All included studies were cohort studies with data derived from birth registries and teratology information services (TIS). Most of the studies had limited adjustment for potential confounding variables. No study adjusted for type or severity of underlying mental illness and only 2 studies attempted to perform secondary analyses to address the potential effect of concomitant medication use.^(13, 22) The two older studies focused on antiemetic use of phenothiazines, a class of medications that include typical antipsychotics and similar compounds, including promethazine^(21, 23), and one study included lithium with antipsychotic medications.⁽¹⁸⁾ These studies reported data for a limited number of specific antipsychotic agents. When the data for reported specific antipsychotic agents was used for analysis rather than the aggregate data, there was no difference in outcome (data available on request).

Seven studies, including 3 346 antipsychotic-exposed and 1 637 011 unexposed infants during pregnancy, were included in the analysis estimating the risk associated with maternal antipsychotic use and major malformations (Figure 2A).^(13, 21, 23–27) The 4 of the included studies limited analysis to women with first trimester exposure.^(21, 23, 25, 26) Of the remaining studies, Sadowski, et al, reported 76% of women used antipsychotics throughout pregnancy⁽¹³⁾, Diav-Citrin, et al. reported first trimester exposure was 78.2%⁽²⁴⁾, and Habermann, et al. reported first trimester exposure rates of 91.4% for atypical antipsychotics and 90.1% for typicals⁽²⁷⁾. Exposure to antipsychotic medications was associated with increased risk of major malformations (OR = 2.12, 95% CI 1.25–3.57, $p = 0.005$). There was a large degree of heterogeneity between trials ($\chi^2 = 37.15$, degree of freedom (df) = 6, $p < 0.001$, $I^2 = 84\%$). Meta-regression demonstrated a significant positive association of study quality and effect size ($\beta = 0.52$, 95% CI 0.32–0.71, $p < 0.001$, $\tau^2 =$

0.08). There was no evidence of publication bias by Egger's test (intercept = 0.98, 95% CI -5.75 – 3.79, $p = 0.62$, $t = 0.53$).

There was no statistically significant difference in the risk of major malformations associated with typical and atypical antipsychotics in stratified subgroup analysis (test for subgroup differences: $\chi^2 = 0.07$, $df = 1$, $p = 0.79$). Five studies reported typical antipsychotic use during pregnancy, which was associated with an increased risk for major malformations during pregnancy compared with unexposed infants (OR = 1.55, 95% CI 1.21 – 1.99, $p = 0.006$). (18, 21, 23, 24, 27) Additionally, 3 studies reported risk of major malformation associated with atypical antipsychotic exposure during pregnancy compared with unexposed infants, which insignificant (OR = 1.39, 95% CI 0.66 – 2.93, $p = 0.38$). (18, 26, 27) Additionally, there was no significant difference found in stratified subgroup analysis comparing studies using data obtained from TIS with other types of populations (test for subgroup differences: $\chi^2 = 0.08$, $df = 1$, $p = 0.78$).

The most common organ affected by malformations is the heart. Four studies reported heart defects, including 2 657 exposed and 1 625 364 unexposed infants. (13, 18, 21, 27) Exposure to antipsychotics in utero was associated with increased risk of heart defects compared with no exposure (Figure 2B; OR = 2.09, 95% CI 1.50 – 2.91, $p < 0.001$). Heterogeneity was not significant ($\chi^2 = 2.50$, $df = 3$, $p = 0.48$, $I^2 = 0\%$).

We evaluated possible associations between antipsychotic use and pregnancy loss. The analysis of elective terminations and spontaneous abortion included the same four studies, with 1 306 antipsychotic-exposed and 2 482 unexposed pregnancies. (24, 26–28) There was a higher rate of elective terminations in the pregnancies exposed to antipsychotic medications (Figure 3A; OR = 5.98, 95% CI 2.94 – 12.14, $p < 0.001$), although there was significant heterogeneity ($\chi^2 = 11.27$, $df = 3$, $p = 0.01$, $I^2 = 73\%$). Meta-analysis did not demonstrate a higher incidence of spontaneous abortion in pregnancies exposed to antipsychotic agents (Figure 3B; OR = 1.05, 95% CI 0.61–1.81, $p = 0.86$). Heterogeneity was present and statistically significant between studies ($\chi^2 = 10.10$, $df = 3$, $p = 0.02$, $I^2 = 70\%$).

