General Approaches to Psychopharmacology

Author, year	*Setting*	*Design/ approach*	*Subjects*	*Intervention*	*Comparator*	*Sample size*	*Outcomes*	*Quality Assessment*	*Results*
Viswanathan 2021	Global	Systematic review and meta-analysis	Pregnant and postpartum women	Treatment	Placebo, one treatment vs another, no treatment	164 studies (131 studies included in analyses)	Symptoms, functional capacity, quality of life, peripartum events, adherence to treatment/care, suicidal events	High quality review	Few studies have been conducted in pregnant and postpartum women on the benefits of pharmacotherapy; many studies report on harms but are of low quality. The limited evidence available is consistent with some benefit, and some studies suggested increased adverse events. However, because these studies could not rule out underlying disease severity as the cause of the association, the causal link between the exposure and adverse events is unclear. Patients and clinicians need to make an informed, collaborative decision on treatment choices.

Gartlehner 2016	Global	Systematic review and meta-analysis	Adults with acute major depressive disorder (MDD)	Antidepressants	Alternative treatments	45 trials	Benefits and harms	High quality review	On the basis of moderate-strength evidence, cognitive behavioral therapy (CBT) and antidepressants led to similar response rates (relative risk [RR], 0.90 [95% confidence interval [CI], 0.76–.07]) and remission rates (RR, 0.98; 95% CI, 0.73–1.32]). In trials, antidepressants had higher risks for adverse events than most other treatment options; no information from nonrandomized studies was available. The evidence was too limited to make firm conclusions about differences in the benefits and harms of antidepressants compared with other treatment options as first-step therapies for acute MDD. For second-step therapies, different switching and augmentation strategies provided similar symptom relief.
Taouk 2018	United States	Survey analysis	Obstetricians-gynecologists	Prenatal depression screening and antidepressant prescription during pregnancy	-	379 responses	Practice	Serious risk of bias	A larger survey on prenatal medication was developed at the American College of Obstetricians and Gynecologists (ACOG) and distributed to a sample of 1,000 Fellows. The overall response rate was 37.9% (N=379). Two hundred eighty-eight provided care to pregnant patients and therefore, responded to questions on prenatal depression screening and antidepressant prescription. Most ob-gyns (87.8%) routinely screened patients for depression at least once during pregnancy. When symptoms of depression were reported, 52.1% "sometimes" prescribed an antidepressant medication with 22.5% doing so "usually or always". While 84.0% prescribed selective serotonin reuptake inhibitors (SSRIs) to pregnant patients, only 31.9% prescribed non-SSRIs. Ob–gyns felt comfortable prescribing SSRIs (78.1%) and counseled patients that the benefits of treating depression pharmacologically outweigh the risks (83.0%), and the use of SSRIs during pregnancy is relatively safe (87.5%). Prescribing SSRIs to pregnant patients was not significantly associated with interpretation of evidence on fetal and neonatal outcomes. Findings suggest most ob-gyns in the United States at least sometimes prescribe antidepressants in response to patient reports of depression symptoms during pregnancy.

Roca 2013	Spain	Prospective	Pregnant women with depressive or anxiety disorder (DSM-IV criteria)	Antidepressant treatment	-	132 women	Discontinuation	Serious risk of bias	Seventy women (53%) discontinued SSRI treatment upon confirmation of pregnancy. Socio-demographic, obstetric, and psychiatric variables did not differ significantly between women who maintained and women who discontinued treatment. Only unplanned pregnancy was associated with a greater risk of discontinuation (OR, 2.7; 95% CI, 1.34–5.52). Women who discontinued treatment also had higher EPDS and STAI scores in the first visit and prenatal visit (34–36 weeks) (p<.05). Of the 70 women who discontinued treatment, 57.1% (N=40) reintroduced treatment, almost half of these in the first trimester of pregnancy.

Yonkers 2011	United States	Prospective cohort	Pregnant women with recurrent depressive illness	Antidepressant treatment	-	778 women	Risk for onset of a major depressive episode, adverse birth outcomes	Serious risk of bias	Antidepressant use decreased early in pregnancy. Twenty-one percent of participants took an antidepressant in the month before pregnancy, decreasing to 18% in Trimester 1, and to 14% in Trimesters 2 and 3. Use of antidepressants returned to 21% after pregnancy. One hundred- twenty-three women (16%) developed a major depressive episode during pregnancy or postpartum. For those who became depressed, most had onset in the first trimester (n=93; 76%). Regarding other psychiatric disorders during pregnancy, 5% of the cohort met criteria for PTSD 15% for generalized anxiety disorder, and 6% for panic disorder. Eight percent of the sample had more than one of these conditions during pregnancy. There was little evidence of an association between antidepressant use and reduced occurrence of depression (unadjusted hazard ratio [HR]= 0.85; 95% CI, 0.52–1.40; adjusted HR, 0.88; 95% 0.51–1.50).
Cohen 2006	United States	Prospective cohort	Pregnant women	Discontinued antidepressant medication	Maintained treatment	201 women	Relapse of major depression	Moderate risk of bias	Among the 201 women in the sample, 86 (43%) experienced a relapse of major depression during pregnancy. Among the 82 women who maintained their medication throughout their pregnancy, 21 (26%) relapsed compared with 44 (68%) of the 65 women who discontinued medication. Women who discontinued medication relapsed significantly more frequently over the course of their pregnancy compared with women who maintained their medication (HR, 5.0; 95% CI, 2.8–9.1; *P*<.001).

Weissman 2004	Global	Review and pooled analysis	Lactating mothers	Antidepressant treatment	-	57 studies	Antidepressant levels (maternal, infant, breast milk), infant-maternal plasma ratio	-	Infants with recent prenatal exposure and symptomatic infants included in case reports were analyzed separately. Infant plasma levels were standardized against the average maternal level for each drug. The average infant-maternal plasma ratio was calculated for each drug, and correlations of infant plasma level to maternal dose, maternal plasma level, and breast milk level were calculated. Nortriptyline, paroxetine, and sertraline usually produce undetectable infant levels. Of drugs currently used, fluoxetine produces the highest proportion (22%) of infant levels that are elevated above 10% of the average maternal level. Based on smaller numbers, the data on citalopram indicate that it produces elevated levels in 17% of infants. The milk-to-plasma ratios for 11 antidepressants had a statistically significant negative association with the percentage of the drug bound to protein.
Kendig 2017	United States	Commentary	Pregnant and postpartum women	Existing recommendations and resources	-	-	Best practice implementation in maternity care settings	-	1. Identify Mental Health Screening Tools to be Made Available in Every Clinical Setting, 2. Establish a Response Protocol and Identify Screening Tools for Use Based on Local Resources, 3. Educate Clinicians and Office Staff on Use of the Identified Screening Tools and Response Protocol, 4. Identify an Individual Who Is Responsible for Driving Adoption of the Identified Screening Tools and Response Protocol, 5. Obtain Individual and Family Mental Health History, 6. Conduct Validated Mental Health Screening During Appropriately Timed Encounters, 7. Provide Awareness Education to Women, Family Members, and Other Support Persons, 8. Initiate a Stage-Based Response Protocol for a Positive Mental Health Screening Result, 9. Activate an Emergency Referral Protocol for Women With Suicidal or Homicidal Ideation or Psychosis, 10.Provide Appropriate and Timely Support for Women, as Well as Family Members and Staff, as Needed, 11. Obtain Follow-up From Mental Health Care Providers on Women Referred for Treatment, 12. Establish a Nonjudgmental Culture of Safety, 13. Perform an Interdisciplinary Review of Adverse Mental Health Outcomes, 14. Establish Local Standards for Recognition and Response to Measure Compliance, Understand Individual Performance, and Track Outcomes

