The Effect of Prenatal Antidepressant Exposure on Neonatal Adaptation: A Systematic Review and Meta-Analysis

Sophie Grigoriadis, MD, PhD, FRCPC; Emily H. VonderPorten, MPH; Lana Mamisashvili, MSW; Allison Eady, BA; George Tomlinson, PhD; Cindy-Lee Dennis, PhD; Gideon Koren, MD, FRCPC, FACMT; Meir Steiner, MD, PhD, FRCPC; Patricia Mousmanis, MD, CCFP, FCFP; Amy Cheung, MD, MSc, FRCPC; and Lori E. Ross, PhD

ABSTRACT

Objective: Conflicting reports on potential risks of antidepressant exposure during gestation for the infant have been reported in the literature. This systematic review and meta-analysis on immediate neonatal outcomes were conducted to clarify what, if any, risks are faced by infants exposed to antidepressants in utero. Subanalyses address known methodological limitations in the field.

Data Sources: MEDLINE, EMBASE, CINAHL, and PsycINFO were searched from their start dates to June 2010. Various combinations of keywords were utilized including, but not limited to, *depressive/mood disorder, pregnancy/pregnancy trimesters, antidepressant drugs*, and *neonatal effects*.

Study Selection: English language and cohort and case-control studies reporting on a cluster of signs defined as poor neonatal adaptation syndrome (PNAS) or individual clinical signs (respiratory distress and tremors) associated with pharmacologic treatment were selected. Of 3,074 abstracts reviewed, 735 articles were retrieved and 12 were included in this analysis.

Data Extraction: Two independent reviewers extracted data and assessed the quality of the articles.

Results: Twelve studies were retrieved that examined PNAS or the signs of respiratory distress and tremors in the infant. There was a significant association between exposure to antidepressants during pregnancy and overall occurrence of PNAS (odds ratio [OR] = 5.07; 95% CI, 3.25–7.90; $P < .0001$). Respiratory distress (OR = 2.20; 95% CI, 1.81–2.66; $P < .0001$) and tremors (OR = 7.89; 95% CI, 3.33–18.73; $P < .0001$) were also significantly associated with antidepressant exposure. For the respiratory outcome, studies using convenience samples had significantly higher ORs ($Q_1 = 5.4$, $P = .020$). No differences were found in any other moderator analyses.

Conclusions: An increased risk of PNAS exists in infants exposed to antidepressant medication during pregnancy; respiratory distress and tremors also show associations. Neonatologists need to be prepared and updated in their management, and clinicians must inform their patients of this risk.

J Clin Psychiatry 2013;74(4):e309–e320

Submitted: *June 21, 2012; accepted October 4, 2012 (doi:10.4088/JCP.12r07967).*
Corresponding author: *Sophie Grigoriadis, MD, PhD, Women's Mood and Anxiety Clinic: Reproductive Transitions, Department of Psychiatry, FG 29, Sunnybrook Health Sciences Centre, 2075 Bayview Ave, Toronto, ON M4N 3M5, Canada (Sophie.Grigoriadis@sunnybrook.ca).*

Major depressive disorder (MDD) during pregnancy is a serious condition that can be life threatening,[1,2] but, nonetheless, often remains undertreated.[3] Concerns over the possible association of adverse effects on the infant partially impede the use of antidepressant medication during pregnancy.[4] Indeed, there have been a variety of reports regarding transient short-term adverse neonatal or neurobehavioral effects observed in the neonate, which have been referred to collectively as poor neonatal adaptation syndrome (PNAS).[5,6] Although the mechanism of PNAS is not completely understood, it most likely represents a withdrawal or discontinuation syndrome[7,8] or is secondary to serotonin toxicity.[9] Symptoms can include respiratory distress, tremors, shaking or jitteriness, irritability, sleep disturbances, poor muscle tone, weak or absent cry, hypoglycemia, and seizures among others. The syndrome has been described to occur in up to 30% of infants that have had serotonergic antidepressant exposure in utero.[6,10] Lattimore et al[11] completed a meta-analysis[11] that pooled the results from studies of various designs reporting on this syndrome following third trimester exposure. The researchers did not find a significant association between poor neonatal adaptation and exposure to selective serotonin reuptake inhibitors (SSRIs) in their primary analysis but did in a secondary analysis (OR = 1.99; 95% CI, 1.43–2.77; $P = .003$), which included a study[12] that was initially excluded because it reported SSRI exposure in the first trimester as well as the third. This meta-analysis, however, was published over 6 years ago, and since then several new studies have been published on this syndrome. Moreover, the Lattimore[11] meta-analysis included studies without a control group, making interpretation problematic.

The aim of the present study was to perform a systematic review and rigorous, up-to-date meta-analysis examining what, if any, relationship exists between prenatal antidepressant exposure at any point in pregnancy and immediate neonatal outcomes. We examined PNAS (as defined by the authors in each study) in addition to 2 individual clinical signs, namely, respiratory distress and tremors. In order to address the methodological limitations of the available research, we also examined whether the effect on PNAS or on individual signs differed in subgroups of studies formed by each of the following potentially effect-modifying variables: the effect of study type, study quality, timing of exposure, and the use of adjusted data.

Clinical Points

- Antidepressant exposure during pregnancy may be associated with poor neonatal adaptation syndrome (PNAS) in the infant.
- Antidepressant exposure during pregnancy may be associated with respiratory distress and tremors in the infant.
- Clinicians must inform and prepare women taking antidepressants during pregnancy that their infant may show signs of PNAS and, in case they occur, how they will be managed.

DATA SOURCES AND STUDY SELECTION

This study is part of a larger program of research examining the effect of perinatal antidepressant medication use as well as depression itself on outcomes; the methods have been described in detail elsewhere.[13] Briefly, 2 professional librarians, with expertise in the areas of psychiatry and psychopharmacology, completed the literature searches independently. Various combinations of keywords were utilized, including but not limited to *depressive/mood disorder, pregnancy/pregnancy trimesters, antidepressant drugs*, and *neonatal effects* (full list of keywords provided in supplementary material). The databases and vendors used included MEDLINE (Ovid), MEDLINE In-Process (Ovid) to access current literature (keyword searching only), PsycINFO (American Psychological Association; Ovid), CINAHL (Nursing; Allied Health), EMBASE (Exerpta Medica, Elsevier; Ovid), and Scopus (Elsevier) to access current literature (keyword searching only). Each database was searched from its start date to June 30, 2010. Reference lists in reviews and meta-analyses were searched but did not produce any further references.

Inclusion and Exclusion Criteria

Cohort and case-control studies were included in the meta-analysis if they (1) were published in the English language; (2) reported original data; (3) reported on neonatal effects following any antidepressant exposure, including (but not limited to) selective serotonin reuptake inhibitors, tricyclic antidepressants, and monoamine oxidase inhibitors; (4) included a comparison group of pregnant women not exposed to the antidepressant examined; and (5) provided sufficient data to calculate an effect size if it was not provided. Because of the volume of potentially eligible studies, we excluded abstracts and conference proceedings and did not search for unpublished data. The following outcomes were included in this meta-analysis: PNAS, respiratory distress, and tremors as defined by the authors of the original publication. During the review of the literature, it became clear that many definitions are used for the cluster of signs identified as PNAS and that the wide variety of signs included in studies of PNAS makes it difficult to pool studies for a meta-analysis. We included all studies that defined PNAS as the presence of 1 or more of the following signs: tremors or shaking, jitteriness, shivering, agitation, irritability, increased or decreased muscle tone, poor feeding, excessive weight loss, seizures, tachypnea or respiratory distress, hypothermia, or hypoglycemia. We specifically selected signs of respiratory distress (*respiratory distress* or *tachypnea* when respiratory distress was not listed as a sign) and tremors (or *shaking* if tremors was not listed as a sign) for further examination, as these signs were deemed the most important clinically, based on feedback by our advisory committee of key stakeholders (including representatives from psychiatry, family medicine, obstetrics, neonatology, public health, patient advocacy, and policy) that was assembled for this program of research.

