# Selected Pregnancy and Delivery Outcomes After Exposure to Antidepressant Medication

## *A Systematic Review and Meta-analysis*

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**Importance:** Untreated depression during pregnancy has been associated with increased morbidity and mortality for both mother and child and, as such, optimal treatment strategies are required for this population.

**Context:** There are conflicting data regarding potential risks of prenatal antidepressant treatment.

**Objective:** To determine whether prenatal antidepressant exposure is associated with risk for selected adverse pregnancy or delivery outcomes.

**Data Sources:** MEDLINE, EMBASE, Cumulative Index to Nursing and Allied Health Literature, PsycINFO, and the Cochrane Library were searched from their start dates to June 30, 2010.

**Study Selection:** English-language studies reporting outcomes associated with pharmacologic treatment during pregnancy were included. We reviewed 3074 abstracts, retrieved 735 articles, and included 23 studies in this meta-analysis.

**Data Extraction:** Study design, antidepressant exposure, adjustment for confounders, and study quality were extracted by 2 independent reviewers.

**Results:** There was no significant association between antidepressant medication exposure and spontaneous abortion (odds ratio [OR], 1.47; 95% CI, 0.99 to 2.17; $P=.055$). Gestational age and preterm delivery were statistically significantly associated with antidepressant exposure (mean difference [MD] [weeks], −0.45; 95% CI, −0.64 to −0.25; $P<.001$; and OR, 1.55; 95% CI, 1.38 to 1.74; $P<.001$, respectively), regardless of whether the comparison group consisted of all unexposed mothers or only depressed mothers without antidepressant exposure. Antidepressant exposure during pregnancy was significantly associated with lower birth weight (MD [grams], −74; 95% CI, −117 to −31; $P=.001$); when this comparison group was limited to depressed mothers without antidepressant exposure, there was no longer a significant association. Antidepressant exposure was significantly associated with lower Apgar scores at 1 and 5 minutes, regardless of whether the comparison group was all mothers or only those who were depressed during pregnancy but not exposed to antidepressants.

**Conclusions and Relevance:** Although statistically significant associations between antidepressant exposure and pregnancy and delivery outcomes were identified, group differences were small and scores in the exposed group were typically within the normal ranges, indicating the importance of considering clinical significance. Treatment decisions must weigh the effect of untreated maternal depression against the potential adverse effects of antidepressant exposure.

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MAJOR DEPRESSIVE DISORDER is the second leading cause of burden of disease in women in the United States[1] and can be chronic and recurrent.[2] Depression is common during pregnancy, exceeding rates in the general female population in both the second (12.8%) and third (12.0%) trimesters.[3] Untreated depression during pregnancy or post partum has been associated[4-6] with increased morbidity and mortality in the mother and her children. Despite this, there is evidence that depression is markedly underdetected and undertreated during pregnancy.[7] One factor thought to contribute to rates of undertreatment is concern regarding potential negative outcomes associated with fetal exposure to antidepressant medications.[8,9] Several poor outcomes have been reported to be associated with maternal use of antidepressants during pregnancy, including congenital malfor-

mations,[10-15] transient short-term adverse neonatal effects,[16-25] neonatal pulmonary hypertension,[26] and even fetal death.[27]

With respect to pregnancy and delivery outcomes, a 2005 meta-analysis[28] identified a statistically significant association between late pregnancy exposure to selective serotonin reuptake inhibitors and infant low birth weight, but not prematurity. Several recent studies have also reported an association between prenatal use of antidepressants and risk for spontaneous abortion[27,29-34] and premature delivery.[12,18,27,35-37] However, these outcomes have also been linked to untreated maternal depression.[29,30,34,35,38] As such, it remains unclear whether there is a causal relationship between exposure to antidepressant medications in utero and pregnancy/delivery complications or whether maternal depression is itself responsible for these increased risks.

To address these conflicting results, it is important to synthesize the available evidence to assist in determining whether the benefits of antidepressants are likely to outweigh the potential risks for a perinatal woman and her child. The aim of this study was to perform a meta-analysis examining what, if any, relationship exists between prenatal antidepressant exposure and poor pregnancy or delivery outcomes (specifically, spontaneous abortion, premature delivery, low birth weight, and low Apgar scores; our team has studied other important outcomes not covered in this article). When possible, we also aimed to use meta-analytic techniques to determine whether any relationships identified persisted when pregnant women with untreated depression served as the comparison group to test our hypothesis that many observed associations between prenatal antidepressant exposure and pregnancy/delivery outcomes may be confounded by exposure to maternal depression.