Five studies including 4 843 antipsychotic-exposed and 1 013 952 unexposed pregnancies evaluated rates of stillbirth (Figure 3C). (19, 21, 24, 26, 27) There was no statistically significant association between antipsychotic use and stillbirth compared to mothers unexposed to antipsychotics (OR = 1.18, 95% CI 0.88 – 1.57, $p = 0.27$) and heterogeneity between studies was not significant ($\chi^2 = 3.54$, $df = 4$, $p = 0.47$, $I^2 = 0\%$).

We identified seven studies reporting rates of preterm birth, including 2 809 anti-psychotic exposed pregnancies and 1 531 541 unexposed pregnancies, eligible for inclusion. (13, 18, 22, 24, 26, 27, 29) Overall, we found a statistically significant association with pre-term delivery in pregnancies involving antipsychotic exposure (Figure 4A; OR = 1.86, 95% CI: 1.45 – 2.39, $p < 0.00001$). However, there was a non-statistically significant trend toward heterogeneity between study results ($\chi^2 = 11.21$, $df = 6$, $p = 0.08$, $I^2 = 46\%$). Preterm delivery was associated with exposure to both typical (OR = 2.03, 95% CI: 1.47 – 2.80, $p < 0.001$) and atypical antipsychotic (OR = 1.61, 95% CI: 1.15 – 2.25, $p = 0.006$) exposure with

no statistically significant difference between typical and atypical antipsychotics (test for subgroup differences: $\chi^2 = 0.96$, $df = 1$, $p = 0.33$). Effect size was not significantly associated with study quality ($\beta = -0.13$, 95% CI $-0.33 - 0.06$, $p = 0.19$, $\tau^2 = 0.06$). There was no evidence of publication bias by Egger's test (intercept = 1.24, 95% CI $-0.86 - 3.35$, $p = 0.19$, $t = 1.52$), though the studies did demonstrate a statistically insignificant right-skewed funnel plot (Figure 5).

While there was an association observed with antipsychotic exposure and preterm birth, the effect on gestational age at birth was small. Three studies reported mean gestational age, (13, 17, 26) which included 730 antipsychotic-exposed and 357 947 unexposed infants. Infants exposed to antipsychotics were born earlier than unexposed infants, but this effect on gestational age was not statistically significant (Figure 4B; WMD = -0.21 wks, 95% CI -0.44 wks $- 0.01$ wks, $p = 0.06$). There was no significant heterogeneity observed ($\chi^2 = 4.51$, $df = 2$, $p = 0.10$; $I^2 = 56\%$).

Another outcome associated with increased neonatal morbidity and mortality is birth weight. Three studies, including 771 antipsychotic-exposed and 357 963 unexposed infants, were used for analysis of birth weight. (13, 17, 26) Infants exposed to antipsychotics in utero weighed less at birth compared with infants without exposure (Figure 4C; WMD = -57.89 g, 95% CI -103.69 g $- -12.10$ g, $p = 0.01$). There was no significant heterogeneity between trials ($\chi^2 = 2.01$, $df = 2$, $p = 0.37$, $I^2 = 0\%$).