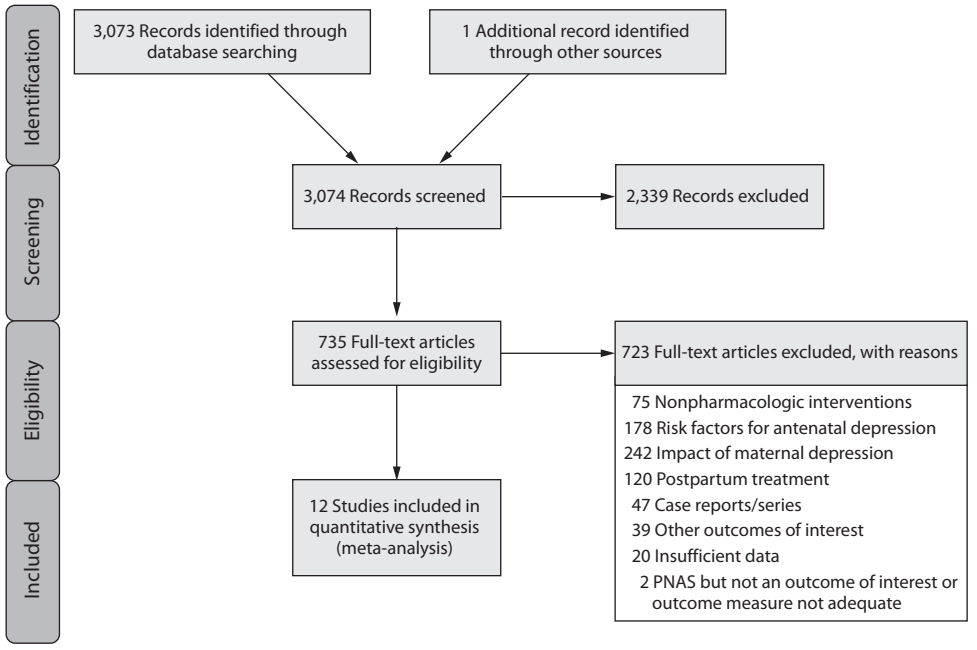
DATA EXTRACTION

The data extraction and quality assessment processes employed in this research program have been described in detail elsewhere.[13] In brief, 2 independent research assistants screened the titles and abstracts of articles, relevant abstracts were reviewed, and those articles meeting inclusion criteria were retrieved. Data extraction forms were modeled after the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement[14] to record relevant data from all eligible studies. The extracted data included source, study design, participants (sample, control, demographics and clinical characteristics), inclusion/exclusion criteria, antidepressants examined, dosage, duration of exposure, primary and secondary outcomes, outcome assessment methods, and loss to follow-up. For publications in which not all data were provided, we contacted the authors with requests for raw data. We extracted adjusted estimates and their variances where they were available. If no adjusted estimates were provided, crude ORs or differences in means (and sample variances) were computed from the published data. We added 0.5 to all cells in studies with a 0 cell count when calculating the OR.

Quality Assessment

The quality assessment tool used for this investigation has been described in detail elsewhere.[13] In brief, the Systematic Assessment of Quality in Observational Research (SAQOR) was based on existing quality assessment instruments, including the checklist developed by Downs and Black[15] and the Newcastle-Ottawa Scale,[16] and adapted to assess the specific criteria necessary for evaluation of data presented in this area of research. Research staff evaluated a total of 19 criteria under the following categories for each study by outcome: (1) sample, (2) control group, (3) quality of exposure/outcome measure, (4) follow-up, and (5) distorting influences. The last category specifically included assessment as to whether analyses controlled for depression, other psychotropic medications, and other potentially relevant confounders, such as smoking, alcohol, and illicit drug use. On the basis of scores on the quality criteria evaluated, a final quality rating (high, moderate, low, very low) was assigned by using a modification of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.[17] High, moderate, and low were deemed

Figure 1. Identification of Independent Studies for Inclusion in Meta-Analysis (adapted from PRISMA 2009 flow diagram[23])



"above quality threshold," whereas the very low were "below quality threshold." Data extraction and quality assessment results for each study were compared between raters, with any differences discussed with the principal investigators until consensus was reached.

Statistical Analyses

In the few cases in which adjusted hazard ratios or relative risks were reported, we treated these as estimated odds ratios. The DerSimonian and Laird random-effects model was used to obtain pooled estimates of the OR for binary outcomes and the weighted mean difference for continuous outcomes.[18] When only 2 studies published data on an outcome, we used a fixed-effects pooled estimate. Publication bias was assessed by visual inspection of funnel plots depicting the individual study estimates (on the log scale for ORs) against their standard error. Further, the number of unpublished studies (k) was estimated by using the L estimator developed by Duval and Tweedie.[19] In brief, if k was 1 or more, then k studies were imputed by reflection of the k largest effects around the summary estimate. The standard errors of the k "reflected" studies were used for the k imputed ones and the summary OR was reestimated in this expanded dataset. If k was estimated to be 0, then there was no evidence for publication bias. For studies with publication bias, Duval and Tweedie's trim-and-fill method[19] was used to estimate exposure effects after adjusting for potential publication bias. Between-study heterogeneity was assessed by Cochrane Q and visual inspection of forest plots and quantified by I^2.

A nonsignificant Q and small I^2 suggest a common underlying effect and that variations in estimated study effects are due only to random variation and not true study-to-study variation (heterogeneity). I^2 can be interpreted as the proportion of the total variance due to heterogeneity. In one interpretation, $I^2 = 25\%$ represents a low degree of heterogeneity; 50%, a moderate degree; and 75%, a high degree.[20] Subgroup analyses were run (regardless of whether Q was significant) to explore sources of heterogeneity by examining within-group effects and between-group differences in pooled effects based on several study characteristics chosen a priori: whether a convenience sample was used (ie, not consecutive or random sample), study quality (ie, those above threshold compared with those below), timing of exposure, and the use of adjusted data. The metafor package[21] in R (2.14.2)[22] was used for the statistical analyses.

RESULTS

Of the 3,074 abstracts reviewed, 2,339 were excluded based on title and abstract. In total, 735 articles were retrieved and assessed for eligibility and 15 articles met the inclusion criteria (Figure 1).[23] Of these, 3 articles were excluded because 1 did not have a control group without antidepressant use for this outcome,[5] 1 did not report on the necessary outcomes,[24] and 1 did not have a comparable outcome measure,[25] leaving 12 studies for inclusion in the quantitative analysis (Table 1).[8,10,12,26–34] Most studies reported data on more than 1 outcome (8 reported on neonatal adaptation syndrome overall, 9 on respiratory signs, and 4 on tremors or shaking). Seven studies used a convenience sample, while 5 studies used either a population- or hospital-based sample. Eleven of the 12 studies were above our quality threshold. Seven studies confirmed third trimester or late exposure. Three studies provided adjusted data.

Table 1. Study Characteristics of 12 Studies in the Poor Neonatal Adaptation Syndrome (PNAS) or Signs Meta-Analyses

Article	Quality Threshold	Country	Sample Size	Confounders	Drug	Results	Outcome Definition
Costei et al,[26] 2002[a,b,c,d]	A	Canada	Paroxetine (third trimester), n = 55 Paroxetine (first or second trimester), n = 27 NTC, n = 27	Matched for maternal age, gravidity, parity, alcohol use, smoking, and nonteratogenic drug use Excluded subjects who discontinued paroxetine prior to the last trimester, used other drugs with known withdrawal-like symptoms	Paroxetine	Neonatal complications: 12 women in paroxetine (third trimester) and 3 in controls (2 in paroxetine [first or second trimester] and 1 in NTC); 22% in paroxetine (third trimester) vs 6% in controls (paroxetine [first or second trimester] and NTC) ($P = .03$) Respiratory distress: 9 women in paroxetine (third trimester) and 1 in controls (1 in paroxetine [first or second trimester] and 0 in NTC)	Neonatal complications that required prolonged hospitalization Paroxetine (third trimester) vs NTC data used in meta-analysis
Laine et al,[27] 2003[a,c]	A	Finland	Any SSRI, n = 20 Control, n = 20	Matched for maternal age, gravidity, parity, pregnancy duration, time of delivery, and delivery mode	SSRIs (fluoxetine, citalopram)	17 SSRI-exposed infants vs 9 controls had at least 1 serotonergic symptom during the first 4 days of life (OR = 6.9; 95% CI, 1.6–29.2; $P = .008$)	Serotonin symptoms based on Serotonin Syndrome Scale. Frequency of infants with at "least 1 serotonergic symptom" used in meta-analysis for PNAS[27(p723)]
Källén,[12] 2004[b]	A	Sweden	Any antidepressant, n = 997 Total population, N = 582,796	Adjusted for birth year, maternal age, parity, smoking in early pregnancy Excluded subjects with multiple births for some outcomes	Any antidepressant	Respiratory distress: Any antidepressant vs total population (AOR = 2.21, 95% CI, 1.71–2.86)	Respiratory distress diagnostic codes in the Swedish Medical Birth Registry
Oberlander et al,[10] 2004[a,b,c]	A	Canada	SSRI alone (group 1), n = 28, SSRI and clonazepam (group 2), n = 18 Control, n = 23	Control group infants did not have psychotropic medication exposure, they were born at term, and their mothers did not have a history of mental illness. Infants who were admitted to NICU after birth were excluded. Women using any other psychotropic medication were excluded	SSRIs (paroxetine, fluoxetine, sertraline)	Transient PNAS: 30% in exposed (groups 1 and 2, n = 14) vs 9% in control (n = 2) (likelihood ratio = 5.64; 95% CI, 1.1–25.3; $P = .018$) Incidence of symptoms did not differ significantly in groups 1 and 2 (7/28 and 7/18) (95% CI, 0.5–6.8) Respiratory distress: 14 in exposed, 2 in control	Transient neonatal symptoms that suggest "altered adaptation in the newborn period (jitteriness, respiratory difficulty, hypoglycemia, lethargy, weak or absent cry, or desaturation on feeding)"[10(p232)]
Levinson-Castiel et al,[8] 2006[a,b,d,e]	A	Israel	SSRI, n = 60 Control, n = 60	Matched for sex, gestational age, birth weight, and mode of delivery Excluded subjects with exposure to other medications or substances (illicit drugs or alcohol), congenital anomalies, other central nervous–affecting conditions, or preterm infants	SSRIs, venlafaxine	Neonatal abstinence syndrome: 30% in exposed (n = 18) vs 0% in control ($P < .001$) Tachypnea: 12 in SSRI group vs 0 in control Tremor: 37 in SSRI groups vs 11 in control group	Neonatal abstinence syndrome defined as a Finnegan score ≥ 4
Oberlander et al,[28] 2006[b]	A	Canada	SSRI and depressed, n = 1,451 Unexposed and depressed, n = 14,234	Excluded subjects with multiple births, use of other psychotropic drugs Included control group without exposure to SSRI or depression and propensity score–matched group to control for differences in maternal characteristics	SSRIs	Respiratory distress: 13.9% in exposed vs 7.8% in unexposed (difference = 0.063; 95% CI, 0.042–0.079; $P < .001$); exposed vs propensity score-matched controls (difference = 0.044; 95% CI, 0.013–0.077; $P = .006$)	*ICD-9* codes

