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REVIEW ARTICLE

A systematic review and meta-analysis of the effects of antenatal anxiety on postpartum outcomes

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Abstract

To systematically review and meta-analyze research investigating the association between maternal anxiety during pregnancy and outcomes for mother and baby following the immediate delivery period. MEDLINE, Medline In-Process & Other Non-Indexed Citations, PsycINFO, Embase, CINAHL, and the Cochrane library were searched. English-language, prospective studies providing data on outcomes following delivery in women with and without antenatal anxiety (defined by clinical diagnosis or score on validated scale) were included. Three-hundred-fifty-eight articles were retrieved and 13 were included. Titles and abstracts were screened; two reviewers independently reviewed full text articles, conducted quality assessments, extracted, and checked the data. Where available for > 2 studies, random effect meta-analysis was conducted and heterogeneity was quantified. Subanalyses explored moderators, regardless of heterogeneity, including type of anxiety assessment and timing, among others. There were two outcomes that were amenable to meta-analysis. Antenatal anxiety was significantly associated with postpartum depression (PPD) measured within 6 months postpartum (pooled odds ratio [OR] = 2.64, 95% CI 2.02–3.46; 8 studies), regardless of restricting analyses to those studies controlling for prenatal depression (2.45, 1.77–3.39; 6 studies). Associations were also significant when PPD was measured at 1–3 months (2.57, 1.94–3.40; 7 studies) and 6–10 months

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(4.42, 1.45–13.49; 3 studies). Maternal anxiety was also associated with reduced odds of breastfeeding (0.63, 0.53–0.74; 5 studies). Antenatal anxiety is associated with PPD up to the first 10 months, independent of prenatal depression, and with lower odds of breastfeeding.

Keywords Antenatal anxiety · Postpartum outcomes · Postpartum depression · Breastfeeding

Introduction

Poor mental health during the perinatal period is not uncommon and has major implications for the well-being of mothers and their children (ACOG 2008; MacQueen et al. 2016). There is increasing recognition that anxiety during pregnancy is particularly widespread, with a prevalence of 15.2% for an anxiety disorder and 22.9% for anxiety symptoms (Dennis et al. (2017), and possibly more common than depression (Fairbrother et al. 2016; Lee et al. 2007; Martini et al. 2015). While only recently gaining research attention, antenatal anxiety appears to be associated with adverse outcomes for both mother and baby following the immediate delivery period including an increased risk of postpartum hemorrhage (Pavlov et al. 2014), neonatal morbidity (Lilliecreutz et al. 2011), and elevated maternal symptoms of depression and anxiety during the postpartum (Davey et al. 2011; Heron et al. 2004; Sutter-Dallay et al. 2004) to list a few. Unfortunately, divergent conclusions have limited the clinical utility of this data, affecting a broad range of clinicians (psychiatrists, obstetricians, pediatricians, family doctors, nurse practitioners, midwives, etc.). For example, Davey et al. (2011) found that antenatal anxiety was associated with postpartum depressive symptoms at 8 weeks, whereas Coelho et al. (2011) did not at 10–12 weeks postpartum. To our knowledge, while reviews (i.e., Alder et al. 2007) and meta-analyses (Ding et al. 2014; Littleton et al. 2007; Rose et al. 2016) have been conducted, they have been limited and a comprehensive meta-analysis quantifying the potential adverse outcomes following delivery is lacking but necessary to inform treatment decisions. As part of a larger program of research examining the impact of antenatal anxiety on maternal, fetal, and neonatal outcomes, we conducted a large systematic review and meta-analyses, where possible. The purpose of this paper is to report on the outcomes for the mother following the immediate delivery period.

Methods

Search strategy and selection criteria

The systematic literature review was steered by an Advisory Committee of key stakeholders, including representatives from psychiatry, primary care/family medicine, pharmacology, obstetrics, neonatology, public health, and patient advocacy. Details of the methods have been previously published for our work on depression and are similar (Ross et al. 2011), and we followed the guidelines of the Meta-analysis of Observational Studies in Epidemiology group (Stroup et al. 2000). Independent literature searches were conducted by two professional librarians with psychiatry and psychopharmacology expertise. Searches were done to June 30, 2018 and included Ovid Medline, Medline In-Process & Other Non-Indexed Citations, PsycINFO, CINAHL, Embase, and the Cochrane Library. Keywords used included, but were not limited to, anxiety/phobia, posttraumatic stress disorder, panic disorder, obsessive compulsive disorder, pregnancy, prenatal or antenatal, postpartum, outcome, infant development, attachment, maternal outcomes (i.e., postpartum hemorrhage, preeclampsia, breastfeeding), adverse events, and postpartum depression. One search strategy was developed and tested through an iterative process by an experienced medical information specialist in consultation with the review team. Prior to search execution, this core strategy was reviewed by another senior information specialist using the Peer Review for Electronic Search Strategies checklist (McGowan et al. 2016). Strategies included a combination of keywords (e.g., prenatal, anxiety, postpartum hemorrhage) and controlled vocabulary (e.g., "Pregnancy," "Anxiety Disorders," "Adverse"). Vocabulary and syntax were adjusted across databases and results were limited to human studies written in the English language, excluding opinion pieces (full list of keywords and full search strategy are available upon request). We also searched reference lists of reviews, meta-analyses, and the final selection of included articles. We adhered to the PRISMA statement for reporting systematic reviews and meta-analyses (Moher et al. 2009).

Studies with original data were eligible if collected prospectively and included an assessment of maternal anxiety at any time during pregnancy as well as an unexposed comparison group. Maternal anxiety assessments included either a clinical diagnosis of any anxiety disorder or use of a validated anxiety self-report tool with a cutoff score to distinguish high- and low-anxiety groups. We excluded pregnancy-specific/pregnancy-related anxiety as this characterizes a distinct concept that is not well measured by current scales (Bayrampour et al. 2016). All studies that examined outcomes in the baby and/or mother during the delivery, neonatal, and/or postpartum/developmental periods were accepted. When a sample was repeated in > 1 publication, the article that most closely addressed our research question was chosen. We excluded

studies that pooled antenatal and postpartum anxiety scores and studies with adolescent samples. Due to the volume of potentially eligible studies, abstracts, conference proceedings, and unpublished data were also excluded. Eligible studies were excluded if outcome data was not comparable to data from at least two other studies (or if the outcome definition did not match that of at least two other studies). Two reviewers (MP, LM, or MG) independently screened all titles and abstracts and retrieved all eligible studies. We contacted five authors to request raw data to include or clarification of methodology/data analysis and two replied.