## METHODS

### SEARCH STRATEGY AND STUDY SELECTION

In this meta-analysis, we followed the Meta-analysis of Observational Studies in Epidemiology guidelines.[39] Literature searches were performed independently by 2 professional librarians with expertise in the areas of psychiatry and psychopharmacology using various combinations of keywords including, but not limited to, *depressive/mood disorder, postpartum/postnatal; pregnancy/pregnancy trimesters; tricyclic antidepressant drugs; antidepressant drug/agent; selective serotonin reuptake inhibitors; monoamine oxidase inhibitors; prenatal* or *antenatal, infant/neonatal outcomes; spontaneous abortion;* and *birth weight* (the detailed search strategy is available from the corresponding author on request). The following databases were searched from their inception to June 30, 2010: MEDLINE (Ovid), In Process MEDLINE (Ovid), PsycINFO (American Psychological Association; Ovid), Cumulative Index of Nursing and Allied Health Literature (Nursing and Allied Health), EMBASE (Excerpta Medica, Elsevier, Ovid), and Scopus (Elsevier). Reference lists of reviews and meta-analyses were searched for additional articles. Studies were considered for inclusion in this analysis if they were published in English and reported original data regarding pregnancy or delivery outcomes associated with exposure to antidepressant medications. Inclusion criteria were (1) exposure to any pharmacologic antidepressant agents including, but not limited to, selective serotonin reuptake inhibitors, tricyclic antidepressants, and monoamine oxidase inhibitors during pregnancy; (2) a comparison group of nonexposed pregnant women; and (3) sufficient data to calculate an effect size and its standard error. Because of the volume of potentially eligible studies, abstracts and unpublished data were not eligible for inclusion. The research team and an advisory committee of key stakeholders (including representatives from psychiatry, family medicine, obstetrics, neonatology, public health, patient advocacy, and policy) identified pregnancy and delivery outcomes of interest. Specifically, this review examined the following pregnancy and delivery outcomes: spontaneous abortion, defined as pregnancy loss prior to 20 weeks' gestation; premature delivery, as defined by the authors of the original studies (described in the "Premature Delivery" subsection of the "Results" section); birth weight; gestational age; and Apgar scores at 1 and 5 minutes. Two independent research assistants (including L.M. and E.H.V.) screened and excluded identified articles on the basis of the title and abstract. If not all data were provided in the publication, we contacted the authors with requests for raw data. However, of 12 authors contacted, only 4 replied, none of whom was able to provide the required data. Retrieved full articles were assessed in detail, and any differences were resolved in discussion among the research team until consensus was achieved.

### DATA EXTRACTION

Data extraction and quality assessment have been described in detail elsewhere.[40] Data from eligible articles were extracted and assessed for study quality by 2 research assistants (including L.M. and E.H.V.) using an a priori standardized form according to Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[41] Data extracted from each selected article included authors, year of publication, study design, setting, inclusion/exclusion criteria, details on antidepressant exposure, and details of the outcomes of interest.

This study was part of a larger research project in which we sought to synthesize all available evidence-based research and develop a reference guide for physicians to aid in treatment decisions for perinatal women. In our main analysis, we included only studies scoring above the threshold on a quality assessment tool we developed[40] based on existing quality assessment instruments, including the checklist developed by Downs and Black[42] and the Newcastle-Ottawa Scale,[43] adapted to delivery outcomes. The quality assessment tool evaluated 19 criteria in the following categories: (1) sample, (2) control group, (3) quality of exposure/outcome measure, (4) follow-up, and (5) confounding. The last category included assessment of whether studies included controls for depression, other psychotropic medications, or other potentially relevant confounders, such as smoking, alcohol, and illicit drug use. On the basis of these 19 criteria, a final quality rating (high, moderate, low, and very low) was assigned using a modification of the Grading of Recommendations Assessment, Development, and Evaluation.[40] Considering that randomized controlled trials are not ethical for examining the research questions of interest, no high-quality studies were available for this analysis. As such, we categorized moderate and low studies as above quality threshold, whereas the very low category was deemed below quality threshold.