Metz 2016	United States	Case series	All women with pregnancy-associated deaths (death during pregnancy or within 1 year postpartum from any cause) from self-harm	-	-	211 deaths	Manner of death, psychiatric diagnosis, toxicology results, social stressors, adverse obstetrical events, treatment	-	Among the 211 total maternal deaths in Colorado over the study interval, 30% (n=63) resulted from self-harm. The pregnancy-associated death ratio from overdose was 5.0 (95% CI, 3.4–7.2) per 100,000 live births and from suicide 4.6 (95% CI, 3.0–6.6) per 100,000 live births. Detailed records were obtained for 94% (n=59) of women with deaths from self-harm. Deaths were equally distributed throughout the first postpartum year (mean 6.21 ± 3.3 months postpartum) with only 6 maternal deaths during pregnancy. Seventeen percent (n=10) had a known substance use disorder. Prior psychiatric diagnoses were documented in 54% (n=32) and prior suicide attempts in 10% (n=6). While half (n=27) of the women with deaths from self-harm were noted to be taking psycho-pharmacotherapy at the start of pregnancy, 48% of them discontinued the medications during pregnancy. Fifty women had toxicology testing available; pharmaceutical opioids were the most common drug identified (n=21).

Safety and Efficacy of Pharmacologic Interventions for Perinatal Depressive Disorders

Author, year	*Setting*	*Design/ approach*	*Subjects*	*Intervention*	*Comparator*	*Sample size*	*Outcomes*	*Quality Assessment*	*Results*

United States Preventive Services Task Force (USPSTF) Interventions to Prevent Perinatal Depression Recommendation Statement 2019	United States	Guideline	Pregnant or postpartum women or their children	Preventive interventions (counseling, health system interventions, physical activity, education, supportive interventions, and other behavioral interventions, such as infant sleep training and expressive writing), pharmacological approaches (use of nortriptyline, sertraline, and omega-3 fatty acids)	One intervention vs another, no intervention	Systematic review/meta-analyses, randomized controlled trials (RCTs), observational studies, literature reviews	Recommendation for perinatal depression prevention	6.65 out of 7	The USPSTF found convincing evidence that counseling interventions, such as cognitive behavioral therapy and interpersonal therapy, are effective in preventing perinatal depression. Women with a history of depression, current depressive symptoms, or certain socioeconomic risk factors (eg, low income or young or single parenthood) would benefit from counseling interventions and could be considered at increased risk. The USPSTF found adequate evidence to bound the potential harms of counseling interventions as no greater than small, based on the nature of the intervention and the low likelihood of serious harms. The USPSTF found inadequate evidence to assess the benefits and harms of other noncounseling interventions. The USPSTF concludes with moderate certainty that providing or referring pregnant or postpartum women at increased risk to counseling interventions has a moderate net benefit in preventing perinatal depression.

National Institute for Health and Care Excellence (NICE) 2014 (reviewed 2020)	United Kingdom	Guideline	Women during pregnancy and the postnatal period (up to 1 year after childbirth) and in women who are planning a pregnancy	Prevention, case identification, diagnosis and assessment, psychosocial interventions, pharmacological interventions	Usual care	Systematic review/meta-analyses, randomized controlled trials (RCTs), observational studies, literature reviews	Diagnosis of a mental disorder, symptomatology, quality of life, relapse, hospitalization, drop-out, side effects, quality of mother-infant interaction and infant care, fetal and infant development	6.48 out of 7	Clinical Guideline Antenatal and postnatal mental health: clinical management and service guidance: Recognise that the range and prevalence of anxiety disorders (including generalised anxiety disorder, obsessive-compulsive disorder, panic disorder, phobias, post-traumatic stress disorder and social anxiety disorder) and depression are under-recognised throughout pregnancy and the postnatal period. At a woman's first contact with primary care or her booking visit, and during the early postnatal period, consider asking depression identification questions as part of a general discussion about a woman's mental health and wellbeing. If a woman responds positively to either of the depression identification questions in recommendation 1.5.4, is at risk of developing a mental health problem, or there is clinical concern, consider: using the Edinburgh Postnatal Depression Scale (EPDS) or the Patient Health Questionnaire (PHQ-9) as part of a full assessment or referring the woman to her GP or, if a severe mental health problem is suspected, to a mental health professional. At all contacts after the first contact with primary care or the booking visit, the health visitor, and other healthcare professionals who have regular contact with a woman in pregnancy and the postnatal period (first year after birth), should consider: using the EPDS or the PHQ-9 as part of monitoring.

Viswanathan 2021	Global	Systematic review and meta-analysis	Pregnant and postpartum women	Treatment	Placebo, one treatment vs another, no treatment	164 studies (131 studies included in analyses)	Symptoms, functional capacity, quality of life, peripartum events, adherence to treatment/care, suicidal events	High quality review	Brexanolone for depression onset in the third trimester or in the postpartum period probably improves depressive symptoms at 30 days (least square mean difference in the Hamilton Rating Scale for Depression, -2.6; p=0.02; N=209) when compared with placebo. Sertraline for postpartum depression may improve response (calculated relative risk [RR], 2.24; 95% CI, 0.95–5.24; N=36), remission (calculated RR, 2.51; 95% CI, 0.94–6.70; N=36), and depressive symptoms (p-values ranging from 0.01 to 0.05) when compared with placebo. Discontinuing use of mood stabilizers during pregnancy may increase recurrence (aHR, 2.2; 95% CI, 1.2–4.2; N=89) and reduce time to recurrence of mood disorders (2 versus 28 weeks, aHR, 12.1; 95% CI, 1.6–91; N=26) for bipolar disorder when compared with continued use. Brexanolone for depression onset in the third trimester or in the postpartum period may increase the risk of sedation or somnolence, leading to dose interruption or reduction when compared with placebo (5% versus 0%). More than 95% of studies reporting on harms were observational in design and unable to fully account for confounding. These studies suggested some associations between benzodiazepine exposure before pregnancy and ectopic pregnancy; between specific antidepressants during pregnancy and adverse maternal outcomes such as postpartum hemorrhage, preeclampsia, and spontaneous abortion, and child outcomes such as respiratory issues, low Apgar scores, persistent pulmonary hypertension of the newborn, depression in children, and autism spectrum disorder; between quetiapine or olanzapine and gestational diabetes; and between benzodiazepine and neonatal intensive care admissions. Causality cannot be inferred from these studies. We found insufficient evidence on benefits and harms from comparative effectiveness studies, with one exception: one study suggested a higher risk of overall congenital anomalies (aRR, 1.85; 95% CI, 1.23–2.78; N=2,608) and cardiac anomalies (aRR, 2.25; 95% CI, 1.17–4.34; N=2,608) for lithium compared with lamotrigine during first trimester exposure.