Data analysis

The methodology for data extraction and quality assessment was similar to that developed by our team for prenatal depression and perinatal outcomes (Ross et al. 2011). Data extraction forms, based on the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) criteria (von Elm et al. 2007), were completed for each eligible study. Extracted data included authors, year of publication, source country, details of study design, participants (sample, control, demographics, and clinical characteristics), inclusion/exclusion criteria, method and type of anxiety assessment, timing of anxiety assessment, outcome definitions and their assessment methods, statistical adjustment for confounders, and loss to follow-up. When outcomes from multiple postpartum time points were presented, we extracted only data that approximated time points from other studies and thus could be reasonably aggregated so that we could pool at least three studies. Adjusted estimates, with their variances, were extracted when available; when adjusted estimates were not provided in the published data we calculated crude odds ratios or mean differences and sample variances. Before calculating the odds ratio for studies that included cells with a 0 count, we added 0.5 to these cells. Data was extracted by one reviewer (MP or MG) and checked by another reviewer and/or the lead authors. Disagreements were resolved by the primary authors, in discussion with the reviewer. Outcomes examined were as defined by the authors of the original publication.

The Systematic Assessment of Quality in Observational Research (SAQOR) was used to assess the quality of included studies. The SAQOR, based on the Downs and Black (1998) checklist and the Newcastle-Ottawa Scale (Wells et al. 2006), was adapted for this specific area of research as previously described (Ross et al. 2011). Articles were assessed by 19 criteria under five categories: (1) sample, (2) control group, (3) quality of exposure/outcome measure, (4) follow-up, and (5) distorting influences/control for confounders. Each article was assigned a quality rating of high, moderate, low, or very low based on the SAQOR criteria and a modification of the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system (Guyatt et al. 2008). Two independent reviewers (MP, LM, or MG) completed the quality assessments for each study and disagreements were resolved on a case-by-case basis by discussion among reviewers, including the study leads as needed, until consensus was reached. Quality ratings were dichotomized into "above quality threshold" (high, moderate, and low) and "below quality threshold" (very low).

The DerSimonian and Laird random effect models were used to obtain pooled estimates of the odds ratio for binary outcomes (DerSimonian and Laird 1986). Where relative risks were given, they were treated as odds ratios, given that events were typically rare but these were few in numbers. To assess for the possibility of publication bias, we visually inspected funnel plots portraying individual study estimates (on the log scale for odds ratios) against their standard error. Egger's weighted regression method was used to formally test for publication bias (Egger et al. 1997). Cochrane Q and visual inspection of forest plots were used to assess between-study heterogeneity, which was quantified by I^2, the percentage of the observed between-study variance in the effect estimate that is in excess of what is expected due to chance. Larger values of I^2 suggest that the effect of anxiety varies quantitatively from study to study. It has been suggested to characterize the amount of heterogeneity into three: low ($I^2 = 25\%$), moderate ($I^2 = 50\%$), and high ($I^2 = 75\%$) (Huedo-Medina et al. 2006). However, I^2 does not indicate qualitative variation, whether the direction of the effect varies—high heterogeneity in the size of an effect can still exist in the context of a large degree of certainty about the direction of the effect.

We explored sources of heterogeneity through subgroup analyses, regardless of the statistical significance of the Q statistic for an outcome. These subgroup analyses examined within-group effects and between-group differences in pooled effects based on a number of study characteristics chosen a priori: (1) study quality (i.e., study quality (above and below quality threshold)), (2) use of a diagnostic measure of anxiety versus cutoff score of self-reported anxiety on a validated scale, (3) adjusted estimates versus unadjusted estimates, (4) assessment time in pregnancy, (5) registry data versus non-registry data, and (6) source country. Fixed effect models were used in subgroup analyses with < 3 papers. Statistical analyses were completed with the metafor package in R (3.3.2) and similar to our other work (Grigoriadis et al. 2013); Review Manager (RevMan) version 5.3 for Windows (Review Manager version 5.3, Cochrane Collaboration; http://tech.cochrane.org/revman) was used to generate forest plots.

Results

Of the 1518 abstracts reviewed, 1160 were excluded; the remaining 358 articles were retrieved and assessed for eligibility, and of these, 13 studies were included in the meta-analysis