(continued)

Table 1 (continued). Study Characteristics of 12 Studies in the Poor Neonatal Adaptation Syndrome (PNAS) or Signs Meta-Analyses

Article	Quality Threshold	Country	Sample Size	Confounders	Drug	Results	Outcome Definition
Davis et al,[29] 2007[b,d]	A	USA	SSRI, n = 874 Unexposed, n = 75,219	Stratified by health system, birth season, and maternal age Excluded subjects for whom 30-day follow-up was unavailable	SSRIs	Respiratory distress syndrome and other respiratory conditions: SSRI (third trimester) vs unexposed (RR = 1.97; 95% CI, 1.65–2.35)	*ICD-9* codes
Ferreira et al,[30] 2007[a,b,c,d,e]	A	Canada	Exposed, n = 76 Unexposed, n = 90	Adjusted for significant maternal characteristics (adjusted only for NAS overall, not respiratory signs, tremors, or shaking) No group difference for maternal age Excluded women using benzodiazepines, barbiturates, or any other antidepressant on a daily basis	SSRIs, venlafaxine	Neonatal behavioral signs: 77.6% in exposed vs 41.1% in unexposed ($P < .001$; AOR = 3.1, 95% CI, 1.3–7.1) Tachypnea: 40.8% in exposed vs 15.6% in unexposed ($P < .001$) Shaking: 19.7% in exposed vs 6.7% in unexposed ($P = .01$)	Neonatal behavioral signs "defined as a composite of signs and symptoms involving central nervous, respiratory, and digestive systems, as well as hypoglycemia and the need for phototherapy. If at least 1 clinical manifestation involving any system cited above was observed during the study period (entered as yes/no in the daily data-collection sheet), it was considered that the infant had had a neonatal behavioral sign"[30(p53)]
Boucher et al,[31] 2008[a,b,d,e]	B	Canada	Any antidepressant, n = 73 Unexposed, n = 73	Adjusted for gestational age at birth (adjusted only for NAS overall and respiratory symptoms, not tremors or shaking) Matched for same hospital, gestational age, and date at delivery (± 1 week) No group difference for smoking, alcohol, or maternal age	Any antidepressant: citalopram, paroxetine, sertraline, fluoxetine, fluvoxamine, venlafaxine, amitriptyline, trazodone, mirtazapine	Global outcome: 78% in exposed vs 38% in unexposed (AOR = 7.0; 95% CI, 3.2–15.3) Respiratory function (tachypnea): 43% in exposed vs 26% in unexposed (AOR = 2.5; 95% CI, 1.1–5.3) Tremors: 30% in exposed vs 3% in unexposed	Primary outcome: "adverse effects on the neonates" Screened for "symptoms and complications reported in the literature in antidepressant-exposed neonates," including "respiratory, metabolic (hypoglycemia), feeding and gastrointestinal problems, lower and higher arousal symptoms, seizures, serotonergic or adrenergic activity alterations, and discontinuation symptoms"[31(p335)] A "global composite outcome" was created (presence of 1 or more of the symptoms analyzed)
Maschi et al,[32] 2008[a,c,d]	A	Italy	Any antidepressant, n = 40 Control, n = 240	Matched for gravity and maternal age Excluded subjects with chronic diseases that affect pregnancy outcome or using other drugs with known withdrawal-type symptoms	Any antidepressant	Poor neonatal adaptation: no statistically significant differences; 12.5% in exposed (in second and third trimesters) vs 3.8% in control ($P = .05$)	"Poor neonatal adaptation defined as a conglomeration of conditions including respiratory distress, hypoglycemia, jitteriness, lethargy, hypotonia, weak or absent cry, feeding difficulties, neonatal convulsions, and hyperbilirubinemia"[32(p284)]

(continued)

Table 1 (continued). Study Characteristics of 12 Studies in the Poor Neonatal Adaptation Syndrome (PNAS) or Signs Meta-Analyses

Article	Quality Threshold	Country	Sample Size	Confounders	Drug	Results	Outcome Definition
Galbally et al,[33] 2009[b,c,d,e]	A	Australia	Exposed, n = 23 Control, n = 27	Matched groups, but no details given other than control group women were not depressed at recruitment No group differences for other psychotropic drugs, smoking, alcohol, illicit drugs, or maternal age Excluded women with substance dependence, inability to provide informed consent, or lack of English proficiency	SSRI, SNRI, or NaSSA	Respiratory distress: 21.7% in exposed vs 11.1% in control (RR = 1.957; 95% CI, 0.5232–7.316; $P = .997$) Tremor: 56.5% vs 0% (RR = 31.5; 95% CI, 1.975–502.479; $P = .015$)	"A purpose-designed questionnaire was used based on neonatal symptoms and complications found in previous studies of antidepressant exposure in pregnancy"[33(p848)] Neonatal serotonin discontinuation syndrome symptoms analyzed include "the nature of the infant's cry, length of sleep after feeding, tremor, yawning, sneezing, feeding problems, reflux, vomiting, and diarrhea…, whether the infant was admitted to either the special care nursery or neonatal intensive care unit…and whether the infant had a diagnosis of respiratory distress, hypoglycemia, jaundice, or convulsions"[33(p848)]
Rampono et al,[34] 2009[a,c]	A	Australia	Any antidepressant, n = 38 Control, n = 18	Report "similar" demographic characteristics for mothers in both groups Excluded subjects who abused substances, took medication known to affect infant behavior (apart from those investigated), delivered preterm infants or infants with congenital anomalies	SSRIs, venlafaxine	Neonatal abstinence: 5% in exposed; exposed (median Finnegan score, 2 [IQR, 0–1.05]) vs control (median Finnegan score, 0 [IQR, 0–6]) on day 1 ($P < .05$) only; no other differences in mean or maximum Finnegan scores (day 1–3)	Finnegan neonatal abstinence scoring system used Neonatal abstinence defined as a score > 12 or 3 scores > 8

[a]Included in our PNAS overall meta-analysis. [b]Included in our respiratory distress meta-analysis. [c]Included in convenience sample subgroup. [d]Late pregnancy antidepressant exposure. [e]Included in our tremors meta-analysis.

Abbreviations: A = above quality threshold, AOR = adjusted odds ratio, B = below quality threshold, IQR = interquartile range, NAS = neonatal adaptation syndrome, NaSSA = noradrenergic and specific serotonergic antidepressant, NICU = neonatal intensive care unit, NTC = nonteratogen control, RR = relative risk, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor.

Poor Neonatal Adaptation Syndrome

Overall, we pooled results from 8 studies; the OR for PNAS and exposure to any antidepressant was 5.07 (95% CI, 3.25–7.90; $P < .0001$; Figure 2). While the ORs for each subanalysis were significant, there were no group differences based on the following modifying variables determined a priori: (1) pooled results from studies with convenience samples versus nonconvenience samples (the latter having a nonsignificantly different higher OR than the first), (2) studies below quality threshold versus those above threshold (with the better quality studies having a lower OR), (3) studies with the use of antidepressants late in pregnancy versus those that did not have exclusive late exposure (with the ORs being similar in magnitude), and (4) studies that reported adjusted data versus those with unadjusted data (with the unadjusted studies pooling to a higher OR) (Table 2).