Since low or high birth weight may be appropriate for the gestational age of infants at birth, we also analyzed the association of antipsychotic exposure with infants born small for gestational age (SGA) and large for gestational age (LGA), which was reported by four studies, with total 973 antipsychotic-exposed and 1 577 933 non-exposed infants. (13, 18, 22, 29) There was an association of antipsychotic exposure with SGA (Figure 4D; OR = 2.44, 95% CI 1.22 $- 4.86$, $p = 0.01$). On the other hand, antipsychotic exposure was not associated with a statistically significant increase in LGA infants (Figure 4E; OR = 2.50, 95% CI 0.77 $- 8.16$, $p = 0.13$); however, this result was significant using fixed-effects analysis (OR = 1.97, 95% CI 1.48 $- 2.62$, $p < 0.001$). There was significant heterogeneity for both outcomes (SGA: $\chi^2 = 15.47$, $df = 3$, $p = 0.001$, $I^2 = 81\%$; LGA: $\chi^2 = 32.60$, $df = 3$, $p < 0.001$, $I^2 = 91\%$).

Conclusion

Our meta-analysis demonstrated a significant association between antipsychotic exposure during pregnancy and increased risk of multiple adverse obstetric and neonatal outcomes related to congenital malformations, fetal growth, and preterm delivery. While we feel the current data are insufficient to conclude that antipsychotics cause increased morbidity during pregnancy, these results suggest that women who take antipsychotic medications during pregnancy represent a population at higher risk for adverse obstetric and neonatal outcomes.

Our findings complement those of recent studies, which suggest that women with mental illnesses such as schizophrenia and bipolar disorder, many of whom are likely taking antipsychotic drugs, have an elevated risk for negative pregnancy outcomes (30, 31). These

findings identify a group that may benefit from additional guidance and monitoring from healthcare providers, as well as cooperative management among patients, obstetricians, and psychiatrists. We do not believe that the data are sufficient to make any conclusions regarding the causal relationship between antipsychotic exposure and pregnancy outcomes because of (1) limited adjustment for potential confounders in the original studies and (2) a large degree of heterogeneity between study results.

There are a number of potentially relevant confounders that could have contributed to the results. Maternal smoking, for example, is controlled for in only a minority of studies included in this review (Table 1) (17–19, 27) and all 5 cohorts that report rates of maternal smoking demonstrated increased rates of smoking in mothers taking antipsychotic medications (13, 17, 19, 24, 26, 27). Substance abuse is an additional relevant confounder in this analysis, as substance abuse rates tend to be higher in populations with psychiatric disorders (36). Only one (27) of the studies used in this analysis controlled for alcohol exposure and none of the studies in this analysis controlled for drugs of abuse exposure. Additionally, obesity is a known side effect of antipsychotic medications, especially atypical antipsychotics (37), which was only controlled for in two studies (25, 27) and four studies demonstrated higher BMI/obesity in the antipsychotic population (13, 17, 19, 26). Furthermore, low socioeconomic status is associated with some psychotic disorders, though it is unclear whether this association is due to social causation or social drift (38). None of the studies in our analysis controlled for socioeconomic status. Thus, without properly controlling for these various confounding factors, we cannot determine whether the association between negative pregnancy outcomes and antipsychotic use is due to causation or simply confounding.

Additional potential sources of confounding are confounding by indication and concomitant medication use. Only one of the studies limited the population to primary psychotic disorders (29) and most studies reported a wide range of reported indications, including mood and anxiety disorders. Depression has been associated with an increased risk of adverse neonatal outcomes (40). Additionally, use of antipsychotics for different indications may be associated with preferential use of specific agents and typically lower doses used. There was insufficient data available in the studies to assess for a possible effect of psychiatric diagnosis on the association of adverse outcomes associated with antipsychotic exposure. Concomitant medication use was very common in the cohorts and likely reflects the diversity of indications (See Table 1). Few studies included in this meta-analysis limited analysis to patients on antipsychotic monotherapy. (13) Use of medications with known fetal risks, such as valproic acid and lithium, when reported were non-trivial with just under 20% of antipsychotic exposed pregnancies using a concomitant antiepileptic medication. (26) (41, 42) Antidepressants were also frequently used by patients in the few studies that reported concomitant medications use. (13, 26) Antidepressants have been associated with small increases in spontaneous abortion, preterm delivery, possible fetal growth restriction, and in the case of paroxetine, increased cardiac malformations. (43, 44) As many of the patients were treated with multiple medications, including medications also associated with adverse outcomes, this is a likely source of confounding that remains unexplored in the available literature.