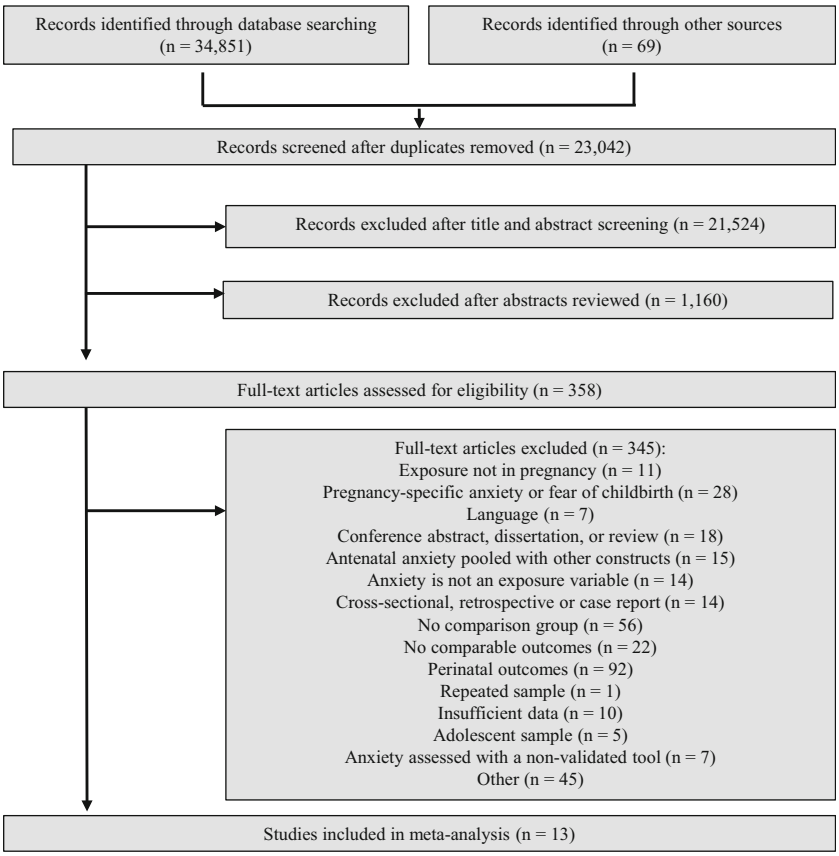

Fig. 1 Identification of studies for inclusion in the meta-analysis of the association of antenatal anxiety with perinatal outcomes

(Fig. 1). Data suitable for the purposes of our analyses were available from eight studies on postpartum depression and five studies of breastfeeding (Table 1). As can be seen in Fig. 1, there were 22 papers that had outcomes which we could not aggregate and thus were not sufficient for meta-analysis. Specifically, we identified seven studies on behavioral outcomes in the child across a wide variety of ages, three studies on cortisol (two of which utilized the same sample); one study each of excessive infant crying, infant colic, and infant feeding and crying outcomes (two of which utilized the same sample); two studies on cognitive control in the child; and one study each on infant temperament, atypical handedness, cardiovascular development, vascular function, asthma, intention to breastfeed, and autism spectrum disorder or attention-deficit hyperactivity disorder.

Postpartum depression

Of the eight studies that examined the association between antenatal anxiety (AA) and postpartum depression (PPD), half were above quality threshold established for this study. Three studies (Coelho et al. 2011; Rambelli et al. 2010; Sutter-Dallay et al. 2004) included a diagnosis of an anxiety disorder during pregnancy while the remaining studies measured antenatal anxiety with a cutoff score on a validated self-report scale. Five studies (Austin et al. 2007; Davey et al. 2011; Lee et al. 2007; Soderquist et al. 2009; Sutter-Dallay et al. 2004) reported PPD measured at 1–3 months postpartum only, two studies (Coelho et al. 2011; Heron et al. 2004) assessed PPD at both earlier and later time points (i.e., at 1–3 months and 8–10 months postpartum), and one study measured PPD at 6 months (Rambelli et al. 2010). Thus, we conducted one overall analysis for PPD measured at any time up to 6 months postpartum ($n = 8$), and separate analyses for PPD assessed at 1–3 months ($n = 7$) and at 6–10 months ($n = 3$).

Pooling eight studies, based on data from approximately 1708 women with antenatal anxiety and 9806 women without antenatal anxiety,[1] maternal antenatal anxiety was significantly associated with an increased risk of PPD when measured up to 6 months postpartum (OR = 2.64, 95% CI 2.02 to 3.46, $p < 0.01$; Fig. 2). Heterogeneity across studies was not significant ($Q_7 = 8.38$, $p = 0.30$, $I^2 = 16\%$). None of the subanalyses examining moderators were significant, although it is worth noting that the OR for studies that utilized a diagnostic measure of antenatal anxiety ($n = 3$) pooled to an OR > 3 (Table 2). The association was attenuated but still highly significant when pooling studies that adjusted for the presence of prenatal depression ($n = 6$) (OR = 2.45, 95% CI 1.77 to 3.39, $p < 0.01$).

[1] Two studies provided only the total sample size but not the number of women with and without antenatal anxiety (Lee et al. 2007; Soderquist et al. 2009).

Table 1 Study details of included articles in the meta-analysis

Article	Country	Sample	Inclusion/exclusion criteria	Anxiety classification	Adjustments	Outcome definition	Results
Postpartum depression							
Austin et al. (2007)[b]	Australia	Anxious in third trimester: $n = 63$ Not anxious in third trimester: $n = 512$ (women took part in a longitudinal study previously published)	Inclusion: attending midwife-based clinic and completed the BMWS during the third trimester Exclusion: women requiring an interpreter, higher obstetric risk (from Austin et al. (2005)—earlier publication referred to)	STAI-trait score > 45, representing the sample mean + 1 SD	Controlled for: past depressive episode, antenatal EPDS score, age, smoking, parity, education level, marital status, and BMWS scores in the third trimester	EPDS score ≥ 13 at 8 weeks postpartum	OR = 3.11; 95% CI 1.38 to 3.99 *Beta* (SE) = 1.14(0.41), $p = 0.006$ Adjusted *beta* (SE) = 0.25(0.47), ns
Coelho et al. (2011)[b]	England	For 10–12 weeks postpartum: anxious in second trimester: $n = 124$ Not anxious in second trimester: $n = 83$ --- For 10 months postpartum: anxious in second trimester: $n = 123$ Not anxious in second trimester: $n = 79$	Inclusion: women at 20-week antenatal scan Exclusion: none stated	Screened at 20-week gestation with the Penn State Worry Questionnaire and the Social Interaction Anxiety Scale and Social Phobia Scale; then SCID-I Diagnosis of GAD, Social phobia or both Screened at 20 weeks but timing of SCID not clear	Adjusted for antenatal depression, age, SES, and ethnicity	EPDS score > 12 at 10–12 weeks postpartum --- EPDS score > 12 at 10 months postpartum (data on postpartum depression at other times given as well, but times points chosen as these were comparable to other studies)	At 10–12 weeks: aOR = 4.57; 95% CI 0.98 to 21.29 (ns) --- At 10 months: aOR = 29.53; 95% CI 3.80 to 229.38 ($p < 0.005$)
Davey et al. (2011)[b]	Canada	Anxious in first or second trimester: $n = 81$ Not anxious in first or second trimester: $n = 1231$ (women were part of a trial on prenatal support)	Inclusion: women calling to book first prenatal appointment Exclusion: < 18 years, had first prenatal appointment prior to baseline interview, did not plan to attend clinic at time of first recruitment call, lived outside region, no longer pregnant at time of contact for recruitment, could not communicate in English, French, Cantonese, Mandarin, Punjabi/Urdu/Hindi, or Arabic languages	Kellner Symptom Questionnaire: anxiety subscale score > 11.58	Unadjusted (adjusted analyses for other outcomes)	EPDS > 12 at 8 weeks postpartum	10/81 (12.4%) in anxious vs 54/1231 (4.4%) in not anxious, $p = 0.001$ Data also provided for EPDS > 10 but not used in our analysis as not comparable
Heron et al. (2004)[a]	England	Anxious in third trimester: $n = 1296$ Not anxious in third trimester: $n = 7027$ Cohort part of a longitudinal study	Inclusion: women residing in Avon, estimated date of delivery between April 1, 1991 and December 31, 1992 Exclusion: none stated	Crown Crisp Experiential Index > 9, reflecting top 15% at 18-week gestation	Adjusted for depression and anxiety at other time points (i.e., 18 weeks and 32 weeks)	EPDS > 12 at 8 weeks postpartum --- EPDS > 12 at 8 months postpartum	At 8 weeks postpartum: aOR = 2.1; 95% CI 1.59 to 2.75, $p < 0.001$ --- At 8 months postpartum: aOR = 2.17; 95% CI 1.60 to 2.93, $p < 0.001$) Several analyses presented; most similar to other papers