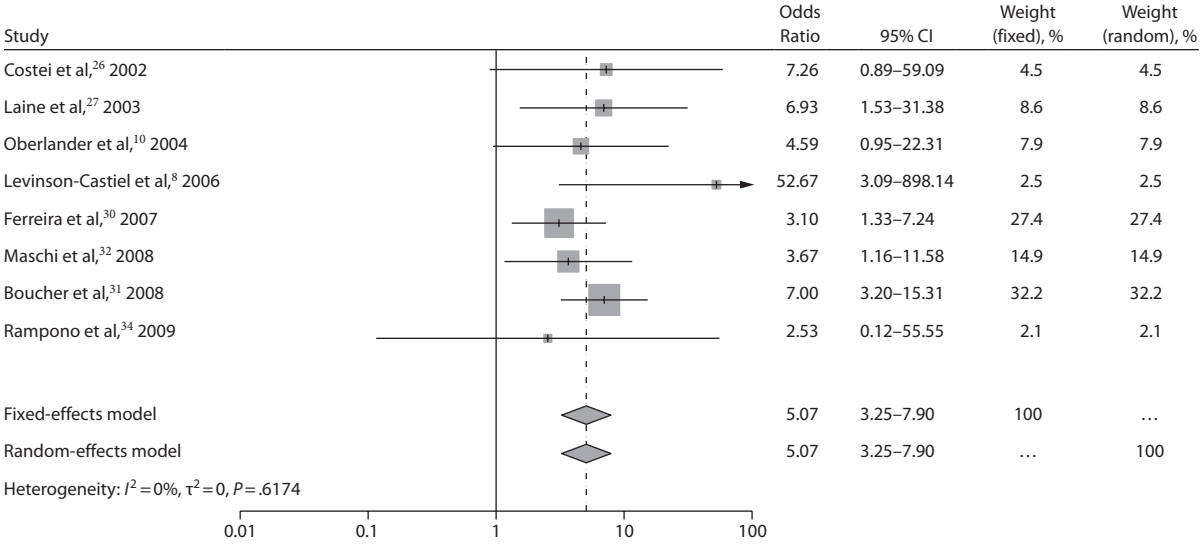
Respiratory Distress

Nine studies reported on signs of respiratory distress (including respiratory distress or tachypnea). The pooled estimate demonstrated a significant association between exposure to antidepressants and immediate neonatal respiratory signs (OR = 2.20; 95% CI, 1.81–2.66; $P < .0001$; Supplementary eFigure 1). The moderator variable of study type was significant. Although pooled estimates from studies using both convenience and nonconvenience samples were significant, the studies using convenience samples had significantly higher ORs ($Q_1 = 5.4$, $P = .020$). No group differences were found in any of the other subanalyses (Table 2), although higher pooled ORs were found in studies that were below quality threshold, had subjects with late exposure, and had results with unadjusted data.

Tremors

Lastly, with regard to tremors (or shaking) in infants as the outcome, 4 studies were pooled, with an OR of 7.89 (95% CI, 3.33–18.73; $P < .0001$; see Supplementary eFigure 2). It was only possible to compare studies with convenience samples versus those without and studies above the quality threshold with those below. No significant differences were found (Table 2) for the moderator with

Figure 2. Exposure to Any Antidepressant and the Risk of Poor Neonatal Adaptation Syndrome[a]



[a]Meta-analysis results for all studies.

higher ORs for the convenience samples and studies below quality threshold.

Publication Bias

We did not find evidence for the presence of publication bias in our main PNAS analysis; heterogeneity was not significant, the funnel plot appeared symmetric around 5, and, when the L estimator of Duval and Tweedie was used,[19] there did not appear to be missing studies. There did appear to be publication bias for the individual symptoms analyses, although the impact was minor on the estimates. For the respiratory distress analysis, the adjusted OR, which was derived from the trim-and-fill procedure,[19] was 2.00 (95% CI, 1.59–2.52; $P < .0001$). The trim-and-fill procedure yielded an adjusted OR of 5.17 (95% CI, 2.11–12.73; $P < .003$) for the tremors outcome.

DISCUSSION

The objective of this study was to determine if any relationship exists between prenatal antidepressant exposure and poor immediate neonatal outcomes. The results of our meta-analysis suggest that there is a genuine increased risk for PNAS. Moreover, as this syndrome appears not to be uniformly defined, we further examined 2 specific clinical signs, namely, respiratory distress and tremors; a significant association was also shown for the aforementioned signs and the infant having been exposed to antidepressants in utero. To our knowledge, ours is the first meta-analysis to examine PNAS as a syndrome as well as individual signs with antidepressant exposure at any point in pregnancy. Our results are similar to those of Lattimore and colleagues,[11] despite their inclusion of only 3 studies (Hendrick et al,[35] Chambers et al,[5] and Goldstein et al[36]) of their pooled 6 that did not provide unexposed control group data. We did not include Zeskind et al,[25] which was included in the Lattimore et al analysis,[11] because the frequency of tremors was not provided.

Strengths and Limitations

The strength of our work rests on the attention paid to potential confounding factors and consideration of methodology. The research examining the potential effects of prenatal antidepressant exposure has been criticized for weak methodology in general[37] and for neglecting to account for potential confounders known to affect pregnancy outcomes. In response, we pooled estimates for all studies, using adjusted data where possible, and then examined the effect of moderator variables that we identified a priori. We assessed the studies for the effect of using convenience samples (ie, those that were not recruited using consecutive or random sampling strategies) and whether study quality affected interpretation. Moreover, we contrasted results by using pooled estimates for studies that did and did not adjust for confounders the authors of the original publication deemed important. We examined the data for a potential effect for timing of exposure,[38] as it has been suggested that third trimester exposure may be an important factor in whether the neonate displays PNAS.[10] Most of the moderator variables did not appear to affect the significance of the results, a finding that suggests a genuine effect of the antidepressants, as almost all subanalyses remained significant and not significantly different from one another, except one. The use of convenience samples did appear to result in statistically higher OR for respiratory distress than the studies that did not use convenience samples. Given that the convenience samples were ones that were not based on random or consecutive sampling, they may have been biased in favor of the infant displaying respiratory distress and inflating the OR. Regardless, the analysis with nonconvenience samples was also statistically significant. Overall, the data exhibit a robust effect, with consistently elevated ORs over 2 suggesting the results are clinically significant as well.[39] The robustness of the OR is reassuring, as it is unethical to conduct the gold standard of randomized controlled trials with pregnant and

Table 2. Exposure to Any Antidepressant and Risk of Poor Neonatal Adaptation Syndrome (PNAS) or Signs: Meta-Analyses Results

				Within Group							
						Heterogeneity			Effect of Moderator		
Analysis	No. of Studies	No. of Cases	Total Sample Size	OR (95% CI)[a]	*P* Value	$Q_{(df)}$ Within	*P* Value	I^2 (%)	$Q_{(df)}$ Between	*P* Value	I^2 (%)
PNAS overall											
All studies	8	270	959	5.07 (3.25–7.90)	<.0001	5.35_7	.617	0.0			
Study type											
Convenience sample	6	167	693	3.96 (2.28–6.85)	<.0001	1.30_5	.935	0.0	1.4_1	.237	26.0
Not convenience sample	2	103	266	11.89 (2.09–67.76)	.005	1.81_1	.179	45.0			
Study quality											
Above quality threshold	7	185	813	4.34 (2.53–7.45)	<.0001	4.38_6	.625	0.0	0.97_1	.325	18.0
Below quality threshold	1	85	146	7.00 (3.20–15.31)[b]	<.0001						
Timing of exposure											
Exposed late	5	226	794	5.13 (2.86–9.21)	<.0001	4.98_4	.290	20.0	0.00053_1	.982	0.0
Unsure/not exposed late	3	44	165	5.20 (1.86–14.57)	.002	0.37_2	.831	0.0			
Confounders											
Adjusted findings	2	181	312	4.74 (2.14–10.52)	<.0001	1.91_1	.167	48.0	0.07_1	.794	1.0
Unadjusted findings	6	89	647	5.46 (2.72–10.97)	<.0001	3.36_5	.644	0.0			
Respiratory distress											
All studies	9	23,224	676,186	2.20 (1.81–2.66)	<.0001	12.9_8	.116	38.0			
Study type											
Convenience sample	4	78	349	4.18 (2.29–7.60)	<.0001	2.40_3	.493	0.0	5.4_1	.020	42.0
Not convenience sample	5	23,146	675,837	2.01 (1.76–2.30)	<.0001	4.84_4	.304	17.0			
Study quality											
Above quality threshold	8	23,174	676,040	2.20 (1.79–2.72)	<.0001	12.6_7	.081	45.0	0.0_1	>.999	0.0
Below quality threshold	1	50	146	2.50 (1.14–5.49)[b]	.022						
Timing of exposure											
Exposed late	6	5,536	76,657	2.64 (1.69–4.14)	<.0001	7.94_5	.160	37.0	0.6_1	.440	5.0
Unsure/not exposed late	3	17,688	599,529	2.14 (1.60–2.86)	<.0001	4.85_2	.089	59.0			
Confounders											
Adjusted findings	2	16,410	583,939	2.24 (1.75–2.86)	<.0001	0.09_1	.770	0.0	0.02_1	.880	0.0
Unadjusted findings	7	6,814	92,247	2.30 (1.72–3.08)	<.0001	12.15_6	.059	51.0			
Tremors											
All studies	4	106	482	7.89 (3.33–18.73)	<.0001	5.41_3	.144	44.5			
Study type											
Convenience sample	2	34	216	11.31 (0.63–204.37)	.100	3.70_1	.054	73.0	0.03_1	.857	1.0
Not convenience sample	2	72	266	8.59 (4.14–17.81)	<.0001	0.76_1	.384	0.0			
Study quality											
Above quality threshold	3	82	336	6.74 (2.39–19.03)	.0003	4.11_2	.128	51.0	0.78_1	.376	14.0
Below quality threshold	1	24	146	15.31 (3.45–68.06)[b]	.0003						
Timing of exposure											
Exposed late	4	106	482	7.89 (3.33–18.73)	<.0001	5.41_3	.144	44.5			
Unsure/not exposed late	0	0	0								
Confounders											
Adjusted findings	0	0	0								
Unadjusted findings	4	106	482	7.89 (3.33–18.73)	<.0001	5.41_3	.144	44.5			

[a]Pooled effect size estimated using random-effects model.
[b]Pooled effect size estimated using fixed-effects model.

depressed women to definitively determine any potential adverse effects of these medications, and we are still currently limited to observational research.