With only 13 studies (involving ten independent cohorts) included in analysis, it is important to recognize shortcomings in this data set. Given the small number of trials we were not able or had limited power to examine possible publication bias. Therefore, it remains possible that publication bias where non-significant associations between antipsychotic exposure and birth outcomes are not published could be causing or at least exaggerating the strength of the association between antipsychotic exposure and birth outcomes. Additionally, the data sources in the study included tetralogy services and birth registries. Biases are inherent in each method of data collection; for example, birth certificates are known to contain some reporting bias, especially relative to labor and delivery complications. As such, data sources must be considered carefully (45).

Another significant problem with reported data is the lack of drug-specific reports. Some studies reported typical and atypical antipsychotic use together, while others stratified by typical and atypical drug type. Both systems for grouping agents are problematic, as there are chemically diverse drugs in each family. In particular, phenothiazines, a subclass of typical antipsychotic, have been associated with birth defects.(9, 21, 23) These drugs could be responsible for elevated risks associated with typical antipsychotics, but we believe the apparent difference between typical and atypical antipsychotic exposure in the risk of malformations and preterm delivery is likely due to the small sample, low event rate, and high heterogeneity. Until drug-specific data are available, we cannot resolve the true risk of these drugs compared to other typical antipsychotics.

Finally, there were not sufficient studies to examine neonatal and obstetric outcomes that might be specifically associated with antipsychotic agents. The FDA has reported concern for neonatal extrapyramidal symptoms and possible medication withdrawal based on data from the Adverse Event Reporting System, although there has been little systemic investigation.(8) Six of the studies reported general neonatal complications, but did not identify extrapyramidal or withdrawal symptoms.(13, 18, 22, 24, 26, 27) Most antipsychotic agents are associated with weight gain and increased risk of metabolic syndrome and diabetes and many have been associated with increased risk of metabolic syndrome and diabetes.(46–48) The 2 studies examining rates of gestational diabetes in women taking antipsychotic agents compared with no exposure reported conflicting results.(13, 17)

The finding of increased rates of elective termination of pregnancy in women taking antipsychotic medication was surprising. Given the increased odds of major malformations associated with antipsychotic exposure, it is possible that the increased rate of elective termination was due to fetal pathology. However, we were unable to perform additional analysis as only 2 studies reported this outcome.(24, 27) There are other possible reasons for an increased rate of elective termination, including psychosocial stressors, factors related to underlying mental illness, concerns due to medication exposure, or use of contraception. However, there is a paucity of data related to rates and reasons for elective terminations in women with severe mental illness. None the less, further investigation related to education-related family planning and engagement in gynecological care by women with mental illness is needed.

In spite of these limitations, this meta-analysis provides substantial evidence for an association between maternal antipsychotic use and congenital malformations, preterm delivery, impaired fetal growth, and elective termination. There are insufficient data to attribute this association to medication exposure or probable confounding. These pregnancies potentially represent a high-risk population, even if the antipsychotic medications are not causative, because the antipsychotic use is associated with other factors such as smoking, polypharmacy, substance use, possible psychosocial stressors, medical comorbidities, and effects of maternal mental illness.(49) As such, these results suggest that women taking antipsychotic medication may benefit from close obstetric monitoring and targeting of modifiable risk factors. Future epidemiologic research should focus on (1) controlling for probable confounders and (2) examining the risks of antipsychotic medications individually. By improving the quality of the antipsychotic reproductive safety data, the women of child-bearing age taking antipsychotic medications and their clinicians will be better informed in making treatment decisions.

Acknowledgments

Supported by the National Institutes of Health (K23MH091240 (MHB), T32MH019961 (KAB), the AACAP/ Eli Lilly Junior Investigator Award (MHB), the Trichotillomania Learning Center (MHB), Brain & Behavior Research Foundation (MHB), the Rembrandt Foundation (MHB) and UL1 RR024139 from the National Center for Research Resources, a component of the National Institutes of Health, and NIH roadmap for Medical Research (MHB).