Table 1 (continued)

Article	Country	Sample	Inclusion/exclusion criteria	Anxiety classification	Adjustments	Outcome definition	Results
							chosen as they could be pooled
Lee et al. (2007)[a]	Hong Kong	Total $N = 244$ Anxious in third trimester: n = not clear Not anxious in third trimester: n = not clear (also assessed at first and second trimesters)	Inclusion: all pregnant women of Chinese ethnicity > 18 years of age, at first presentation in antenatal clinic, regional hospital in Hong Kong Exclusion: women with significant medical diseases, those who may terminate pregnancy, or IVF conception	HADS score 7/8	Adjustments for analysis presented not clear	EPDS 12/13 at 6 weeks postpartum, Chinese version	aOR = 3.84; 95% CI 1.92 to 7.65 ($p < 0.001$) Multiple other analyses conducted but not usable in our analyses
Rambelli et al. (2010)[b]	Italy	Anxious in third month: $n = 24$ Not anxious in third month: $n = 576$	Inclusion: 12–15 weeks of gestation, willing to sign informed consent, available by telephone Exclusion: < 18 years, poor knowledge of Italian, no fixed address	SCID-I Diagnosis of panic disorder	Adjusted for the Postpartum Depression Predictors Inventory-Revised (PDPI-R) total score, history of major depression, and current major depression in pregnancy	EPDS > 12 at 6 months postpartum, confirmed with DSM-IV diagnostic criteria of the mood module of the SCID-I (minor or major depressive episode)	6/24 in anxious vs 34/576 in not anxious OR = 5.8; 95% CI 2.2 to 15.8 aOR = 4.25; 95% CI 1.48 to 12.19 Other analyses also conducted
Soderquist et al. (2009)[a]	Sweden	Total $N = 908$ Anxious in second trimester: n = not clear Not anxious in second trimester: n = not clear	Inclusion: visited the Department of Obstetrics and Gynecology in Linkoping or Kalmar for first ultrasound (gestation week 12–15 in Linkoping and 16–20 in Kalmar), speaking/understanding Swedish, no plans for termination of pregnancy, and no obstetric complications that needed specialist ultrasound examination Exclusion: none stated	STAI-trait score ≥ 37, representing top 25th percentile	Adjusted for: prenatal depression at 12–20-week gestation (via modified BDI cutoff of ≥ 9), low stress coping at 12–20-week gestation (via Stress Coping Inventory, lowest 25th percentile = sum-scores ≤ 64), low perceived social support in pregnancy (via The Social Contact Questionnaire, lowest 25th percentile = sum scores ≤ 164), and multiparity	Modified BDI score ≥ 9 (excluded somatic items) at 1 month postpartum	aOR = 4.3; 95% CI 1.8 to 10.6 Other analyses also conducted
Sutter-Dallay et al. (2004)[a]	France	Anxious in third trimester: $n = 120$ Not anxious in third trimester: $n = 377$ Cohort part of prospective survey	Inclusion: written informed consent, fluent in French, living in the hospital area, no history of psychotic illness, no multiple pregnancy or IVF, < 1-week hospitalization for pregnancy complications, no planned deliver via C-section Exclusion: premature birth or unplanned C-section	Any anxiety disorder diagnosed via the MINI including GAD, social phobia, OCD, agoraphobia, PD, and PTSD	Adjusted for: maternal age, education level (< 12 years, ≥ 12 years), mean income (< 1500 Euro, ≥ 1500 Euro), parity, dyadic adjustment, and pregnancy MDD (via MINI) Other confounders assessed	EPDS score > 12 at 6 weeks postpartum	aOR = 2.7; 95% CI 1.1 to 6.3, $p = 0.03$ Other analyses also conducted
Breastfeeding							
Brouwers et al. (2001)[b]	Netherlands	High anxiety in third trimester: $n = 20$	Inclusion: women with adequate free thyroxine at 12-week gestation, stratified random	STAI-state score ≥ 39 or STAI-trait score ≥ 37,	Unadjusted Other outcomes adjusted	Breastfed (4 feedings per day)	12/20 in anxious vs 64/85 in not anxious Other analyses also conducted

Table 1 (continued)