It is important to note that not all of the studies included in this meta-analysis defined PNAS in the same way; 2 used an objective scoring system to measure it, although each applied the system slightly differently, and 1 used a scale (ie, Levinson-Castiel,[8] Rampono,[32] and Laine[25]). Several researchers have identified different clusters of signs that they found to be associated with antidepressant exposure during pregnancy. The studies included in this meta-analysis had significant overlap in the clinical signs they identified, but they were also diverse. We also assessed the presence of 2 individual signs that experts in our advisory committee agreed are highly specific to this syndrome, at least clinically, and they were also significant. Although we analyzed the 2 individual signs to circumvent the diversity in the way the syndrome was operationalized at the time the original studies were conducted, this method can also be considered a limitation of our meta-analysis, as the signs we chose may not be universally accepted as always occurring in this syndrome. Although we grouped studies according to timing of exposure, we were able to segregate only those that did and did not report third trimester exposure. Thus, the studies in the "not confirmed" category had infants exposed from any trimester of pregnancy, which could have included the third.

It is important that future studies specify timing of exposure by trimesters of pregnancy to definitively determine whether timing is an important factor for the emergence of PNAS. Moreover, future studies should objectively measure PNAS, preferably with a validated assessment measure.

Although the 2 studies that did employ an objective measure used the Finnegan score,[40] which is used to assess neonatal withdrawal symptoms following exposure to opioid drugs to determine the need for intervention, it has not been validated for antidepressant exposure as far as we are aware. One of the most important limitations, however, stems from the original studies that did not commonly control for the potential effects of depression itself. As we do not completely understand the pathophysiology of depression, we cannot be confident about what adverse effects can be present in the infant. With the emerging data on how maternal mood can affect fetal development,[41] future studies must account for the role of maternal depression.

Implications

A review[42] of the various studies that examined immediate neonatal symptoms in infants exposed to antidepressants in utero concluded that infants exposed to all classes of antidepressants displayed a spectrum of symptoms similar to those that may be seen in adults exposed to the same drugs. Since "up to 85% of adults may suffer from withdrawal" symptoms after abrupt discontinuation of antidepressant medication, it seems likely that infants who are no longer being exposed to antidepressants through their mothers would experience similar symptoms, although PNAS does not universally occur, as approximately one-third of exposed infants display it.[42(p177)] The issue is that most adult studies report on subjective symptoms, which cannot be elicited from infants. The debate continues though regarding this phenomenon being secondary to overstimulation,[9] as it is difficult to differentiate withdrawal reactions from toxicity leading to overstimulation symptoms in infants "because such patterns of antidepressant-induced complications are clinically similar in the neonate."[42(p181)] Some argue that withdrawal reactions and symptoms of serotonergic toxicity occur along a continuum.[42] "Serotoninergic antidepressants with a short half-life may be present in adequate concentrations at birth to induce toxicity and decrease over time at rates sufficient to induce withdrawal signs."[42(p181)] The third causal explanation postulates that the signs of PNAS may result from changes in early formation of the lungs or brain that are sustained but become evident with the novel demands during neonatal adaptation.[43] However, given that a constellation of signs has been reported for PNAS, it is possible that different signs may result from varying mechanisms.[28] Tremors, for example, can be typical of withdrawal.[7,8] Respiratory signs may result from serotonergic stimulation, as serotonin is known to have a role in the development and modulation of the lungs[31]; in more severe cases, signs may present as respiratory distress and, some suggest, as mild persistent pulmonary hypertension, although this hypothesis remains to be determined.[44] It might also be possible that the mechanism differs among patients and specific drugs.[45] Those with a shorter half-life, for example, may be more likely to cause PNAS, as is the case with discontinuation syndrome in adults following the cessation of a short-acting antidepressant. It is not known at this time if the phenomenon is dose related and there can be an interaction with maternal metabolism and perhaps genetic susceptibility or predisposition.[46] Some clinicians argue the antidepressant dose should be reduced prior to delivery to reduce the incidence of PNAS. This is likely related to the US Food and Drug Administration[47] and Health Canada[48] issuing advisories in 2004. However, this approach will put the mother at risk of undertreatment during a critical time. Only with future research will the mechanism or mechanisms be clearly understood and their implications. Specific drug effects as opposed to pooling various antidepressants also need more attention.

Encouragingly, the signs associated with exposure to antidepressants in utero are believed to be most commonly mild, have a limited course, can begin within hours after birth, and typically resolve within days to 2 weeks.[8,10,49] However, more work is necessary to fully understand this syndrome. The studies pooled in this meta-analysis varied in their reporting of the clinical features listed above. For example, the timing of signs was not always reported. Onset of signs was noted as within the first 24 hours following birth by 3 studies[10,30,34] and within the first 48 hours by 2 studies.[8,31] Duration of signs was documented to be most commonly up to the first 48 hours post delivery in 2 studies,[10,31] although a median of 3 days' duration was reported by another study,[30] and signs still noted at 4 days by another.[8] Not all studies reported on the effect of the signs on the length of hospital stay, but of those that did, 4 documented "longer" or "prolonged" hospital stays,[26,28–30] whereas 2 studies[10,31] reported the signs had no significant effect on hospital stay. As described above, the type of signs reported for PNAS vary, including among the pooled studies. For example, although respiratory distress was not significant in one study[33] and another reported no treatment was necessary for any infant,[8] others reported that some infants did require intubation[26] (3 infants in total) and "ventilatory support" (number of infants not provided).[30] Two studies[12,29] documented significantly more convulsions in infants exposed to antidepressants. Thus far, long-term sequelae have not been reported for PNAS, but the long-term outcomes have not been well studied. Longer term data were provided by only one study[27] of those pooled in which significant differences were not evident at 2 months post-delivery between antidepressant-exposed versus unexposed infants. Clearly, more systematic work is needed to characterize PNAS and determine which infants are most at risk, including those that will develop serious signs and any that may experience long-term sequelae.

The effect of breastfeeding on PNAS is unknown. If this syndrome results from a discontinuation phenomenon, breastfeeding would seem advantageous as the infant would continue to get some exposure through breast milk. Note, however, that in 1 of the pooled studies in this meta-analysis, all the infants were breastfed, yet the antidepressant-exposed group still developed signs of PNAS.[33] Although this may be related to a lower level of antidepressant exposure via lactation than during gestation, future research should examine the impact of breastfeeding on the development and evolution of PNAS.

The decision of whether or not to use antidepressant medication requires weighing the risks of the effects of depression itself as well as the effects of the medication on the fetus, neonate and child; beneficial effects on the mother and risk of relapse if medication is discontinued must also be reviewed. Both mother and baby must be considered in any decision. Women who choose to use antidepressant medication while pregnant must be counseled that the infant may develop PNAS, and that, to date, data suggest this syndrome is usually transient, although more severe symptoms have been reported. The woman and her family must be supported in their decision regarding the use of antidepressant medication and assured that should complications arise, they will be identified and treated immediately. This work highlights the ongoing need to collaborate with the entire health care team and in particular increase the awareness of neonatologists of antidepressant exposure in the infant such that appropriate care is expeditiously provided if necessary. Moreover, the family may require ongoing support if a prolonged neonatal intensive care unit admission occurs; arrangements for such can be more quickly arranged if clinicians have prior knowledge.

Drug names: citalopram (Celexa and others), clonazepam (Klonopin and others), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), mirtazapine (Remeron and others), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft and others), trazodone (Oleptro and others), venlafaxine (Effexor and others).

Author affiliations: Department of Psychiatry, Women's College Hospital, Toronto (Dr Grigoriadis and Mss VonderPorten, Mamisashvili, and Eady); Women's College Research Institute, Toronto, (Drs Grigoriadis and Dennis); Department of Psychiatry, University Health Network, and Clinical Trials Resource Center, Toronto General Research Institute (Dr Grigoriadis); Department of Psychiatry, Sunnybrook Health Sciences Center, Toronto (Drs Grigoriadis and Cheung and Mss VonderPorten and Mamisashvili); Sunnybrook Research Institute, Toronto (Drs Grigoriadis and Cheung); Department of Psychiatry (Drs Grigoriadis, Dennis, Cheung, and Ross), Department of Medicine (Dr Tomlinson), Faculty of Nursing (Dr Dennis), Departments of Pediatrics, Pharmacology, Pharmacy, and Medical Genetics (Dr Koren), and Institute of Medical Sciences (Dr Steiner), University of Toronto, Toronto; Center for Innovation in Complex Care, Toronto General Hospital, Toronto (Dr Tomlinson); Division of Clinical Decision-Making and Health Care, Toronto General Research Institute, Toronto (Dr Tomlinson); Motherisk Program, The Hospital for Sick Children, Toronto; and Departments of Medicine, Pediatrics and Physiology/Pharmacology, University of Western Ontario, London (Dr Koren); Departments of Psychiatry and Behavioural Neurosciences and Obstetrics and Gynecology, McMaster University; Women's Health Concerns Clinic, St Joseph's Hospital; and St Joseph's Healthcare, Hamilton (Dr Steiner); Healthy Child Development Program, Ontario College of Family Physicians, Toronto; York Central Hospital, Richmond Hill; and Markham Stouffville Hospital, Markham (Dr Mousmanis); and Center for Addiction and Mental Health, Toronto (Dr Ross), Ontario, Canada. Dr Grigoriadis is now with the Department of Psychiatry, Sunnybrook Health Sciences Center, and Sunnybrook Research Institute, Toronto. Mss VonderPorten and Mamisashvili are with the Department of Psychiatry, Sunnybrook Health Sciences Center, Toronto, Ontario, Canada.