Al-Fadel 2021	Global	Systematic review	Children	Exposure to antidepressants (including SSRIs, serotonin and noradrenaline reuptake inhibitors (SNRIs), noradrenergic and specific serotonergic antidepressants (NaSSAs), and tricyclic antidepressants (TCAs)) during pregnancy	Control	14 studies	Motor and intellectual disability outcomes	Low quality review	Studies have reported conflicting effects on motor development in infants with maternal exposure to antidepressants. Furthermore, not all of the studies included that assessed intellectual disabilities in infants found an association between maternal exposure to antidepressants and intellectual disabilities. However, methodological flaws existed in the studies, such as the use of scales with inadequate reliability or validity, a lack of statistical power, or confounding by indication or disease severity.
Brown 2021	Global	Systematic review and meta-analysis	Postpartum women	Antidepressant treatment	Placebo, treatment as usual or other forms of treatment	11 randomized controlled trials	Efficacy of treatment	High quality review	Meta-analysis showed that there may be a benefit of SSRIs over placebo in response (55% versus 43%; pooled RR; 1.27, 95% CI, 0.97–1.66; remission (42% versus 27%; RR, 1.54; 95% CI, 0.99–2.41); and reduced depressive symptoms (standardised mean difference (SMD) −0.30, 95% CI −0.55 to −0.05; 4 studies, 251 women), at 5 to 12 weeks' follow-up. We were unable to conduct meta-analysis for adverse events due to variation in the reporting of this between studies. There was no evidence of a difference between acceptability of SSRI and placebo (27% versus 27%; RR, 1.10; 95% CI 0.74–1.64; 4 studies; 233 women). The certainty of all the evidence for SSRIs was low or very low due to the small number of included studies and a number of potential sources of bias, including high rates of attrition. There was insufficient evidence to assess the efficacy of SSRIs compared with other classes of antidepressants and of antidepressants compared with other pharmacological interventions, complementary medicines, psychological and psychosocial interventions or treatment as usual. A substantial proportion of women experienced adverse effects but there was no evidence of differences in the number of adverse effects between treatment groups in any of the studies. Data on effects on children, including breastfed infants, parenting, and the wider family were limited, although no adverse effects were noted.

Chow 2021	Global	Systematic review	Postpartum women	Interventions for postpartum depression (PPD)	One intervention vs another	83 studies	Efficacy of intervention	Low quality review	Based on the systematic reviews with the highest methodological quality, we found that use of antidepressants and telemedicine were the most effective treatments for PPD. Symptoms of PPD were also improved by traditional herbal medicine and aromatherapy. Current evidence for physical exercise and cognitive behavioural therapy in treating PPD remains equivocal. A significant, but weak relationship between AMSTAR score and journal impact factor was observed (p=0.03, r=0.24; 95% CI, 0.02–0.43) whilst no relationship was found between the number of total citations (p=0.27, r=0.12; 95% CI, − 0.09 to 0.34), or source of funding (p=0.19).
Lee 2021	Global	Systematic review and meta-analysis	Women with peripartum depression	Repetitive transcranial magnetic stimulation	Other treatment	10 studies	Degree of depression alleviation, safety of mother and fetus	High quality review	The therapeutic effect size of repetitive transcranial magnetic stimulation for peripartum depression was 1.394 (95% CI, 0.944–1.843), and the sensitivity analysis effect size was 1.074 (95% CI, 0.689–1.459), indicating a significant effect. The side effect size of repetitive transcranial magnetic stimulation for peripartum depression was 0.346 (95% CI, 0.214–0.506), a meaningful result. There were no severe side effects to the mothers or fetuses.
Leshem 2021	Global	Systematic review and meta-analysis	Pregnant women and offspring	Exposure to SSRIs and SNRIs	No exposure	18 studies	Risk for autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD)	High quality review	Found an association between SSRIs/SNRIs prenatal use and the risk for ASD and ADHD (OR, 1.42; 95% CI, 1.23–1.65, I2=58%; OR, 1.26; 95% CI, 1.07–1.49; I2=48%, respectively). Similar findings were obtained in women who were exposed to SSRIs/SNRIs before pregnancy, representing statistically significant association with ASD (OR, 1.39; 95% CI, 1.24–1.56; I^2=33%) and ADHD (OR, 1.63; 95% CI, 1.50–1.78; I^2=0%) in the offspring, although they were not exposed to those medications in utero.
Uguz 2021	Global	Systematic review	Pregnant women	Antidepressant medication use	No antidepressant medication use	21 meta-analyses	Neonatal and childhood outcomes	Critically low quality review	Most of the meta-analyses reported that compared to non-users, the risks of preterm birth, low birth weight, spontaneous abortion, persistent pulmonary hypertension, autism spectrum disorders, and ADHD in offspring of antidepressant users were significantly higher. Some meta-analyses also noted that the elevated risks were no longer statistically significant when pregnant women with psychiatric diagnoses treated with an antidepressant were compared with control patients who remained untreated.

Vlenterie 2021	Global	Systematic review and meta-analysis	Pregnant women	Depression, depressive symptoms, or use of antidepressants during pregnancy	Pregnant women not suffering from depression/depressive symptoms and not using antidepressants	401,375 women from 27 study databases	Gestational age, birth weight, SGA, and Apgar scores	Low quality review	Increased risks were observed for preterm birth among women with a clinical diagnosis of depression during pregnancy irrespective of antidepressant use (OR, 1.6; 95% CI, 1.2–2.1) and among women with depression who did not use antidepressants (OR, 2.2; 95% CI, 1.7–3.0), as well as for low Apgar scores in the former (OR 1.5, 95% CI, 1.3–1.7), but not the latter group. Selective serotonin reuptake inhibitor (SSRI) use was associated with preterm birth among women who used antidepressants with or without restriction to women with depressive symptoms or a diagnosis of depression (OR, 1.6; 95% CI, 1.0–2.5 and OR, 1.9; 95% CI, 1.2–2.8, respectively), as well as with low Apgar scores among women in the latter group (OR, 1.7; 95% CI, 1.1–2.8).
Araujo 2020	Global	Systematic review	Pregnant women and offspring	Maternal exposure to antidepressants (ADs)	No exposure	50 studies	Risks of autism spectrum disorders (ASD), attention deficit/hyperactivity disorders (ADHD), schizophrenia and other mental illnesses, and cognitive and developmental deficits in infants or preschool children	Low quality review	Twenty studies addressed ASD and/or ADHD risks while 30 focused on developmental and cognitive deficits in infants or preschool children. Most studies detected no association of antenatal AD with ASD after adjustment of risk ratios for maternal depression or psychiatric disorders. Some studies showed that maternal depression, regardless of whether it is treated or untreated, increased ASD risks. Seven out of 8 studies found no increase in ADHD risk associated with antenatal exposure to selective serotonin reuptake inhibitors, the most commonly used AD. No consistent evidence was found linking AD in pregnancy to neurocognitive developmental deficits in infants or preschool children. A residual confounding by indication (depression severity) remained in almost all studies.
Bayrampour 2020	Global	Systematic review and meta-analysis	Pregnant women	Antidepressant discontinuation	Maintained, discontinuation attempt, change in dosage, no medication	8 studies	Relapse of depression during pregnancy	Low quality review	Pooled data did not show higher risk of relapse of depression during pregnancy for women who discontinued antidepressants than for those who continued antidepressants (RR, 1.74; 95% CI, 0.97–3.10; *P*=.06). In the subanalysis based on the severity and recurrence of depression in the study populations, the risk of relapse was significantly higher for populations suggestive of severe or recurrent depression (RR, 2.30; 95% CI, 1.58–3.35) but not for populations suggestive of mild or moderate depression severity (RR, 1.59; 95% CI, 0.83–3.04).