Article	Country	Sample	Inclusion/exclusion criteria	Anxiety classification	Adjustments	Outcome definition	Results
		Not high anxiety: $n = 85$	sampling further used to get to $n = 131$ Exclusion: Gemelli (multiple births), gestational diabetes, fertility issue history, premature delivery, missing data, one woman and one child excluded because of death, another because of repeated suicidal behavior Antenatal use of psychotropic medication unknown, comorbidity possible	reflecting > 1 SD above the mean, or both			
Clavarino et al. (2010)[b]	Australia	Anxious during pregnancy: $n = 626$ (combined "anxiety during pregnancy but not after," $n = 298$, and "anxiety all the time," $n = 332$) Not anxious: $N = 2952$ (without missing data) Anxiety in pregnancy measured "… on average 18-week gestation"	Inclusion: live, singleton births Exclusion: none stated	7-item anxiety subscale of the Delusions Symptoms-States Inventory: State of Anxiety and Depression score above the 90th percentile	Unadjusted Other outcomes adjusted	Breastfeeding < 4 months + breastfeeding 4+ months vs never	470/626 in anxious and 2437/2952 in not anxious Breastfeeding: 7.94% + 6.36% "anxiety during pregnancy" + 9.24% + 6.08% in "anxiety all the time" vs 72.07% + 78.59% in not anxious
Ibanez et al. (2015)[b]	France	Anxious at 24–28 weeks: $n = 135$ Not anxious: $n = 1154$ Cohort part of a larger study	Inclusion: French-speaking women, before the 24th week of gestation at Nancy and Poitiers maternity centers, between September 2003 and January 2006 Exclusion: twin pregnancy, prepregnancy diabetes, plan to move out of region in the next 3 years, and high depressive symptoms (measured by CES-D score ≥ 16 at 24–28-week gestation)	STAI-state score ≥ 37, reflecting the 80th percentile	Unadjusted Other outcomes adjusted	Breastfeeding initiation, also defined as breastfeeding status during the hospital stay and at discharge (obtained from medical records)	67.2% in anxious vs 73.5% in not anxious, $p = 0.12$ Other analyses also conducted
Lilliecreutz et al. (2011)[a]	Sweden	Anxious in second trimester: $n = 78$ Not anxious in second trimester:	Inclusion: women approached in 12–16 weeks of pregnancy Exclusion: inability to understand Swedish, and women with	Injection Phobia Scale Anxiety (IPSA) score ≥ 20 was used to screen, followed by diagnosis of blood and	Adjusted for: "sociodemographic variables, smoking, and psychiatric history"	"Breastfeeding"	64/78 in anxious vs 167/185 in not anxious (aOR = 0.87; 95% CI 0.36 to 2.12; $p = 0.759$)

Table 1 (continued)

Article	Country	Sample	Inclusion/exclusion criteria	Anxiety classification	Adjustments	Outcome definition	Results
		$n = 185$ (randomly stratified for age and parity) Screened at 12–16-week gestation (not clear when diagnosis made)	intrauterine fetal death, twins, and cesarean deliveries due to preeclampsia	injection phobia according to DSM-IV criteria (by phone)			
Mehta et al. (2011)[a]	USA	Anxious at 24–29-week gestation: $n = 138$ Not anxious at 24–29-week gestation: $n = 455$ (also measured at 15–20 weeks) Cohort part of a larger study	Inclusion: 15- and 20-week gestation at second ultrasound visit, live-born infants delivered between October 2002 and December 2005, lived within a 2-h radius of the University of North Carolina Exclusion: < 16 years of age, non-English-speaking, ≥ 20-week gestation on their second prenatal visit, not continuing care or deliver at study site, multiple gestations, medical constraints, unreachable, > 5 months postpartum, "those for whom study protocols were not in place at the time of their eligibility window"	STAI-state score ≥ 39	Unadjusted Other outcomes adjusted	"Breastfeeding initiation" question at 3 months postpartum (question: "Did you ever breastfeed this baby?")	32/138 in anxious vs 181/455 in not anxious Other analyses also conducted

STAI State Trait Anxiety Inventory, SD standard deviation, EPDS Edinburgh Postnatal Depression Scale, OR odds ratio, SE standard error, ns not significant, SCID-I Structured Clinical Interview for DSM-IV Axis 1 Disorders, GAD generalized anxiety disorder, SES socioeconomic status, aOR adjusted odds ratio, IVF in vitro fertilization, HADS Hospital Anxiety and Depression Scale, DSM-IV The Diagnostic and Statistical Manual of Mental Disorders, BDI Beck Depression Inventory, C-section caesarian section, MINI Mini-International Neuropsychiatric Interview, OCD obsessive compulsive disorder, PD panic disorder, PTSD posttraumatic stress disorder, MDD major depressive disorder, CES-D Center for Epidemiological Studies Depression Scale, BMI body mass index

Antenatal anxiety was associated with a significantly increased risk of PPD measured at 1–3 months postpartum when pooling seven studies (OR = 2.57, 95% CI 1.94 to 3.40, $p < 0.01$). Heterogeneity was not significant ($Q_6 = 7.38$, $p = 0.29$, $I^2 = 18\%$). Anxiety during pregnancy was also significantly associated with an increased risk of PPD at 6–10 months postpartum when pooling three studies (OR = 4.42, 95% CI 1.45 to 13.49); however, there was significant heterogeneity across studies in this last analysis, accounting for 73% of the variance ($Q_2 = 7.31$, $p = 0.03$, $I^2 = 73\%$).

Breastfeeding

Of the five studies included in the meta-analysis of breastfeeding (see Table 1 for definitions of breastfeeding as provided by the authors), two studies (Lilliecreutz et al. 2011; Mehta et al. 2011) were above quality threshold established for this study. Only one study examined the association between a diagnosed anxiety disorder in pregnancy (blood and injection phobia) and breastfeeding (Lilliecreutz et al. 2011), while the remaining four studies used a cutoff score on a validated scale to characterize high antenatal anxiety.

The pooled effects of five studies found that antenatal maternal anxiety was associated with significantly lower odds of breastfeeding (OR = 0.63, 95% CI 0.53 to 0.74, $p < 0.01$; Fig. 3), based on 997 women with antenatal anxiety and 4831 women without antenatal anxiety. Heterogeneity was not significant ($Q_4 = 3.53$, $p = 0.47$, $I^2 = 0\%$), and none of the subgroup analyses indicated significant moderators (Table 2).