Author contributions: Conception and design: Drs Grigoriadis and Ross; data analysis and interpretation: Drs Grigoriadis, Tomlinson, Ross, Dennis, Koren, Steiner, Mousmanis, and Cheung and Mss VonderPorten, Mamisashvili, and Eady; drafting or revision of the manuscript: Drs Grigoriadis, Ross, Tomlinson, Dennis, Koren, Steiner, Mousmanis, and Cheung and Mss VonderPorten, Mamisashvili, and Eady; and approval of the final version of the manuscript for publication: Drs Grigoriadis, Ross, Tomlinson, Dennis, Koren, Steiner, Mousmanis, and Cheung and Mss VonderPorten, Mamisashvili, and Eady. Drs Grigoriadis and Ross had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Potential conflicts of interest: In the last 5 years, **Dr Grigoriadis** has received honoraria as a consultant and a member of an advisory committee or for lectures from Wyeth Pharmaceuticals, GlaxoSmithKline, Pfizer, Servier, Eli Lilly Canada, and Lundbeck; and has received research grant support from the Canadian Institutes of Health Research (CIHR), Ontario Ministry of Health, Ontario Mental Health Foundation, and CR Younger Foundation. **Dr Steiner** has been a consultant to AstraZeneca, Azevan, Servier, Bayer Canada, and Lundbeck; has received grant/research support from CIHR, Pfizer, Eli Lilly, and Lundbeck; and has received honoraria from the Society for Women's Health Research and AstraZeneca. **Drs Tomlinson, Dennis, Koren, Mousmanis, Cheung, and Ross and Mss VonderPorten, Mamisashvili**, and **Eady** have no financial disclosures to report.

Funding/support: This research was funded by a Research Syntheses grant from the CIHR, KRS-83127, and the Ontario Ministry of Health and Long-Term Care through the Drug Innovation Fund, grant # 2008-005. Dr Grigoriadis has a new investigator award in women's health research from the CIHR in partnership with the Ontario Women's Health Council, award NOW-88207. Dr Ross is supported by a new investigator award from CIHR and the Ontario Women's Health Council, award NOW-84656. In addition, support to the Center for Addiction and Mental Health for salary of scientists and infrastructure has been provided by the Ontario Ministry of Health and Long-Term Care.

Disclaimer: The views expressed here do not necessarily reflect those of the Ministry of Health and Long-Term Care.

Previous presentations: Preliminary results of this study were presented at the ▪ Motherisk Update 2012 (paper title: The effect of antidepressant medications on mothers and babies—an updated systematic analysis); May 23, 2012; Toronto Ontario, Canada ▪ Canadian Psychiatric Association Conference (paper title: Evidence-based discussion guide for antidepressant treatment in depressed pregnant and postpartum women); October 13–15, 2011; Vancouver, British Columbia, Canada ▪ Canadian Institutes for Health Research, Innovations in Gender, Sex and Health Research Conference (paper titles: [1] Effects of in utero exposure to antidepressant medication during pregnancy: a meta-analysis and [2] Short-term and long-term impact of untreated maternal depression on the child); November 22–23, 2010; Toronto, Ontario, Canada ▪ Canadian Psychiatric Association Conference (paper title: Outcomes associated with antidepressant medication use during pregnancy: a meta-analysis); September 23–26, 2010; Toronto, Ontario, Canada ▪ 36th Annual Meeting of the North American Society for Psychosocial Obstetrics and Gynecology (poster title: Preliminary results from the Reproductive Life Stages Algorithm Project: use of antidepressant medication during pregnancy and lactation: development of an evidence-based decision tool); February 10–13, 2010; Richmond, Virginia ▪ Organization for the Study of Sex Differences 3rd Annual Meeting (poster title: An evidence-based algorithm to quantify risk-benefit decision-making for use of antidepressant medication during pregnancy and lactation); June 4–6, 2009; Toronto, Ontario, Canada ▪ 35th Annual Meeting of the North American Society for Psychosocial Obstetrics and Gynecology (poster title: Use of antidepressant medication during pregnancy and lactation: development of an evidence-based decision tool); February 4–7, 2009; New Haven, Connecticut ▪ Canadian College of Neuropsychopharmacology Annual Meeting (poster title: An evidence-based algorithm to quantify risk-benefit decision-making for use of antidepressant medication during pregnancy and lactation. Research in progress: current state of knowledge); June 6–9, 2008; Toronto, Ontario, Canada.

Acknowledgments: The authors thank their advisory committee members for providing valuable input and lending their expertise to this project: Hiltrud Dawson, RN (Health Nexus, Toronto, Canada); Michael Dunn, MD (Sunnybrook Health Sciences Center, Toronto, Canada); Adrienne Einarson, RN (The Hospital for Sick Children, Toronto, Canada); Alicja Fishell, MD (Women's College Hospital, Toronto, Canada); Jasmine Gandhi, MD (Ottawa Hospital, Ottawa, Canada); Jan Kasperski, RN, MHSc (Ontario College of Family Physicians, Toronto, Canada); Sidney Kennedy, MD (University Health Network, Toronto, Canada); Diane Meschino, MD (Women's College Hospital, Toronto, Canada); Irena Nulman, MD, PhD (The Hospital for Sick Children, Toronto, Canada); Sagar Parikh, MD (University Health Network, Toronto, Canada); Paula Ravitz, MD (Mount Sinai Hospital, Toronto, Canada); Sarah Romans, MD (University of Otago, Wellington, New Zealand); Simone Vigod, MD (Women's College Hospital, Toronto, Canada); Jennifer Blake, MD (Sunnybrook Health Sciences Center, Toronto, Canada); and Karen Wade, RN, MScN (Toronto Public Health, Toronto, Canada). The authors would also like to thank Lindsay Witton, MSW (Women's College Hospital, Toronto, Canada); Maura O'Keefe, MSW (Women's College Hospital, Toronto, Canada); and Svetlana Emelianova, MD (North York General Hospital, North York, Canada) for providing their feedback during many research meetings. Sheila Lacroix, MLS (Center for Addiction and Mental Health, Toronto, Canada), and Ani Orchanian-Cheff, MISt (University Health Network, Toronto, Ontario), devised search strategies and completed literature search. The authors also thank Alex Kiss, PhD (Sunnybrook Health Sciences Center, Toronto, Canada),

for performing preliminary meta-analyses and Jenna McKay, BA (Women's College Hospital, Toronto, Canada), and Kimberly Radford, BA (Women's College Hospital, Toronto, Canada), for assisting with data extraction and quality assessment processes. Dr Kennedy has received research funding or honoraria in the past from AstraZeneca, Biovail, Eli Lilly, GlaxoSmithKline, Janssen-Ortho, Lundbeck, Pfizer, St Jude Medical, and Servier. Ms Einarson has conducted research funded by an unrestricted grant from Eli Lilly Canada. Dr Nulman has held a CIHR Collaborative grant with Duchesnay. Dr Parikh has had education or research grants or served on advisory boards or as a speaker for AstraZeneca, Apotex, Biovail, Bristol-Myers Squibb, CIHR, Canadian Network for Mood and Anxiety Treatments, Canadian Psychiatric Association, GlaxoSmithKline, Genpharm, Janssen, Eli Lilly, Lundbeck, Novartis, Pfizer, and Wyeth. There were no conflicts of interest or relevant financial disclosures reported by any of the other acknowledged individuals.
Additional information: This work was carried out at the Departments of Psychiatry, Women's College Hospital, University Heath Network, Center for Addiction and Mental Heath, and University of Toronto, Toronto, Ontario, Canada.
Supplementary material: See accompanying pages.