Chang 2020	Global	Systematic review and meta-analysis	Pregnant women	Use of antidepressants during pregnancy	One medication vs another	23 cohort studies	Preterm birth (PTB)	High quality review	The risk of PTB was increased in women with depression [1.58 (1.23–2.04)] and in the general pregnant female population [1.35 (1.11–1.63)] who used antidepressants during pregnancy. Similar results were observed in depressed women treated with SSRIs during pregnancy [1.46 (1.32–1.61)]. There was no significantly increased risk of PTB observed with SSRI use in the general pregnant female population [1.25 (1.00–1.57)], and the heterogeneity of these studies was high.
Fitton 2020	Global	Systematic review	Pregnant women and offspring	Antidepressant exposure	Untreated (no exposure)	16 studies	Adverse birth outcomes, congenital birth defects, neurodevelop mental disorders	Low quality review	Antidepressant exposure was associated with an increased risk of lower gestational age, preterm birth, but not low birthweight or being small for gestational age compared to untreated depression. There is some evidence that congenital defects are associated with antidepressant use, particularly between cardiac defects and paroxetine use. There is conflicting evidence regarding neurodevelopment in offspring, with some reports of increased incidence of autistic spectrum disorders and depression, but also reports of no problems when measuring emotional symptoms, peer problems, conduct problems and hyperactivity-inattention scores.
Li 2020	Global	Systematic review and meta-analysis	Pregnant women	Psychotherapy	Conventional obstetric care, one intervention vs another	22 articles	Depression, anxiety, maternal quality of life	High quality review	This systematic review presents a 1b level of evidence supporting the use of psychotherapy for reducing depression, anxiety and enhancing maternal quality of life. The meta-analysis reveals the beneficial effects of psychotherapy for reducing depression (Hedge g: -0.48), anxiety (-0.47) and enhancing maternal quality of life (0.19) as compared to conventional obstetric care.
Molenaar 2020	Global	Systematic review and meta-analysis	Pregnant women	Antidepressant use	One medication vs another	40 cohorts	Prevalence	Low quality review	Included studies had a low risk of bias, often reporting on large representative cohorts. Selective serotonin reuptake inhibitors (SSRIs) were the most commonly used antidepressants during pregnancy, with an international prevalence estimate of 3.0% (95% CI, 2.3–3.7). While Europe and Australasia had pooled prevalence estimates of 1.6% and 1.3% respectively, Northern America had a prevalence estimate of 5.5% (Q-value=126.19; df=2; p value< 0.01). Highest SSRI prevalence rates were found for sertraline (1.10%), followed by citalopram and fluoxetine (0.77% and 0.76% respectively) (Q-value = 121.25; df = 5; p-value<0.01). Qualitative analysis indicated an increase in antidepressant use over subsequent calendar years.

Salameh 2020	Global	Systematic review	Pregnant women	Treatment	-	28 articles	Depression, anxiety, substance use disorders, treatment receipt	Critically low quality review	Two trend studies showed that illicit drug use disorder increased in pregnant women over the past decade, particularly opioid and marijuana use disorders. Three studies reported an increase in treatment admissions for these disorders from 1992 to 2012; however, the overall treatment admission rate for pregnant women remained relatively stable at 4%. Three studies identified an increase in antidepressant use from 1995 to 2010 in pregnant women. Nine of 19 population-based studies revealed that White ethnicity, older reproductive age, college education, and health insurance coverage were associated with mental health and substance use treatment receipt among pregnant women.
Schoretsanitis 2020	Global	Systematic review and meta-analysis	Women using antidepressants	Antidepressant use in pregnant state (3rd trimester and baseline)	Antidepressant use in non-pregnant state	11 articles	Ratio between the dose-adjusted plasma concentration of the antidepressant in the 3rd trimester and the dose adjusted plasma concentrations at baseline (pregravid and/or postpartum)	Low quality review	Data for several antidepressants display clear alteration patterns during pregnancy. On the basis of the alteration ratios trimipramine, fluvoxamine and nortriptyline show a prominent decrease in dose-adjusted levels especially in the 3rd trimester. Clomipramine, imipramine, citalopram and paroxetine show smaller decreases in dose-adjusted concentrations in the third trimester. For escitalopram, venlafaxine and fluoxetine, changes are considered negligible. For sertraline, there was a tendency towards increased dose-adjusted concentrations in pregnancy. Table 1 contains all relevant data retrieved from the eleven studies finally included.
Sharma 2020	Global	Systematic review	Women with postpartum depression	Antidepressant medication and dosage	One medication vs another	15 articles	Treatment outcome (response, remission)	Critically low quality review	Antidepressants are the mainstay of drug treatment for moderate to severe postpartum depression. Several open-label studies and some randomized controlled trials support the use of antidepressants in women with postpartum depression. Our systematic review found some potential predictors of response or non-response to antidepressants; however, given the limited number of available studies and the heterogeneous nature of postpartum depression, the findings need to be interpreted cautiously.

Xing 2020	Global	Systematic review and meta-analysis	Pregnant mothers and their children	Antidepressant use during pregnancy	No antidepressant use	54 studies	Risks of adverse perinatal outcomes	High quality review	In cohort studies, children whose mothers received antidepressants during pregnancy had higher risks of preterm birth (RR, 1.62; 95% CI, 1.37–1.90), low birth weight (RR, 1.37; 95% CI, 1.04–1.80), and admissions to neonatal intensive care unit (RR, 1.60; 95% CI, 1.38–1.85) when compared with children born by depressed but untreated pregnant women. The risks of spontaneous abortions (RR, 1.49; 95% CI, 1.29–1.73), large for gestational age (RR, 1.11; 95% CI, 1.03–1.20), stillbirths (RR, 1.16; 95% CI, 1.02–1.32), low Apgar score at 5 min (RR, 1.91; 95% CI, 1.42–2.56), and neonatal convulsions (RR, 1.97; 95% CI, 1.56–2.48) increased in children whose mothers received antidepressants during pregnancy when compared with children born by healthy pregnant women.
Cooper 2019	Global	Meta-analysis	Pregnant women	Brexanolone, selective serotonin reuptake inhibitors (SSRIs)	Selective serotonin reuptake inhibitors (SSRIs), placebo	26 studies	Hamilton Rating Scale for Depression (HAM-D) total score	Critically low quality review	For all time points, MAICs showed larger differences in CFB for brexanolone compared with SSRIs. Differences (95% CIs) between brexanolone and SSRIs were 12.79 (8.04–17.53) [day 3], 5.87 (− 1.62 to 13.37) [week 4] and 0.97 (− 6.35 to 8.30) [last observation] for the HAM-D. For the EPDS, the differences in CFB were 7.98 (5.32–10.64) [day 3], 6.35 (3.13–9.57) [week 4] and 4.05 (0.79–7.31) [last observation]. Other analytical approaches are also presented to demonstrate the similarity of results, using a network meta-analysis approach, and the importance of using the MAIC method to control for the important heterogeneity between placebo arms.
Grigoriadis 2019	Global	Systematic review and meta-analysis	Pregnant women and their offspring	Antenatal benzodiazepine exposure as monotherapy and in combination with antidepressants	Not exposed	8 studies	Risk of congenital malformations	High quality review	Prenatal benzodiazepine use was not associated with an increased risk of congenital malformations (OR, 1.13; 95% CI, 0.99–1.30, 8 studies, n = 222/5,195 exposed and 64,335/2,082,467 unexposed), including with first trimester exposure specifically (OR, 1.08; 95% CI, 0.93–1.25; *P*=.33; 5 studies, n=181/4,331 exposed and 64,308/2,081,463 unexposed). There was no significant association with cardiac malformation following exposure (OR, 1.27; 95% CI, 0.98–1.65, *P*=.07; 4 studies, n= 61/4,414 exposed and 19,260/2,033,402 unexposed). However, concurrent use of benzodiazepine and antidepressants during pregnancy was associated with a significantly increased risk of congenital malformations (OR, 1.40; 95% CI, 1.09–1.80, *P*=.008; 3 studies).