The assessment of publication bias was not possible for PPD and breastfeeding outcomes using a funnel plot as there were insufficient data to produce one. Likewise, for both outcomes, the number of included studies was too low to conduct Egger's test. However, there was no evidence of asymmetry based on visual inspection.

Discussion

To our knowledge, ours is the first meta-analysis to assess multiple outcomes following the delivery period potentially associated with exposure to maternal anxiety during pregnancy. We found an association for anxiety during pregnancy and a greater than two-fold increased risk of PPD within 6 months postpartum, even when controlling for the presence of depression during pregnancy. The significant effect was seen when PPD was measured between 1 and 3 months postpartum and when measured up to 10 months postpartum. The magnitude of the OR for the PPD outcome is above 2.5, where 2 is the threshold for clinical significance in this area. The magnitude of this effect size is clinically meaningful. Anxiety during pregnancy was also associated with significantly decreased likelihood of breastfeeding. The latter finding is perhaps not surprising given the link between prenatal anxiety and PPD and between PPD and breastfeeding difficulties and shorter breastfeeding duration (Dennis and McQueen 2009). This finding is also consistent with the depression literature and of about the same magnitude; we previously reported that maternal depression was associated with a lower likelihood of breastfeeding initiation (Grigoriadis et al. 2013). Both of our findings have important clinical implications and consequences for the well-being of mothers, their children, and their families.

Although our aim was to pool the data for many outcomes during the postpartum given the presence of the literature, this was not possible given the diverse outcome definitions used. Thus, despite identifying 22 potentially eligible studies, we were only able to meta-analyze two outcomes. This is a limitation and reflects the status of the area in general. Another limitation reflective of the area centers around differences across studies in criteria for assessing antenatal anxiety and its severity. Various definitions of anxiety were used and severity was not controlled for, although we did conduct subanalyses of studies that defined anxiety via self-report scales compared to diagnosed disorders and found this to be a nonsignificant moderator. Anxiety disorders are a heterogeneous category that included generalized anxiety disorder (GAD), generalized social phobia (GSP), or both (Coelho et al. 2011), panic disorder (Rambelli et al. 2010), blood and injection phobia (Lilliecreutz et al. 2011), and any anxiety disorder (Sutter-Dallay et al. 2004). High levels of anxiety were defined by study authors based on cutoff scores on self-report scales. These scales included the State-Trait Anxiety Inventory (STAI) with assorted cutoff scores (Austin et al. 2007; Brouwers et al. 2001; Clavarino et al. 2010; Soderquist et al. 2009), the Kellner Symptom Questionnaire (Davey et al. 2011), Crown Crisp Experiential Index (Heron et al. 2004), the Hospital Anxiety and Depression Scale (HADS) (Lee et al. 2007), and the Delusions Symptoms-States Inventory: State of Anxiety and Depression anxiety subscale (Clavarino et al. 2010). "Anxiety" is a general category; a specific phobia, which is an anxiety disorder, may have different implications than a generalized anxiety disorder which by definition is more pervasive but both are defined as a disorder when they cause functional limitation. Although a diagnosis is based on functional limitation, a score on a self-report measure is just that with typically no reference to functioning. The majority of the studies used a self-report measure and thus a general measure of anxiety; future research can examine if there is a relationship with a specific anxiety disorder versus a "generalized anxious state" as well as severity. We were unable to assess for publication bias as there were too few studies. Moreover, just over half of the studies were of lower quality which is striking and further indicative of the "primitive" stage of the literature in the perinatal area. Given the impact on generations, perinatal psychiatry must become a research priority.

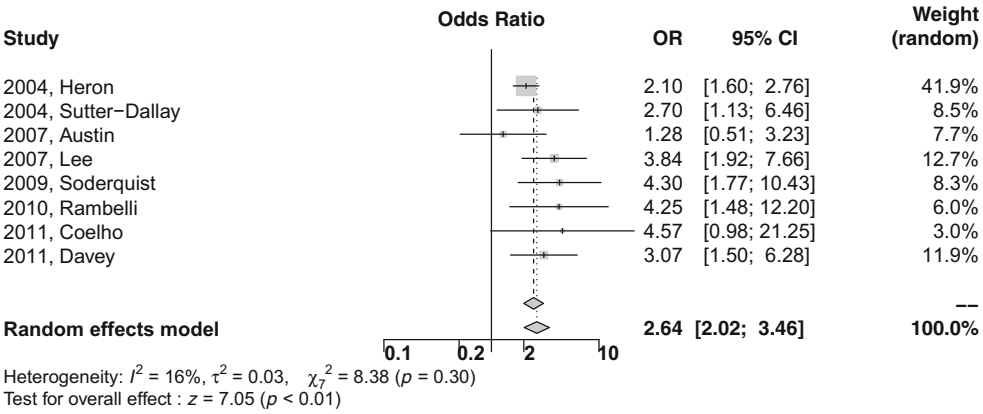

Fig. 2 Pooled association between antenatal anxiety and postpartum depression within 6 months postpartum

Postpartum depression

A major strength of our work is its contribution to a better understanding of the risk factors for PPD, which represents a significant public health concern due to its high prevalence (prevalence rate for a major depressive episode in the first postpartum year is 13% (O'Hara and Swain 1996)) in combination with adverse effects on both mother and child. Particularly disquieting are recent studies reaffirming the link between depression and anxiety with suicide during the perinatal period (Grigoriadis et al. 2017; Khalifeh et al. 2016). Although recent reviews have confirmed that anxiety during pregnancy is a significant risk factor for PPD (Goodman et al. 2014; Norhayati et al. 2015), the strength of this relationship was not previously appreciated to our knowledge. Robertson et al. (2004) described the effect size for antenatal anxiety as a risk factor for PPD as strong/moderate and similar in magnitude to that of depression during pregnancy, but our meta-analysis provides a pooled effect size with updated literature. Although it is difficult to know exact baseline rates, we can make estimates with information we do have. The baseline rate for PPD is about 13% (O'Hara and Swain 1996). For simplicity, if we assume that about 10% of women with PPD do not have anxiety, and with our OR of 2.64, the risk difference with an anxiety disorder in pregnancy becomes about 13%. That is, if we took 100 women with an anxiety disorder and treated them to remission, then we would see 13 fewer cases of PPD. At the population level, assuming 10% rate for PPD (without anxiety), and 15.2% for an antenatal anxiety disorder (Dennis et al. 2017), the calculation works out to 16.7% of cases of PPD being attributable to anxiety, assuming all else is equal. Although these numbers are estimates, it is clear that antenatal anxiety is a substantial risk factor.