REFERENCES

1. Yonkers KA, Wisner KL, Stewart DE, et al. The management of depression during pregnancy: a report from the American Psychiatric Association and the American College of Obstetricians and Gynecologists. *Gen Hosp Psychiatry*. 2009;31(5):403–413.
2. Lindahl V, Pearson JL, Colpe L. Prevalence of suicidality during pregnancy and the postpartum. *Arch Women Ment Health*. 2005;8(2):77–87.
3. Dietz PM, Williams SB, Callaghan WM, et al. Clinically identified maternal depression before, during, and after pregnancies ending in live births. *Am J Psychiatry*. 2007;164(10):1515–1520.
4. Dennis CL, Allen K. Interventions (other than pharmacological, psychosocial or psychological) for treating antenatal depression. *Cochrane Database Syst Rev*. 2008;(4):CD006795.
5. Chambers CD, Johnson KA, Dick LM, et al. Birth outcomes in pregnant women taking fluoxetine. *N Engl J Med*. 1996;335(14):1010–1015.
6. Koren G, Matsui D, Einarson A, et al. Is maternal use of selective serotonin reuptake inhibitors in the third trimester of pregnancy harmful to neonates? *CMAJ*. 2005;172(11):1457–1459.
7. Stiskal JA, Kulin N, Koren G, et al. Neonatal paroxetine withdrawal syndrome. *Arch Dis Child Fetal Neonatal Ed*. 2001;84(2):F134–F135.
8. Levinson-Castiel R, Merlob P, Linder N, et al. Neonatal abstinence syndrome after in utero exposure to selective serotonin reuptake inhibitors in term infants. *Arch Pediatr Adolesc Med*. 2006;160(2):173–176.
9. Isbister GK, Dawson A, Whyte IM, et al. Neonatal paroxetine withdrawal syndrome or actually serotonin syndrome? *Arch Dis Child Fetal Neonatal Ed*. 2001;85(2):F147–F148.
10. Oberlander TF, Misri S, Fitzgerald CE, et al. Pharmacologic factors associated with transient neonatal symptoms following prenatal psychotropic medication exposure. *J Clin Psychiatry*. 2004;65(2):230–237.
11. Lattimore KA, Donn SM, Kaciroti N, et al. Selective serotonin reuptake inhibitor (SSRI) use during pregnancy and effects on the fetus and newborn: a meta-analysis. *J Perinatol*. 2005;25(9):595–604.
12. Källén B. Neonate characteristics after maternal use of antidepressants in late pregnancy. *Arch Pediatr Adolesc Med*. 2004;158(4):312–316.
13. Ross LE, Grigoriadis S, Mamisashvili L, et al. Quality assessment of observational studies in psychiatry: an example from perinatal psychiatric research. *Int J Methods Psychiatr Res*. 2011;20(4):224–234.
14. von Elm E, Altman DG, Egger M, et al; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet*. 2007;370(9596):1453–1457.
15. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health*. 1998;52(6):377–384.
16. Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. Department of Epidemiology and Community Medicine, University of Ottawa, Canada. Ottawa Hospital Research Institute Web site. http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm. Accessed November 7, 2012.
17. Guyatt GH, Oxman AD, Vist GE, et al; GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336(7650):924–926.
18. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7(3):177–188.
19. Duval S, Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics*. 2000;56(2):455–463.
20. Huedo-Medina TB, Sánchez-Meca J, Marín-Martínez F, et al. Assessing heterogeneity in meta-analysis: Q statistic or I2 index? *Psychol Methods*. 2006;11(2):193–206.
21. Viechtbauer W. Conducting meta-analyses in R with the metafor package. *Journal of Statistical Software*. 2010;36(3):1–48. http://www.jstatsoft.org/v36/i03/ Accessed November 21, 2012.
22. The R Project for Statistical Computing. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0. http://www.R-project.org/. Accessed October 22, 2012.
23. Moher D, Liberati A, Tetzlaff J, et al; PRISMA Group. Reprint—preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Phys Ther*. 2009;89(9):873–880.
24. Wen SW, Yang Q, Garner P, et al. Selective serotonin reuptake inhibitors and adverse pregnancy outcomes. *Am J Obstet Gynecol*. 2006;194(4):961–966.
25. Zeskind PS, Stephens LE. Maternal selective serotonin reuptake inhibitor use during pregnancy and newborn neurobehavior. *Pediatrics*. 2004;113(2):368–375.
26. Costei AM, Kozer E, Ho T, et al. Perinatal outcome following third trimester exposure to paroxetine. *Arch Pediatr Adolesc Med*. 2002;156(11):1129–1132.
27. Laine K, Heikkinen T, Ekblad U, et al. Effects of exposure to selective serotonin reuptake inhibitors during pregnancy on serotonergic symptoms in newborns and cord blood monoamine and prolactin concentrations. *Arch Gen Psychiatry*. 2003;60(7):720–726.
28. Oberlander TF, Warburton W, Misri S, et al. Neonatal outcomes after prenatal exposure to selective serotonin reuptake inhibitor antidepressants and maternal depression using population-based linked health data. *Arch Gen Psychiatry*. 2006;63(8):898–906.
29. Davis RL, Rubanowice D, McPhillips H, et al; HMO Research Network Center for Education, Research in Therapeutics. Risks of congenital malformations and perinatal events among infants exposed to antidepressant medications during pregnancy. *Pharmacoepidemiol Drug Saf*. 2007;16(10):1086–1094.
30. Ferreira E, Carceller AM, Agogué C, et al. Effects of selective serotonin reuptake inhibitors and venlafaxine during pregnancy in term and preterm neonates. *Pediatrics*. 2007;119(1):52–59.
31. Boucher N, Bairam A, Beaulac-Baillargeon L. A new look at the neonate's clinical presentation after in utero exposure to antidepressants in late pregnancy. *J Clin Psychopharmacol*. 2008;28(3):334–339.
32. Maschi S, Clavenna A, Campi R, et al. Neonatal outcome following pregnancy exposure to antidepressants: a prospective controlled cohort study. *BJOG*. 2008;115(2):283–289.
33. Galbally M, Lewis AJ, Lum J, et al. Serotonin discontinuation syndrome following in utero exposure to antidepressant medication: prospective controlled study. *Aust N Z J Psychiatry*. 2009;43(9):846–854.
34. Rampono J, Simmer K, Ilett KF, et al. Placental transfer of SSRI and SNRI antidepressants and effects on the neonate. *Pharmacopsychiatry*. 2009;42(3):95–100.
35. Hendrick V, Smith LM, Suri R, et al. Birth outcomes after prenatal exposure to antidepressant medication. *Am J Obstet Gynecol*. 2003;188(3):812–815.
36. Goldstein DJ. Effects of third trimester fluoxetine exposure on the newborn. *J Clin Psychopharmacol*. 1995;15(6):417–420.
37. Gentile S. Selective serotonin reuptake inhibitor exposure during early pregnancy and the risk of birth defects. *Acta Psychiatr Scand*. 2011;123(4):266–275.
38. Pedersen LH, Henriksen TB, Olsen J. Fetal exposure to antidepressants and normal milestone development at 6 and 19 months of age. *Pediatrics*. 2010;125(3):e600–e608.
39. Einarson A, Choi J, Einarson TR, et al. Incidence of major malformations in infants following antidepressant exposure in pregnancy: results of a large prospective cohort study. *Can J Psychiatry*. 2009;54(4):242–246.
40. Finnegan LP, Connaughton JF Jr, Kron RE, et al. Neonatal abstinence syndrome: assessment and management. *Addict Dis*. 1975;2(1–2):141–158.
41. Weinberg MK, Tronick EZ. The impact of maternal psychiatric illness on infant development. *J Clin Psychiatry*. 1998;59(suppl 2):53–61.
42. Gentile S. On categorizing gestational, birth, and neonatal complications following late pregnancy exposure to antidepressants: the prenatal antidepressant exposure syndrome. *CNS Spectr*. 2010;15(3):167–185.
43. Koren G. SSRIs in late pregnancy: the risk of neonatal respiratory distress and seizures. *Acta Psychiatr Scand*. 2011;123(4):318–319, author reply 318–319.
44. Occhiogrosso M, Omran SS, Altemus M. Persistent pulmonary hypertension of the newborn and selective serotonin reuptake inhibitors: lessons from clinical and translational studies. *Am J Psychiatry*. 2012;169(2):134–140.

45. Sie SD, Wennink JM, van Driel JJ, et al. Maternal use of SSRIs, SNRIs and NaSSAs: practical recommendations during pregnancy and lactation [published online ahead of print July 27, 2011]. *Arch Dis Child Fetal Neonatal Ed*.
46. Oberlander TF, Bonaguro RJ, Misri S, et al. Infant serotonin transporter (*SLC6A4*) promoter genotype is associated with adverse neonatal outcomes after prenatal exposure to serotonin reuptake inhibitor medications. *Mol Psychiatry*. 2008;13(1):65–73.
47. Safety Alerts for Human Medical Products. Effexor and Effexor XR (venlafaxine HCl). US Food and Drug Administration (FDA) Web site. http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm154975.htm. Updated June 19, 2009. Accessed November 7, 2012.
48. Potential adverse effects of SSRIs and other anti-depressants on newborns–Health Canada Advisory 2004-08-09. Health Canada Web site. http://www.antidepressantsfacts.com/2004-08-09-HealthCan-SSRIs-newborns.htm. Accessed November 7, 2012.
49. Moses-Kolko EL, Bogen D, Perel J, et al. Neonatal signs after late in utero exposure to serotonin reuptake inhibitors: literature review and implications for clinical applications. *JAMA*. 2005;293(19):2372–2383.

Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Women's Mental Health section. Please contact Marlene P. Freeman, MD, at mfreeman@psychiatrist.com.

Supplementary material follows this article.