Halvorsen 2019	Global	Systematic review and meta-analysis	Pregnant women and offspring	Exposure to selective serotonin reuptake inhibitors (SSRIs)	No exposure	20 studies	Risk of developing mental or behavioural disorders	High quality review	Found a statistically significant positive association between in utero exposure to SSRIs and mental or behavioural disorders such as autism spectrum disorder (hazard ratio (HR), 1.27; 95% CI, 1.10–1.47), attention-deficit/hyperactivity disorder (HR, 1.33; 95% CI, 1.06–1.66) and mental retardation (HR, 1.41; 95% CI, 1.03–1.91). Confounding by indication was identified in five of seven studies investigating this aspect.
Masarwa 2019	Global	Systematic review and meta-analysis	Pregnant women and offspring	Exposure to selective serotonin reuptake inhibitors or serotonin norepinephrine reuptake inhibitors during pregnancy	No exposure	11 studies	Risk for persistent pulmonary hypertension of the newborn	High quality review	A total of 156,978 women and their offspring were exposed to selective serotonin reuptake inhibitors or serotonin norepinephrine reuptake inhibitors during pregnancy. Persistent pulmonary hypertension of the newborn was detected among 452 exposed offspring, representing an incidence rate of 2.9 cases per 1,000 live births and a number needed to harm of 1,000. The risk for persistent pulmonary hypertension of the newborn was significantly increased in the analysis of exposure to selective serotonin reuptake inhibitor/serotonin norepinephrine reuptake inhibitor in any trimester (OR, 1.82; 95% CI, 1.31–2.54; I^2 = 72%), as well as in analysis restricted to exposure week >20 (OR, 2.08; 95% CI, 1.44–3.01; I^2 = 76%). In network meta-analysis, sertraline was ranked most likely to have the lowest risk for persistent pulmonary hypertension of the newborn among the different selective serotonin reuptake inhibitors (*P*=.83).
Ng 2019	Global	Systematic review and meta-analysis	Pregnant women	Maternal SSRI use	No exposure, control	9 studies	Persistent pulmonary hypertension of the newborn (PPHN)	High quality review	Random-effects meta-analysis of eight studies revealed a significantly increased risk of PPHN with maternal SSRI use during pregnancy, with a pooled OR of 1.516 (95% CI, 1.035–1.997, p<.001). Overall, the absolute increase in risk of PPHN with SSRI use appears small, with an absolute risk difference of 0.619 per 1,000 livebirths and a number needed to harm of 1,615 women.

O'Connor 2019	Global	Systematic review and meta-analysis (evidence report and SR for USPSTF Interventions to Prevent Perinatal Depression)	Pregnant and postpartum women	Primary care–relevant/counseling interventions for prevention	One approach versus another	50 studies	Depression status; depression symptoms; maternal, infant, and child health outcomes	High quality review	Counseling interventions were the most widely studied interventions. Compared with controls, counseling interventions were associated with a lower likelihood of onset of perinatal depression (pooled RR, 0.61; 95% CI, 0.47–0.78; 17 RCTs [n=3,094]; I2 = 39.0%). The absolute difference in the risk of perinatal depression ranged from 1.3% greater reduction in the control group to 31.8% greater reduction in the intervention group. Health system interventions showed a benefit in 3 studies (n = 5,321) and had a pooled effect size similar to that of the counseling interventions, but the pooled effect was not statistically significant using a method appropriate for pooling a small number of studies (restricted maximum likelihood RR, 0.58; 95% CI, 0.22–1.53; n=4,738; I2 = 66.3%; absolute risk reduction range, −3.1% to −13.1%). None of the behavior-based interventions reported on harms directly. A smaller percentage of participants prescribed sertraline had a depression recurrence compared with those prescribed placebo (7% versus 50%, *P*=.04) at 20 weeks postpartum in 1 very small RCT (n=22 analyzed) but with an increased risk of adverse effects to the mother.
Stevens 2019	Global	Systematic review	Patients diagnosed with bipolar disorder (BD) or major depressive disorder (MDD) prior to pregnancy	Medication	One medication versus another	22 studies	Recurrence (medication continuation/discontinuation)	Critically low quality review	Included studies reported a wide variation in the recurrence rate of bipolar disorder and major depressive disorder during pregnancy (BD: mean=19%, range=4%–73%; MDD: mean=8%, range=1%–75%). Observational data showed a relative risk reduction of maintenance therapy during pregnancy of 66% in women with BD and 54% for women with MDD, a significant difference (95% CI, 9.4–14.6; p<0.001).
Uguz 2019	Global	Systematic review	Pregnant women and newborns	Use of selective serotonin reuptake inhibitors	Control	9 studies	Neonatal outcomes	Critically low quality review	The prevalence rates of neonatal seizures in the antidepressant groups and control groups were 0.30% to 0.91% and 0.10% to 0.30%, respectively. The use of selective serotonin reuptake inhibitors was associated with up to 5-fold increase in the risk of neonatal seizures. Compared with the controls, higher risks were reported in newborns of pregnant women using any antidepressant or tricyclic antidepressants albeit in a limited number of studies. Exposure to antidepressants in the third trimester of pregnancy appeared to be associated more with neonatal seizures compared with earlier exposure.

Youash 2019	Global	Systematic review	Pregnant women	Antidepressant exposure or diagnosis of depression	No exposure or diagnosis	20 studies	Gestational hypertension, preeclampsia or eclampsia	Critically low quality review	Ten specifically examined the relationship between depression and hypertension in pregnancy. Only two of these did not find a significant association. Of the ten studies that concentrated on antidepressant medications, all except one found an association with hypertension in pregnancy to varying degrees.
Zheng 2019	Global	Systematic review and meta-analysis	Postpartum women	Brexanolone infusion	Another antidepressant	2 articles	Efficacy and safety	High quality review	Two articles reporting 3 RCTs with 4 active arms (n=267) covering 156 women with PPD receiving brexanolone infusion and 111 women with PPD on placebo were included. Compared with placebo, women suffering from PPD who received brexanolone had significantly greater response that started after 24 hours (RR,1.34; 95% CI, 1.03–1.73), peaked at 36 hours (RR, 1.50; 95% CI, 1.06–2.13, *P*=0.02) and lasted until day 7 (RR, 1.32; 95% CI, 1.01–1.73). Similarly, PPD women treated with brexanolone had significantly greater remission starting at 24 hours (RR, 1.86; 95% CI, 1.03–3.34), peaking at 60 hours (RR, 2.20; 95% CI, 1.31–3.70) and lasting until 72 hours (RR, 1.96; 95% CI 1.41–2.72). Brexanolone infusion led to significantly higher rate of discontinuation for any reasons (RR, 2.68; 95% CI, 1.35–5.32). Discontinuation due to intolerability and adverse drug reactions was similar between the active agent and placebo.

Cipriani 2018	Global	Systematic review and meta-analysis	Adults with major depressive disorder	Antidepressant drug treatment	Placebo	522 trials comprising 116,477 participants	Efficacy, acceptability	High quality review	In terms of efficacy, all antidepressants were more effective than placebo, with ORs ranging between 2.13 (95% credible interval [CrI], 1.89–2.41) for amitriptyline and 1.37 (1.16–1.63) for reboxetine. For acceptability, only agomelatine (OR, 0.84; 95% CrI 0.72–0.97) and fluoxetine (0.88, 0.80–0.96) were associated with fewer dropouts than placebo, whereas clomipramine was worse than placebo (1.30, 1.01–1.68). When all trials were considered, differences in ORs between antidepressants ranged from 1.15 to 1.55 for efficacy and from 0.64 to 0.83 for acceptability, with wide CrIs on most of the comparative analyses. In head-to-head studies, agomelatine, amitriptyline, escitalopram, mirtazapine, paroxetine, venlafaxine, and vortioxetine were more effective than other antidepressants (range of ORs 1.19–1.96), whereas fluoxetine, fluvoxamine, reboxetine, and trazodone were the least efficacious drugs (0.51–0.84). For acceptability, agomelatine, citalopram, escitalopram, fluoxetine, sertraline, and vortioxetine were more tolerable than other antidepressants (range of ORs 0.43–0.77), whereas amitriptyline, clomipramine, duloxetine, fluvoxamine, reboxetine, trazodone, and venlafaxine had the highest dropout rates (1.30–2.32). 46 (9%) of 522 trials were rated as high risk of bias, 380 (73%) trials as moderate, and 96 (18%) as low; and the certainty of evidence was moderate to very low.
Grove 2018	Global	Systematic review and meta-analysis	Pregnant women	Exposure to antidepressants during pregnancy	Not exposed to antidepressants during pregnancy	24 articles	Impaired motor development in children	High quality review	The total pooled results were based on random effects models and revealed a significant association between exposure to antidepressants during pregnancy and overall occurrence of poorer motor outcomes in children (effect size = 0.22; 95% CI, 0.07–0.37) with a moderate degree of heterogeneity (I^2 = 56.6%).