### STATISTICAL ANALYSES

Relative risk (RR) and odds ratio (OR) were treated as equivalent measures of risk because of the low prevalence of outcomes. Inverse variance–weighted DerSimonian-Laird random effects models[44] were used to derive an overall effect size for each delivery outcome because of vastly different study designs and/or

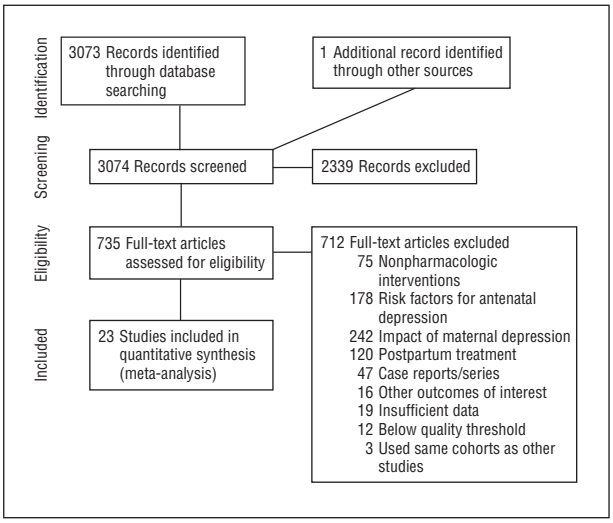


**Figure.** Identification of independent studies for inclusion in meta-analysis (Adapted from Preferred Reporting Items for Systematic Reviews and Meta-analyses 2009 flow diagram[49]).

substantial heterogeneity between studies. When available, we used adjusted data in all analyses. When no measure of risk was reported, we calculated the effect measure (OR, mean difference [MD], or standardized mean difference [SMD]) and their corresponding standard error from the raw numbers from a $2 \times 2$ table for dichotomous outcomes, or mean (SD) for continuous outcomes reported in the primary studies. If such data were provided, we also calculated the mean difference in grams (birth weight), weeks (gestational age), or Apgar scores between groups. When multiple exposure groups were compared with one control group, we combined these to derive one risk estimate per primary study. To evaluate the effect of maternal depression on our findings, we calculated the pooled effect of any antidepressant exposure in comparison with a control group of depressed pregnant women in a subanalysis involving only studies above the quality threshold. We further conducted subanalyses for studies reporting adjustment for any confounders by outcome of interest. Between-study heterogeneity was quantified by the Cochran $Q$[45] and $I^2$ tests.[46] The $I^2$ value can be interpreted as the proportion of the total variation in the estimated slopes for each study that is the result of heterogeneity between studies. Publication bias was examined using the Egger regression-based test[47] and, in the presence of such bias, we conducted sensitivity analyses using the Duvall and Tweedie[48] trim and fill method. The influence of any particular study was examined by reestimating the pooled effect, excluding studies one by one. Our main analysis excluded very-low-quality studies and unpublished research and therefore did not comprise the entire population of studies on this topic. There were few changes in results and no changes in our conclusions when studies of very low quality were included or when only studies of moderate quality were used in a sensitivity analysis (as described in the "Sensitivity Analyses" subsection of the "Results" section).

## RESULTS

Of 3074 citations identified, 735 articles were retrieved in full and a total of 51 articles reporting on outcomes of interest met the meta-analysis inclusion criteria. After exclusion of 12 studies that fell below the quality threshold and 16 studies reporting on other outcomes of interest to the larger systematic review, 23 studies were included in our analyses of delivery outcomes (**Figure**).[49]

A full listing of the identified articles, together with a list of studies retrieved but excluded from the analysis, is available from the project's website (see author material at http://sunnybrook.ca/content/?page=physician_reference_guide_pregnancy_depression). Overall, we identified 11 studies for analysis of spontaneous abortion, 22 studies reporting on gestational age, 19 for the analysis of premature delivery, 31 for birth weight analysis, 10 for analysis of Apgar scores at 1 minute, and 15 for analysis of Apgar scores at 5 minutes. Of these, 23 studies were above the quality threshold: 3 studies on spontaneous abortion, 15 on gestational age, 20 on birth weight, 13 on premature delivery, 10 on 1-minute Apgar scores, and 14 reporting on 5-minute Apgar scores were considered above the quality threshold (number of articles does not equal the total number of studies included in the analysis because some reported on more than 1 outcome). As such, these 23 studies formed the basis for our primary analysis (eTable 1; http://jamapsych.com).* Of these, 6 provided data that permitted analysis of a potential effect of maternal depression on the outcomes of interest, either through the inclusion of a control group without antidepressant exposure but current or past depression[38,51,57,58] or through matching on psychiatric history variables.[35,54] Two studies[35,54] provided 2 comparisons with separate control groups; each comparison was included as a separate effect estimate.