THE JOURNAL OF CLINICAL PSYCHIATRY

Supplementary Material

Article Title: The Effect of Prenatal Antidepressant Exposure on Neonatal Adaptation: A Systematic Review and Meta-Analysis

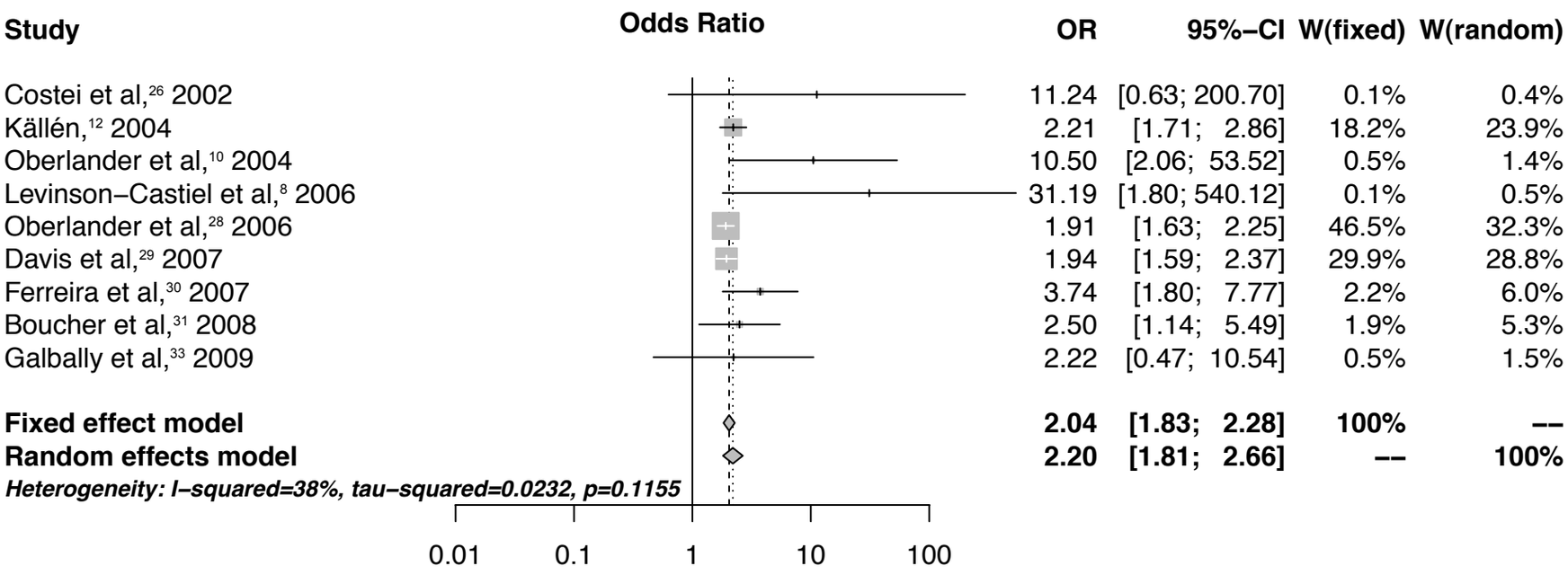
Author(s): Sophie Grigoriadis, MD, MA PhD, FRCPC; Emily H. VonderPorten, MPH; Lana Mamisashvili, BSc (Hons); Allison Eady, BA; George Tomlinson, PhD; Cindy-Lee Dennis, PhD; Gideon Koren, MD, FRCPC, FACMT; Meir Steiner, MD, PhD, FRCPC; Patricia Mousmanis, MD, CCFP, FCFP; Amy Cheung, MD, MSc, FRCPC; and Lori E. Ross, PhD

DOI Number: 10.4088/JCP.12r07967

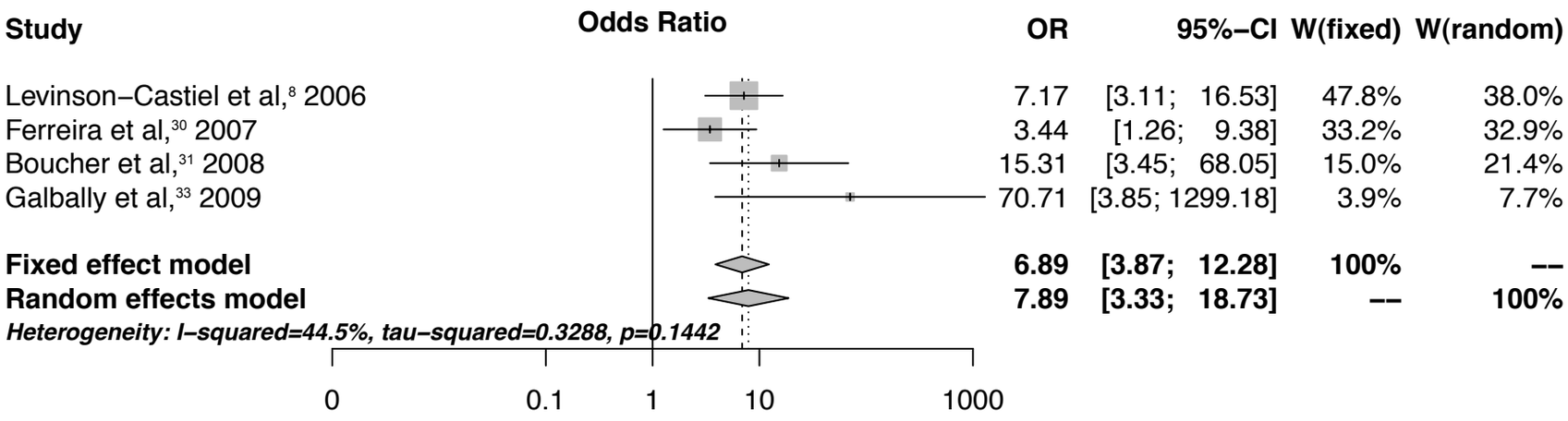
List of Supplementary Material for the article

Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.



Supplementary eFigure 1. Exposure to any antidepressant and the risk of respiratory distress in the neonate: meta-analysis results for all studies. Abbreviations: see Figure 2.



Supplementary eFigure 2. Exposure to any antidepressant and the risk of tremors in the neonate: meta-analysis results for all studies. Abbreviations: see Figure 2.

Keywords

- **Antenatal Antidepressant** (search words: Major Depression; Depression; depressive disorder, mood disorder, dysthymic disorder, pregnancy, trimester, pregnancy unplanned/unwanted, prenatal care, pregnant women; antenatal/pregnant/prenatal/perinatal/puerperal; Neonatal withdrawal, neonatal abstinence syndrome, poor adaptation syndrome, neonatal adaptation, prenatal exposure/delayed effects, substance withdrawal symptoms, spontaneous abortion, miscarriage, fetus, fetal, neonatal, newborn, infant, infant outcome; maternal outcome, suicide, maternal suicide; premature birth, premature delivery, neurocognitive outcome or development, neurological outcome or development, infant development/child development, abnormalities, drug induced; attachment/mother/maternal, maternal behaviour; prenatal exposure, first trimester pregnancy/second trimester pregnancy/third trimester pregnancy/pregnancy complication; Tricyclic Antidepressant Drugs/Antidepressant Drugs/SSRIs/Monoamine Oxidase Inhibitors/Pregnancy*)
- **Antenatal Non Drug** (search words: Psychotherapy/ Brief Psychotherapy/Interpersonal Psychotherapy; Support Groups; Counseling; Interpersonal Therapy or Interpersonal Psychotherapy; Supportive Therapy or Narrative Therapy; Cognitive Therapy or Cognitive Behavioral Therapy; Psychoeducational or Psychodynamic; Psychosocial Intervention or Psychological Intervention; Psychosocial care, psychosocial rehabilitation, primary prevention, social support, prevention, therapy; Motivational Interview; emotion-focused counseling, non-directive counseling; Major Depression/Depression; Pregnancy/Prenatal or Antenatal)
- **Antenatal Risk Factors for Depression** (search words: Major Depression; depressive disorders, dysthymic disorders, Depression; Pregnancy; unwanted/unplanned pregnancy, adolescent pregnancy, Prenatal or antenatal; Risk Assessment/ Risk Management/ At Risk Populations/ Risk Factors; Protective Factors; psychosocial support, social support)
- **Postnatal Antidepressant** (search words: depressive disorder/mood disorder, dysthymic disorder; postpartum/postnatal; Major Depression; Depression; Tricyclic Antidepressant Drugs/Antidepressant Drugs/SSRIs/Monoamine Oxidase Inhibitors)
- **Lactation / Breastfeeding**: Postpartum Depression, Antidepressants, etc. (search words: Breast milk, Breast Feeding/ Lactation/ Lactating, weaning; Depression, puerperal depression, postpartum depression, dysthymic disorders, depressive disorders; breast milk and antidepressants, Antidepressant Drugs/Antidepressants*)
- **Postnatal Non Drug** (search words: Postpartum, postnatal; pregnancy, Psychotherapy/ Brief Psychotherapy/Interpersonal Psychotherapy; Support Groups; Counseling; Interpersonal Therapy or Interpersonal Psychotherapy; Supportive Therapy or Narrative Therapy; Cognitive Therapy or Cognitive Behavioral Therapy; Psychoeducational or Psychodynamic; Psychosocial Intervention or Psychological Intervention; psychological rehabilitation, social support, psychoeducational support, Motivational Interview; non-directive counseling, emotion-focused counseling, cognitive rehabilitation, psychotherapeutic techniques, Major Depression/Depression; Postnatal)
- **Risk Factors for Postpartum Depression** (search words: Postpartum/postnatal, postpartum period, prevention/control, therapy, psychosocial care, social support, psychosocial rehabilitation, psychosocial intervention; risk assessment/risk management, at risk populations, risk factors, primary mental health prevention, protective factors, unwanted/unplanned pregnancy, pregnancy; depressive disorders, dysthymic disorders; Postpartum Depression/ Risk Assessment/At Risk Populations/Risk Factors/Risk Management; Protective Factors; child development, attachment behaviour, infant/child behaviour, maternal behaviour, untreated depression, neurocognitive development, mother-child relations, infant care, neurological/neurocognitive development).