Guan 2018	Global	Systematic review and meta-analysis	Pregnant women	Use of prenatal selective serotonin reuptake inhibitor (SSRI) monotherapy	Nonusers	7 cohort studies	Gestational hypertension and preeclampsia	High quality review	Compared with nonusers, those undertaking prenatal SSRI monotherapy were more likely to develop gestational hypertension or preeclampsia (summarized RR, 1.21; 95% CI, 1.05–1.40, I^2 = 71.3%), gestational hypertension (summarized RR, 1.14; 95% CI, 1.00–1.30; I^2 = 5.7%), and preeclampsia (summarized RR, 1.32; 95% CI, 0.99–1.78, I^2 = 83.3%). In addition, although subgroup analyses, which were stratified by study design, number of cases, geographic location, duration of SSRI monotherapy, registry databases, and adjustment for potential confounders and risk factors, were consistent with the main findings, not all of these showed statistical significance. No evidence of publication bias was detected.
Jiang 2018	Global	Systematic review and meta-analysis	Pregnant mothers	Antidepressant use during pregnancy	No use	6 cohort studies	Attention-deficit/hyperactivity disorder (ADHD) in children	Moderate quality review	The literature search identified six relevant cohort studies with association between antidepressant exposure during pregnancy and the risk of ADHD in children (HR, 1.34; 95% CI, 1.14–1.57). However, the association was not statistically significant when the reference group was mothers with psychiatric disorders not treated during pregnancy (HR, 0.96; 95% CI, 0.76–1.2; n=2 studies). Moreover, prepregnancy exposure to antidepressants was significantly associated with increased risk of ADHD (HR, 1.82; 95% CI, 1.54–2.15; n=3 studies).
Man 2018	Global	Systematic review and meta-analysis	Pregnant women and offspring	Prenatal use of antidepressants	No use	8 studies	Attention-deficit/hyperactivity disorder (ADHD) in children	Moderate quality review	The seven studies included in the meta-analysis comprised a total of 2,886,502 children. The pooled estimates comparing prenatal exposure to non-exposure showed an adjusted rate ratio (aRR) of 1.39 (95% CI, 1.21–1.61). Similarly, an increased risk was found comparing previous antidepressant users and non-users (aRR,1.56; 95% CI, 1.25–1.95). The relationship between maternal psychiatric conditions and ADHD in children yielded an aRR of 1.90 (95% CI, 1.47–2.45). Three studies conducted sibling-matched analyses with aRR of 0.94 (95% CI, 0.75–1.16).

Mitchell 2018	Global	Systematic review	Pregnant women	Antidepressant medications	No medication/ treatment	11 studies	Spontaneous abortion, preterm delivery, low birth weight	Critically low quality review	Risk of low birth weight and related outcomes do not differ between antidepressant-treated pregnant women and untreated depressed women. Average gestational lengths tend to be slightly shorter with antidepressant use but it is unclear whether these differences are clinically meaningful or extend to preterm delivery. Very limited research on spontaneous abortion did not allow conclusions to be drawn regarding that outcome. The low number of studies meeting criteria highlights the need for further research to aid in risk-benefit analysis for women considering antidepressant use in pregnancy.
Molyneaux 2018	Global	Systematic review	Pregnant women or women who had given birth in the previous six weeks	Initiation of antidepressants (alone or in combination with another treatment)	Other treatment, placebo or standard care	Two primary study reports with an additional eight secondary publications for the two trials	Onset of postnatal depression, adverse events experienced by the mother, or the fetus/breastfed infant, or both	Moderate quality review	Two trials including a total of 81 participants fulfilled the inclusion criteria for this review. All participants in both studies had a history of postnatal depression and were not taking antidepressant medication at baseline. Both trials were conducted by the same research group. Risk of bias was low or unclear in most domains for both studies. We were unable to perform a meta-analysis due to the small number of studies. One study compared nortriptyline with placebo and did not find any evidence that nortriptyline was effective in preventing postnatal depression. In this study, 23% (6/26) of women who took nortriptyline and 24% (6/25) of women who took placebo experienced postnatal depression (RR, 0.96; 95% CI, 0.36–2.59; very low-quality evidence) in the first 17 weeks postpartum. One woman taking nortriptyline developed mania; and one side effect, constipation, was more common among women taking nortriptyline than those taking placebo. The second study compared sertraline with placebo. In this study, 7% (1/14) of women who took sertraline developed postnatal depression in the first 17 weeks postpartum compared with 50% (4/8) of women who took placebo. It is uncertain whether sertraline reduces the risk of postnatal depression (RR, 0.14; 95% CI, 0.02–1.07; very low-quality evidence). One woman taking sertraline had a hypomanic episode. Two side effects (dizziness and drowsiness) were more common among women taking sertraline than women taking placebo.

Morales 2018	Global	Systematic review and meta-analysis	Pregnant women	Antidepressant exposure	Unexposed	22 studies	Autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD)	High quality review	Variation in confounding adjustment existed between studies. Updated effect estimates for the association between maternal antidepressant exposure during pregnancy vs. all unexposed women remained statistically significant for ASD (adjusted random-effects risk ratio [RaRR], 1.53; 95% CI, 1.31–1.78). Similar significant associations were observed using pre-pregnancy maternal antidepressant exposure (RaRR, 1.48, 95% CI, 1.29–1.71) and paternal antidepressant exposure during pregnancy (1.29; 95% CI, 1.08–1.53), but analyses restricted to using women with a history of affective disorder (1.18; 95% CI, 0.91–1.52) and sibling studies (0.96; 95% CI, 0.65–1.42) were not statistically significant. Corresponding associations for risk of ADHD with exposure were: RaRR, 1.38; 95% CI, 1.13–1.69 (during pregnancy), RaRR, 1.38; 95% CI, 1.14–1.69 (during pre-pregnancy), RaRR 1.71; 95% CI, 1.31–2.23 (paternal exposure), RaRR 0.98, 95% CI 0.77–1.24 (women with a history of affective disorder), and RaRR 0.88, 95% CI 0.70–1.11 (sibling studies).
Nillni 2018	Global	Systematic review	Pregnant and postpartum women	Treatment of depression, anxiety, and trauma-related disorders	One treatment vs another, placebo	78 studies	Treatment efficacy	Low quality review	The majority of studies focused on perinatal depression (n=73). Of the five studies focused on anxiety or trauma-related disorders, only one was a randomized controlled trial (RCT). The most studied treatment was cognitive behavioral therapy (CBT; n=22), followed by interpersonal psychotherapy (IPT; n=13). Other interventions reviewed include other talk therapies (n=5), collaborative care models (n=2), complementary and alternative medicine approaches (n=18), light therapy (n=3), brain stimulation (n = 2), and psychopharmacological interventions (n=13). Eleven studies focused specifically on treatment for low-income and/or minority women. Both CBT and IPT demonstrated a significant benefit over control conditions. However, findings were mixed when these interventions were examined in low income and/or minority samples. There is some support for complementary and alternative medicine approaches (e.g., exercise). Although scarce, SSRIs demonstrated good efficacy when compared to a placebo. However, SSRIs did not outperform another active treatment condition (e.g., CBT).