### SPONTANEOUS ABORTION

Three studies reported on spontaneous abortion resulting in a pooled OR of 1.47 (95% CI, 0.99-2.17) (eFigure 1). There was no between-study heterogeneity ($I^2=0$). Two studies provided matched or adjusted data, which yielded a similar effect size with larger CIs (eTable 2). Analyses with a depressed control group were not possible because of lack of data.

### PREMATURE DELIVERY

Thirteen studies providing 14 estimates of the association between antidepressant use and preterm delivery resulted in a pooled OR of 1.55 (95% CI, 1.38-1.74; $P<.001$) (eFigure 2) with low between-study heterogeneity ($I^2=16\%$). Of the 13 studies, 10 defined preterm birth as less than 37 weeks' gestation and 2 as less than 36 weeks' gestation; 1 study did not provide a definition. Restricting the analysis to studies adjusting or matching for any confounder showed a slightly stronger association. Finally, a comparison with depressed mothers showed a similar effect size in 5 studies, but the 95% CI included 1 (ie, the pooled OR was not statistically significant) (eTable 2).

### GESTATIONAL AGE

The 15 studies providing a total of 16 estimates of the association between antidepressant use and gestational age yielded an SMD of −0.23 (95% CI, −0.34 to −0.12; $P<.001$) (eFigure 3). Between-study heterogeneity ($I^2$) was 71%. Expressed in terms of MD in weeks, gestational age was less than 0.5 weeks shorter among de-

**References 18, 20, 23, 27, 32, 34, 35, 37, 38, 50-63.*

pressed mothers with antidepressant exposure (MD, −0.45; 95% CI, −0.64 to −0.25). Results were very similar for the 7 studies providing matched or adjusted data and for the 5 studies comparing a group exposed to antidepressants with a depressed group not exposed to antidepressants (eTable 3).

### BIRTH WEIGHT

Twenty studies providing 21 risk estimates were included in the analysis of birth weight. The SMD between mothers exposed to any antidepressants and those who were not exposed to antidepressants was small (SMD, −0.10; 95% CI, −0.16 to −0.03) (eFigure 4). The $I^2$ was moderate (52%). Expressed in terms of grams, the MD for birth weight was −74 g (95% CI, −117 to −31 g; $P = .001$). Including only studies that provided adjusted data, results were very similar; however, when the control group was depressed mothers without antidepressant exposure, the association was close to null, with high precision and little heterogeneity (eTable 3).

### APGAR SCORES

Ten studies examined Apgar scores at 1 minute and 14 at 5 minutes in our main analysis. Both outcomes showed statistically significant effects for in utero exposure to antidepressants (SMD, −0.19 [95% CI, −0.30 to −0.08] and −0.33 [95% CI, −0.47 to −0.20], respectively, eFigure 5). The mean difference was −0.37 points in Apgar scores at 1 minute and −0.18 points at 5 minutes. Findings were similar in magnitude and statistical significance when only adjusted studies were included. A comparison between depressed mothers exposed to antidepressants and depressed mothers not exposed to antidepressants also yielded similar effect sizes, although the number of studies available for such an analysis was reduced; thus, the results should be interpreted with caution (eTable 3).

### SENSITIVITY ANALYSES

Some evidence for publication bias was detected for premature delivery ($P = .02$). After imputation of 5 presumably missing studies,[48] the OR was 1.49 (95% CI, 1.29-1.72); this was very similar compared with the results of our primary analysis. One study had a particularly strong effect in the analysis of premature delivery.[62] Omitting this study from the analysis yielded a slightly stronger association (OR, 1.65; 95% CI, 1.46-1.86), but it was also the largest study and was adjusted for several important confounders. Inclusion of studies below our quality threshold had no significant influence on our conclusions in all analyses. In addition, including only studies with moderate quality resulted in similar results compared with our main analysis and for comparisons involving a depressed control group.