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Figure 1.
Selection of studies. *Two articles overlapped.

Figure 2.

Risk of congenital malformations associated with antipsychotic exposure during pregnancy. Major congenital malformations, structural, or functional abnormalities present at birth resulting in severe functional impairment, serious cosmetic defect, or death (**A**). Cardiac malformations (**B**). M-H, Mantel-Haenszel; CI, confidence interval.

Figure 3.

Association of antipsychotic exposure during pregnancy with pregnancy outcome. Elective termination (A); spontaneous abortion, pregnancy loss early in gestation (B); and stillbirths, late pregnancy loss prior to completion of delivery (C). M-H, Mantel-Haenszel; CI, confidence interval.

Figure 5.

Funnel plot examining publication bias in studies reporting preterm birth associated with antipsychotic exposure. Published reports (*circles*) are plotted for effect size and inverse standard error. The *diamond* represents the point estimate and 95% confidence interval (CI) of the odds ratio of preterm birth after antipsychotic exposure. The line indicates the 95% CI for the expected results of trials given this estimated underlying effect size.

Table 1

Characteristics of Included Studies. We identified 12 studies involving, including 6,289 antipsychotic-exposed and 1,618,039 unexposed pregnancies and 6,057 antipsychotic-exposed and 1,641,187 unexposed infants during pregnancy that were eligible for inclusion in this review.

Author	Year	Antipsychotic pregnancies	Unexposed pregnancies	Outcome of Interest				Method to address confounding (specific outcome)	Potential confounders						Newcastle-Ottawa Total Score
				Congenital Malformation	Pregnancy loss	Gestational Age	Birth Weight		Maternal Age	Smoking	Alcohol	Drugs	BMI/obesity	Polypharmacy	
Boden [†] (16)	2012	507 [°]	357,696 [°]			x	x	Logistic regression (SGA, LGA)	•	•	nr	nr	*	nr	•
Diav-Citrin(23)	2005	215	631	x	x	x		None	*	*	nr	nr	nr	75.1% total	3
Haberman(26)	2013	845	1122	x	x	x		Logistic regression (malformations)	•	•	•	nr	•	58.0% total	4
Kallen [†] (17)	2013	548	1,551,834	x		x	x	Stratified analysis (all outcomes)	•	•	nr	nr	•	nr	5
Lin(28)	2010	424 [°]	3480 [°]			x	x	Logistic regression (SGA, LGA, Preterm birth)	•	nr	nr	nr	nr	nr	4
McKenna(25)	2005	151	151	x	x	x	x	Subject matching	m	*	nd	nr	*	17% antiepileptics 12.4% valproate 6% lithium 57% antidepressants	2
Newham(21)	2008	70	38			x	x	none	ns	nr	nr	nr	nr	64.3% total	2
Paulus(27)	2005	95	578		x			none	nr	nr	nr	nr	nr	nr	2
Reis [†] (18)	2008	570	958,729		x			Stratification (all outcomes)	•	•	nr	nr	*	nr	6
Rumeau-Rouquette(22)	1977	315 [°] (61 chlorpromazine exposed) [†]	11,099 [°]	x				none	nr	nr	nr	nr	nr	nr	4
Sadowski(12)	2013	133	133	x		x	x	Subject matching	m	*	ns	nr	*	72.2% total 34.6% antidepressants	4
Slone(20)	1977	3,675 [°]	48,973 [°]	x	x			none	nr	nr	nr	nr	nr	nr	3
Heinonen [†] (19)	1977	352 [°]	52207 [°]	x											

Abbreviations:

- [†] subset of larger cohort, not included in primary analysis,
- [°] overlaps with larger cohort so used only in analyses where data was unavailable from larger study; x=outcome reported in article,
- potential confounder both reported and controlled for in analysis,

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potential confounder reported in study and significantly different between exposed and nonexposed groups, ns=confounder reported in study and not significantly different between exposed and nonexposed groups, nr=confounder not reported in the study, m=matched, * live births, not pregnancies