Prady 2018	Global	Systematic review	Pregnant mothers and offspring	Antidepressant use during pregnancy	No antidepressant use	11 cohort studies	Low birth weight (LBW) and neurodevelopmental and neurobehavioural outcomes for children	Critically low quality review	Four studies reporting a LBW outcome (all with higher risk of bias) and seven reporting a neurodevelopmental outcome (five with higher risk of bias). We found only limited evidence of gestational age-adjusted LBW in exposed children in two studies which had a higher risk of bias and did not control for depressive symptom severity. Only five (7.5%) neurodevelopmental outcomes and one (12.5%) neurobehavioural outcome showed evidence of a statistically significant effect, three out of four were from studies with a higher risk of bias.
Uguz 2018	Global	Systematic review	Pregnant women	Use of antidepressant	One medication vs another	7 studies	Attention-deficit/hyperactivity disorder (ADHD) in children	Critically low quality review	The studies reported that compared with nonusers adjusted risks of ADHD in children were 1.2 to 1.6 for the use of any antidepressant, 0.91 to 1.66 for selective serotonin reuptake inhibitors, 1.1 to 1.4 for selective serotonin-norepinephrine reuptake inhibitors, and 1.1 to 1.8 for tricyclic antidepressants. There was some scientific evidence suggesting a connection between antidepressant use during all trimesters of pregnancy and increased risk of ADHD in children. In addition, the study results suggest that underlying maternal anxiety or depressive disorders may also contribute to increased risk of ADHD.
Zhao 2018	Global	Systematic review and meta-analysis	Pregnant women	Selective serotonin reuptake inhibitors (SSRIs) use	One SSRI vs another	15 articles	Low birth weight (LBW) and small for gestational age (SGA)	High quality review	Articles involved 1,977,446 subjects were identified that tested the relationship between the SSRIs use, LBW and SGA outcomes. Statistical analyses revealed a significant association between SSRIs use and suboptimal fetal growth (RR 1.45; 95% CI, 1.18–1.76, Z=3.62, p=0.00 for SGA; RR, 1.38; 95% CI=1.13–1.69, Z=3.14, p=0.00 for LBW).
Zhou 2018	Global	Systematic review and meta-analysis	Pregnant women	Exposure to antidepressant	No exposure	14 studies	Autism spectrum disorder (ASD) in children	High quality review	Pooled adjusted RR for cohort studies (n=2,839,980) was 1.13 (0.93–1.39) showed a non-significant association; while two studies were potentially missing from the test of publication bias, filled estimates also showed a non-significant association (filled RR, 0.97; 95% CI, 0.79–1.19). Pooled OR was 1.51 (1.15–1.99) for case-control studies (n=117,737) showed a significant association; two studies were potentially missing; however, the filled estimates suggested a non-significant association (filled OR, 1.26; 95% CI, 0.98–1.62). Analyses restricted to sibling studies also showed a non-significant association (RR, 0.99; 95% CI, 0.81–1.22).

Grigoriadis 2014	Global	Systematic review and meta-analysis	Pregnant women	Exposure to antidepressants	No exposure	7 studies	Risk for persistent pulmonary hypertension of the newborn	High quality review	Although exposure to selective serotonin reuptake inhibitors (SSRIs) in early pregnancy was not associated with persistent pulmonary hypertension of the newborn (OR, 1.23; 95% CI, 0.58–2.60; *P*=.58), exposure in late pregnancy was (2.50, 1.32–4.73; *P*=.005). Effects were not significant for any of the moderator variables examined, including study design, congenital malformations, and meconium aspiration. It was not possible to assess for the effect of caesarean section, body mass index, or preterm delivery. The absolute risk difference for development of persistent pulmonary hypertension of the newborn after exposure to SSRIs in late pregnancy was 2.9 to 3.5 per 1,000 infants; therefore, an estimated 286 to 351 women would need to be treated with an SSRI in late pregnancy to result in an average of one additional case of persistent pulmonary hypertension of the newborn.
McDonagh 2014	Global	Systematic review and meta-analysis	Pregnant or postpartum women	Antidepressant treatment	No treatment	21 studies	Benefits and harms	High quality review	Low-strength evidence suggested neonates of pregnant women with depression taking selective serotonin reuptake inhibitors had higher risk of respiratory distress than did neonates of untreated women (13.9% compared with 7.8%; *P*<.001) but no difference in risk of neonatal convulsions (0.14% compared with 0.11%; *P*=.64) or preterm birth (17% compared with 10%; *P*=.07). Indirect evidence from studies of pregnant women receiving antidepressants for mixed or unreported reasons compared with pregnant women not taking antidepressants (depression status unknown) suggested future research should focus on congenital anomalies and autism spectrum and attention deficit disorders in the child. In postpartum depression, low-strength evidence suggested symptom response was not improved when sertraline was added to psychotherapy or when cognitive-behavioral therapy was added to paroxetine. Evidence was insufficient for other outcomes, including depression symptoms, functional capacity, breastfeeding, and infant and child development. A serious limitation is the lack of study populations of exclusively depressed pregnant and postpartum women.

Grigoriadis 2013	Global	Systematic review and meta-analysis	Pregnant women	Antidepressants	No exposure	12 studies	Immediate neonatal outcomes, occurrence of poor neonatal adaptation syndrome (PNAS)	High quality review	There was a significant association between exposure to antidepressants during pregnancy and overall occurrence of PNAS (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 (Q1=5.4, *P*=.020). No differences were found in any other moderator analyses.
Gartlehner 2011	Global	Systematic review and meta-analysis	Adults with major depressive disorder (MDD)	Second-generation antidepressants	No use	234 studies	Benefits and harms	High quality review	No clinically relevant differences inefficacy or effectiveness were detected for the treatment of acute, continuation, and maintenance phases of MDD. No differences in efficacy were seen in patients with accompanying symptoms or in subgroups based on age, sex, ethnicity, or comorbid conditions. Individual drugs differed in onset of action, adverse events, and some measures of health-related quality of life.
Gartlehner 2011	Global	Systematic review and meta-analysis	Adults	Second-generation antidepressants	Comparisons between types of antidepressants	248 studies	Benefits and harms	High quality review	From a total of 3,722 citations, 248 studies of good or fair quality were identified. Overall, no substantial differences in efficacy could be detected among second-generation antidepressants for the treatment of acute-phase MDD. Statistically significant differences in response rates between some drugs are small and likely not clinically relevant. No differences in efficacy were apparent in patients with accompanying symptoms or in subgroups based on age, sex, ethnicity, or comorbidities, although evidence within these subpopulations was limited. Differences exist in the incidence of specific adverse events and the onset of action. Venlafaxine leads to higher rates of nausea and vomiting, sertraline to higher rates of diarrhea, and mirtazapine to higher rates of weight gain than comparator drugs. Bupropion causes lower rates of sexual dysfunction than other antidepressants. The evidence is insufficient to draw conclusions about the comparative efficacy and effectiveness for the treatment of dysthymia and subsyndromal depression.