## COMMENT

This meta-analysis examined the risk for various pregnancy and delivery outcomes associated with prenatal exposure to antidepressant medication and whether maternal depression altered the strength of any observed associations. To our knowledge, this is the first meta-analysis to examine gestational age, birth weight, and Apgar scores among infants exposed to antidepressant medications in utero. The results yielded statistically significant associations for all these pregnancy outcomes. However, all the effects identified in this analysis were small (approximately 3 days shorter gestational age, 75 g lower birth weight, and less than half a point on the 1- and 5-minute Apgar scores), with values in the exposed group typically falling within the normal range. The clinical significance of these risks is therefore questionable. For example, Apgar scores of 7 and higher signify that a neonate's condition is normal to excellent.[64] Because the weighted mean score of the exposed group at 1 minute was 7.52 and at 5 minutes was 8.65 (data not shown), most neonates included in this analysis were faring well even at 1 minute.

With respect to spontaneous abortion, the pooled OR bordered on statistical significance (lower 95% CI, 0.99) and only 3 studies of adequate quality could be identified for inclusion in this analysis. As such, lack of statistical power may have contributed to the nonsignificant finding for this outcome. Each of 2 meta-analyses of 6[65] and 5[66] original studies reported significantly increased risk for spontaneous abortion among women using antidepressant medications during pregnancy. Both included reports that were excluded from our analysis because of poor study quality. Furthermore, most available studies on this issue do not provide sufficient data to distinguish induced from spontaneous abortions. If women with depression are more likely than those without depression to terminate an unplanned pregnancy, the rates of spontaneous abortions could be inflated. Additional research on this issue, ideally isolating spontaneous from induced abortions and including studies with adequate control for maternal depression, is necessary to reconcile these conflicting findings.

Despite the very small difference in gestational age between exposed and unexposed groups, our results may indicate an increased risk for preterm birth among women exposed to antidepressant medication during pregnancy. An association between maternal depression or stress and preterm delivery is well documented.[58,67,68] Few studies examining an association between maternal depression and preterm birth have controlled for antidepressant treatment, such that prenatal exposure to antidepressant medications may be an important confounder. The biological mechanisms for an effect of antidepressant exposure on preterm birth are not known. However, it has been reported[69] that women using antidepressant medication during the second half of pregnancy had higher saliva estriol levels compared with women with a history of depression but limited or no antidepressant exposure during pregnancy as well as women with no history of depression or antidepressant treatment. Elevated estriol levels have been associated[70] with preterm birth, particularly those occurring after 35 weeks' gestation.

The studies included in this meta-analysis defined premature delivery as a categorical variable, where deliveries at gestational age of less than 37 weeks (and in 2 cases,

less than 36 weeks) were classified as premature delivery. Although it is thought that medical comorbidities associated with preterm birth are predominantly associated with birth at less than 33 weeks' gestation,[71] there are several clinical outcomes that merit attention for near-term or later preterm infants defined as those born at less than 37 weeks but 35 weeks or more.[72-77] For example, one study found that, relative to full-term infants, near-term infants had a statistically significantly higher risk for respiratory distress (4.2% vs 28.9%), temperature instability (0% vs 10%), and jaundice (37.9% vs 54.4%) and had received intravenous infusions more frequently (5.3% vs 26.7%).[73] Other studies have described an increased rate of morbidity and mortality in late preterm infants (34-36 weeks) compared with full-term infants (37-41 weeks)[74] and increased risk for respiratory distress in infants born at 35 and 36 weeks.[75] Similarly, a recent review[78] of long-term outcomes of later preterm infants reported that the rates of respiratory distress, persistent pulmonary hypertension of the newborn, intraventricular hemorrhage, hypoglycemia, and feeding difficulties are considerably higher in late preterm infants than in full-term infants. Our analysis of association between gestational age and in utero antidepressant exposure remained statistically significant, even when looking only at studies that provided a comparison of pregnant women exposed to an antidepressant during pregnancy with depressed pregnant women who were not taking antidepressants during pregnancy. There were 5 studies with 6 estimates of association yielding an SMD of −0.19 (95% CI, −0.37 to −0.02; $P = .03$). Even when we restricted this analysis to 3 studies that not only had a depressed unexposed comparison group but also adjusted for smoking and number of prior births, the association remained statistically significant (SMD, −0.21; 95% CI, −0.40 to −0.02; $P = .03$). However, in light of established risks associated with untreated prenatal depression for both mother and infant,[4-6] the clinical relevance of these increased risks should be interpreted with caution.[58,79]

Existing literature converges on the notion that neonatal morbidity and mortality increase with a decrease in gestational age.[80-82] This stands even when comparing late preterm infants born at 37 weeks with infants born at 39 weeks.[76] In addition to the risks of late preterm delivery, one study including 175 112 neonates born between 34 and 36 weeks found that infants born at 34 weeks had a higher rate of 5-minute Apgar score less than 7 compared with infants born between 37 and 40 weeks (adjusted OR, 5.51; 95% CI, 5.16-5.88).[83] As such, it is possible that the small associations between antidepressant exposure and birth weight/Apgar score identified in this analysis may be secondary to the associations with gestational age and preterm birth.