Furthermore, another strength of our work is our analyses controlling for the presence of prenatal depression which is both highly comorbid with prenatal anxiety (Goodman et al. 2014; Littleton et al. 2007) and itself a significant risk factor for PPD (Norhayati et al. 2015; Robertson et al. 2004; Underwood, Waldie, D'Souza, Peterson, & Morton 2016) and thus a potential moderator of the association between antenatal anxiety and PPD. For example, depression can relapse during the postpartum and the antenatal depression may be the predictor of a subsequent episode rather than anxiety. Both subanalyses (controlling versus not for depression) were significant however, although the magnitude of the effect was lower for studies that controlled for prenatal depression. Finally, our results are strengthened and made clinically relevant by inclusion of a broad time span in assessing for PPD and assessing it at different time points across the first postpartum year. Although PPD is "purely" diagnosed as occurring within the first 4 weeks postpartum in the DSM-5, it is widely understood that depression can occur beyond this restrictive window including up to 6 months (Sharma and Mazmanian 2014) or 12 months postpartum, as reflected in research which does not restrict to the first 4 weeks typically (Dennis et al. 2012; Goodman et al. 2014; Norhayati et al. 2015; O'Hara and McCabe 2013). Our inclusion of measuring it at about 10 months postpartum matches the timeline of suicide reports in relation to postpartum mood and anxiety disorders (Grigoriadis et al. 2017; Khalifeh et al. 2016), highlighting the importance of ongoing difficulties beyond the first month after giving birth.

A limitation follows from those discussed above; PPD was assessed in different ways across studies. Only one study diagnosed PPD according to structured criteria (Rambelli et al. 2010); six defined PPD according to an EPDS cutoff of ≥ 13 (Austin et al. 2007; Coelho et al. 2011; Davey et al. 2011; Heron et al. 2004; Lee et al. 2007; Sutter-Dallay et al. 2004) and one study used a modified BDI score ≥ 9 (Soderquist et al. 2009). Thus, altogether, only one study examined the association between a diagnosed anxiety disorder in pregnancy and a diagnosis of PPD (Rambelli et al. 2010). This once again speaks to the effects that severity may play on potential consequences. Other studies also showed significant associations between antenatal anxiety and PPD but were not included in our analysis, most commonly because of the use of continuous measures of anxiety and/or depression; less common reasons

Table 2 Effect of antenatal anxiety on postpartum depression and breastfeeding: meta-analysis results

		Within group						
				Heterogeneity			Effect of moderator	
Analysis	No. of studies	Odds ratio or mean difference (95% CI)	*P* value	$Q_{(df)}$ within	*P* value	I^2 (percentage of variance explained)	$Q_{(df)}$ between	*P* value
Postpartum depression								
All studies	8	2.64 (2.02 to 3.46)	< 0.01	8.38_7	0.30	16.0		
Study quality							0.00_1	0.99
Above quality threshold	4	2.72 (1.88 to 3.92)	< 0.01	4.42_3	0.22	32.0		
Below quality threshold	4	2.72 (1.57 to 4.71)	< 0.01	3.79_3	0.29	21.0		
Diagnostic measure of anxiety							0.61_1	0.43
Diagnostic	3	3.43 (1.85 to 6.35)	< 0.01	0.58_2	0.75	0.0		
Not diagnostic	5	2.58 (1.80 to 3.70)	< 0.01	6.56_4	0.16	39.0		
Any adjusted data							0.13_1	0.72
Adjusted findings	7	2.66 (1.93 to 3.66)	< 0.01	7.99_6	0.24	25.0		
Unadjusted findings	1	3.07 (1.50 to 6.28)[a]	< 0.01					
Anxiety assessment time							3.13_1	0.08
Second trimester	4	3.80 (2.47 to 5.84)	< 0.01	0.53_2	0.91	0.0		
Third trimester	4	2.30 (1.62 to 3.27)	< 0.01	4.13_4	0.25	27.0		
Registry data								
Registry	0							
Non-registry	8	2.64 (2.02 to 3.46)	< 0.01	8.38_7	0.30	16.0		
Country							0.27_2	0.87
North America	1	3.07 (2.50 to 6.28)[a]	< 0.01					
Europe	5	2.55 (1.88 to 3.46)	< 0.01	4.45_4	0.35	10.0		
Other	2	2.32 (0.80 to 6.77)	0.12	3.48_1	0.06	71.0		
Control for prenatal depression							1.27_1	0.26
Yes	6	2.45 (1.77 to 3.39)	< 0.01	6.07_5	0.30	18.0		
No	2	3.45 (2.10 to 5.67)	< 0.01	0.19_1	0.66	0.0		
Breastfeeding								
All studies	5	0.63 (0.53 to 0.74)	< 0.01	3.53_4	0.47	0.0		
Study quality							0.25_1	0.62
Above quality threshold	2	0.56 (0.31 to 1.00)	0.05	1.63_1	0.20	39.0		
Below quality threshold	3	0.65 (0.55 to 0.78)	< 0.01	0.82_2	0.66	0.0		
Diagnostic measure of anxiety							0.54_1	0.46
Diagnostic	1	0.87 (0.36 to 2.11)[a]	0.76					
Not diagnostic	4	0.62 (0.53 to 0.73)	< 0.01	3.03_3	0.39	1.0		
Any adjusted data							0.54_1	0.46
Adjusted findings	1	0.87 (0.36 to 2.11)[a]	0.76					
Unadjusted findings	4	0.62 (0.53 to 0.73)	< 0.01	3.03_3	0.39	1.0		
Anxiety assessment time							0.25_1	0.62
Any time in pregnancy	0							
Second trimester	2	0.65 (0.53 to 0.79)	< 0.01	0.45_1	0.50	0.0		
Third trimester	3	0.58 (0.41 to 0.83)	< 0.01	2.87_2	0.24	30.0		
Registry data								
Registry	0							
Non-registry	5	0.63 (0.53 to 0.74)	< 0.001	3.56_4	0.47	0.0		
Country							2.83_2	0.24
North America	1	0.46 (0.30 to 0.71)[a]	< 0.01					
Europe	3	0.73 (0.52 to 1.02)	0.06	0.74_2	0.69	0.0		
Other	1	0.64 (0.52 to 0.78)[a]	< 0.01					