Our study contributes to the literature on this topic through an examination of the potential role for maternal depression in explaining associations between antidepressant exposure and pregnancy and delivery outcomes. However, relatively few studies provided adequate data to enable this analysis, limiting our statistical power. Furthermore, it is very difficult to obtain a perfectly disease-matched comparison group. It is likely that many untreated cases have less severe depression than do women who receive antidepressants. Similarly, women using antidepressants may receive suboptimal treatment or may not be adherent and therefore may experience residual symptoms. In this case, the fetus would be exposed to both potential effects of the drug and effects of the disease. As such, our findings in this regard should be interpreted with caution pending the availability of more rigorous studies on this topic. However, it is notable that, in our analysis of birth weight, the risk for lower birth weight was small when antidepressant use was compared with all mothers without such exposure, and there was no evidence for such an association when the control group was depressed mothers without antidepressant exposure during pregnancy ($P = .59$). This lack of association suggests that maternal depression may mediate the relationship between antidepressant exposure and birth weight. In contrast, the results for gestational age, preterm delivery, and Apgar scores (at 1 and 5 minutes) were similar whether the control group was all mothers or only depressed mothers, although the sample size was reduced for the latter comparison. This similarity suggests that exposure to antidepressants may be the determining factor for these detrimental pregnancy and delivery outcomes. Differential study design and settings, incomplete dosage and adherence data, as well as variable inclusion and exclusion criteria indicate a need for additional studies with untreated depressed comparison groups to determine whether there is an independent effect of antidepressant exposure on risk for these pregnancy and delivery outcomes.

The primary limitation of this analysis is the variable quality of the primary studies. Because of the low amount of available data, we opted to include studies using a variety of designs and sampling methodologies (eg, retrospective cohort, convenience sampling). The established limitations of these approaches should be considered in the interpretation of our findings. Furthermore, relatively few studies provided adequate data on important confounding variables, such as smoking, consumption of alcohol and other drugs, comorbid diagnoses, and use of other psychiatric medications during pregnancy. All these variables could have independent effects on the outcomes examined in this analysis. Similarly, few studies provided optimal data about the exposure, such as specific antidepressant used, indication, dosage, or adherence, limiting our capacity to examine drug- or class-specific effects, effects associated with the timing of the exposure, or effects associated specifically with use of antidepressant medication to treat depression rather than other indications, such as anxiety and panic disorder. Finally, the relatively small number of methodologically sound studies that could be included also limits our meta-analyses, although an evaluation restricted to moderate-quality studies yielded similar results. The most common limitations of the poor-quality studies excluded from our analyses included inadequate measures of exposure and outcome and no control for important confounders. Owing to the small sample sizes in studies that did not meet our quality criteria, pooled effects using all studies, regardless of quality, were very similar to those of our main analyses.

Although there are clear feasibility issues inherent in this type of research (ie, in identifying a sufficiently large sample with adequate data on antidepressant exposure

and pregnancy/delivery outcomes), some improvements in study design are possible at minimal added cost. In particular, adequate control for maternal depression is essential to separate the observed effects of the antidepressant drug from those of the disease. This can be accomplished through prenatal administration of a depression symptom scale, such as the Edinburgh Postnatal Depression Scale[84] (cohort studies), or linking with psychiatric diagnostic codes (population database or registry studies). Similarly, there is sound evidence that smoking during pregnancy is associated with premature delivery[85] (as well as other important outcomes, such as birth weight[86]), and women with depression may be more likely to smoke during pregnancy.[87,88] As such, maternal smoking data should be included in any analysis of the relationships between depression, antidepressant treatment, and delivery outcomes. Such controls will provide essential information for clinicians and their patients attempting risk-benefit analyses for use of antidepressant medications during pregnancy.

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**Author Contributions:** Drs Ross and Grigoriadis had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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