Pooled effect size estimated using random effect model unless otherwise specified

[a] Pooled effect size estimated using fixed effect model

for exclusion were presentation of unclear or unusable data, use of a non-validated tool to assess antenatal anxiety, and aggregation of PPD across multiple postnatal time points. Although the heterogeneity was very low, which indicates consistency among the studies which actually strengthens our confidence in our results, nevertheless, future research must operationalize outcomes in ways that can be easily replicated and summarized.

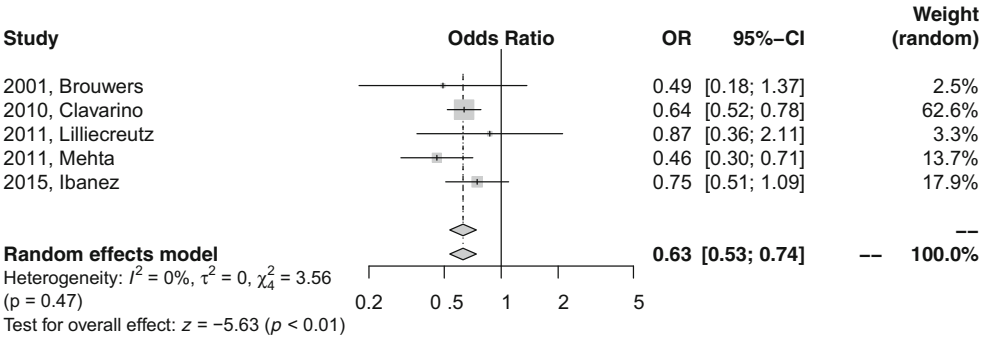

Fig. 3 Pooled association between antenatal anxiety and breastfeeding

Breastfeeding

It is widely understood that breastfeeding is an important contributor to maternal and infant health, as echoed by the World Health Organization and United Nations Children's Fund's joint recommendation that infants be exclusively breastfed for the first 6 months of life (WHO 2003). Nevertheless, global rates of exclusive breastfeeding to 6 months range from 37 to 47% (Fallon et al. 2016), suggesting a need to better understand the contributors and barriers to breastfeeding practices. To our knowledge, there has been only one systematic review (Fallon et al. 2016) to date examining the association between antenatal anxiety and infant feeding outcomes (specifically breastfeeding intention, initiation, and duration); however, according to the authors, too many inconsistencies in the definitions of feeding outcomes precluded conducting a meta-analysis of the data. Although they found that high levels of antenatal anxiety were associated with decreases in breastfeeding intention and exclusivity, they reported that there was insufficient evidence to draw conclusions between antenatal anxiety and infant feeding outcomes. Our conclusions are also limited by methodological inconsistencies across included studies on the type of breastfeeding outcomes examined (Table 1). Our grouping of breastfeeding outcomes included two outcomes defined by the authors as breastfeeding initiation, although one article (Ibanez et al. 2015) assessed at hospital discharge while the other (Mehta et al. 2011) asked about "ever breastfed" at 3 months postpartum. Two outcomes are listed by the authors as "breastfeeding, yes/no" where the assessment time was unclear (Brouwers et al. 2001; Lilliecreutz et al. 2011), and one outcome where we chose to combine "breastfeeding for < 4 months" with "breastfeeding for 4+ months" in comparison to "never" to be more comparable to other breastfeeding outcome groupings (Clavarino et al. 2010). The variation in definitions of breastfeeding outcomes we noted here is similar to what has been found in the depression and breastfeeding literature (Pope and Mazmanian 2016). This field can be further strengthened by a greater number of prospective studies following women from pregnancy, using standard definitions as others have suggested (Dias and Figueiredo 2015; Pope and Mazmanian 2016).

It is important to note that breastfeeding can be challenging and is associated with a learning curve, pain initially for some women, ongoing sleep deprivation, and fatigue. Breastfeeding may not always be the right choice for women with mood and anxiety issues when prioritizing their health as ongoing frustration, sleep deprivation, and exhaustion may contribute to a worsening prognosis. The primary aim of any mother is to ensure her infant feeds. Moreover, with other forms of feeding, the other parent can participate, which supports the mother; support is a known protective factor (Biaggi et al. 2016). Thus, not breastfeeding is not necessarily an "adverse outcome," but this is highly controversial and beyond the scope of this paper but nevertheless must be noted.

Conclusions

Antenatal anxiety is significantly associated with an increased risk of postpartum depression and with decreased breastfeeding, although the latter relationship is more tentative given the limitations of the original studies. It is important to fully understand the impact of antenatal anxiety as it may herald further psychiatric issues and other outcomes which can lead to further adversity. The pregnancy and postpartum phases of life are ones that can have lasting effects on both the mother and her family. It is imperative if we assess and treat women suffering with significant anxiety at this remarkable point in their lives to contribute to improving their outcomes. Although our team was only able to meta-analyze two outcomes, it is evident from the number of papers that there has been attention paid to antenatal anxiety and the potential consequences. Researchers must consider using uniform definitions and criteria to advance the field.

Role of the sponsor The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

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Compliance with ethical standards

Conflicts of interest SG has received other fees from Allergan, personal fees from Pfizer, other fees from Sage, and personal fees from Bristol Myers Squibb, outside the submitted work; no other relationships or activities that could appear to have influenced the submitted work. LG, MP, LM, GT, SNV, CLD, MS, CB, AC, HD, NR, MG, and MR report no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work.

Ethics This article does not contain any studies with human participants performed by any of the authors.

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