Li 2020	United States	Randomized controlled trial	Postpartum women	Transdermal 17β-estradiol (100 mcg/day)	Placebo patch	12 women	Treatment response and remission	High risk of bias (study terminated)	By week 6, 5 women receiving TE responded to treatment and 4 showed symptom remission, compared to 2 responders and 1 remitter in the placebo group. This difference was not significant (p=0.24). In a mixed-model of BDI ratings, TE was associated with a 9.2-point decrease at 3 weeks (95% CI − 19.5 to + 1.0, p = 0.074) and a 10.5-point decrease at 6 weeks (95% CI − 21.0–0.0, p = 0.049) compared to placebo, though these differences did not survive multiple comparisons correction. Analogous effects were found for HAM-D but not EPDS scores. Interestingly, no significant difference in plasma estradiol levels existed between groups. We were unable to demonstrate a significant therapeutic benefit of TE compared with placebo in PPD. Although limited by under-recruitment and loss to follow-up, our results suggest TE is a feasible option for outpatient PPD management, with preliminary evidence (based on secondary outcomes) for efficacy.
Molenaar 2020	Netherlands	Randomized controlled trial	Pregnant and postpartum women	Preventive Cognitive Therapy (PCT) and discontinuation of antidepressants	Continuation of antidepressants	44 women	Postnatal depression, anxiety, depression, relapse	High risk of bias	Six women (13.6%) experienced a recurrence of depression during study participation, 3 in the GO group (15.0%) and 3 in the STOP group (12.5%; OR, 1.24; 95% CI, 0.22–6.92; *P*=.58). Overall mean time to relapse from baseline (T0) was 143 days (STOP: 101 days, GO: 185 days). The log–rank test showed no statistically significant difference in time to recurrence (*P*=.93). We observed no differences in mood symptoms between the two groups over time.
O'Hara 2019	United States	Randomized controlled trial	Women experiencing a major depressive episode in the first year postpartum	Interpersonal Psychotherapy (IPT), sertraline-clinical management (CM)	Pill placebo-CM	162 women	Depression and social adjustment	High risk of bias	There was no significant effect for treatment condition associated with the primary outcome measure, the HamD-17, but there was a significant effect for sertraline-CM relative to the IPT and placebo conditions over the duration of the trial based on the General Depression scale of the Inventory of Depression and Anxiety Symptoms. There was a main effect for time in that study subjects across all three conditions showed significant improvement for the duration of the trial.

Vigod 2019	Canada	Randomized controlled trial	Pregnant women	Online patient decision aid (PDA) about antidepressant use in pregnancy	Control condition that guided participants to publicly available resources for advice	96 women	Feasibility	High risk of bias	About 88.9% of eligible participants consented to participate. Women's views of the tool were positive; 88.7% of participants provided follow-up data. At follow-up, mean DCS score had decreased by 19.9 points in the PDA group versus 13.3 in controls (adjusted mean difference, MD, 7.01; 95% CI, −14.3 to 0.30). In the nonspecialist setting, DCS scores decreased more for PDA users (25.5 points) than controls (10.5 points; adjusted MD −15.1; 95% CI, −25.6 to −4.55); the MD was negligible in the specialist setting.
Vigod 2019	Canada	Randomized controlled trial	Pregnant women	Transcranial direct current stimulation (tDCS)	Sham-control	20 women	Feasibility, acceptability, and protocol adherence	Low risk of bias	Of 20 women randomized, 16 completed treatment and provided data (124 tDCS, 122 sham sessions). Views of treatment were positive with no serious adverse events. Post-treatment estimated marginal mean MADRS scores were 11.8 (standard error, SE 2.66) for tDCS and 15.4 (SE 2.51) for sham (p=0.34). At 4 weeks postpartum, 75.0% of tDCS women were remitted versus 12.5% sham-control (p=0.04).

Meltzer-Brody 2018	United States	Randomized controlled trial	Postpartum women	Single intravenous injection of either brexanolone 90 µg/kg per h (BRX90), brexanolone 60 µg/kg per h (BRX60)	Matching placebo	138 women	Depression score	Low risk of bias	In study 1, at 60 h, the least-squares (LS) mean reduction in HAM-D total score from baseline was 19·5 points (SE 1·2) in the BRX60 group and 17·7 points (1·2) in the BRX90 group compared with 14·0 points (1·1) in the placebo group (difference –5·5 [95% CI –8·8 to –2·2], p=0·0013 for the BRX60 group; –3·7 [95% CI –6·9 to –0·5], p=0·0252 for the BRX90 group). In study 2, at 60 h, the LS mean reduction in HAM-D total score from baseline was 14·6 points (SE 0·8) in the BRX90 group compared with 12·1 points (SE 0·8) for the placebo group (difference –2·5 [95% CI –4·5 to –0·5], p=0·0160). In study 1, 19 patients in the BRX60 group and 22 patients in the BRX90 group had adverse events compared with 22 patients in the placebo group. In study 2, 25 patients in the BRX90 group had adverse events compared with 24 patients in the placebo group. The most common treatment emergent adverse events in the brexanolone groups were headache (n=7 BRX60 group and n=6 BRX90 group vs n=7 placebo group for study 1; n=9 BRX90 group vs n=6 placebo group for study 2), dizziness (n=6 BRX60 group and n=6 BRX90 group vs n=1 placebo group for study 1; n=5 BRX90 group vs n=4 placebo group for study 2), and somnolence (n=7 BRX60 group and n=2 BRX90 group vs n=3 placebo group for study 1; n=4 BRX90 group vs n=2 placebo group for study 2). In study 1, one patient in the BRX60 group had two serious adverse events (suicidal ideation and intentional overdose attempt during follow-up). In study 2, one patient in the BRX90 group had two serious adverse events (altered state of consciousness and syncope), which were considered to be treatment related.
Hantsoo 2014	United States	Randomized controlled trial	Pregnant women with depression onset within 3 months of delivery	Selective serotonin reuptake inhibitor (SSRI) sertraline 50 mg	Placebo	38 women	Hamilton Depression Rating Scale (HAM-D) and Clinical Global Impressions (CGI) scores, rats of response and remission	Low risk of bias	Sertraline produced a significantly greater response rate (59%) than placebo (26%) and a more than 2-fold increased remission rate (53% versus 21%). Mixed models did not reveal significant group by time effects, although in the subset of women who met DSM-IV criteria, there was a statistically significant group by time effect for the HAM-D, Hamilton Anxiety Rating Scale (HAM-A) and CGI.

Epperson 2023	United States	Pooled analysis of 3 RCTs	Adults with postpartum depression	60-h infusion of brexanolone 90 ug/kg/h (BRX90)	Placebo	3 randomized, placebo controlled clinical trials	Change from baseline in Hamilton Rating Scale for Depression (HAMD-17) total score, HAMD-17 anxiety/somatization and insomnia subscales, and Clinical Global Impression of Improvement (GCI-I) scale	Moderate risk of bias	Patients receiving BRX90 (n=102) versus placebo (n=107) achieved a more rapid HAMD-17 response (median, 24 versus 36 h; p=.0265), with an Hour-60 cumulative response rate of 81.4% versus 67.3%; results were similar for time to CGI-I response (median, 24 versus 36 hours; p=.0058), with an Hour-60 cumulative response rate of 81.4% versus 61.7%. CFB in HAMD-17 Anxiety/Somatization and Insomnia subscales also favored BRX90 versus placebo, starting at Hour 24 through day 30 (all p<.05), and response rates for both subscales were higher with BRX90.
Fay 2021	United States	Prospective	Pregnant women to postpartum	Chronic bupropion (BUP) use	Quality control	8 women	Steady-state plasma concentrations of BUP and its metabolites between pregnancy and postpartum	Moderate risk of bias	No significant changes were observed in the steady-state plasma concentrations, metabolite to parent ratios, formation clearances, or renal clearance of any of the compounds during pregnancy when compared to postpartum. The umbilical cord venous plasma concentrations of BUP and its metabolites were 30-60% lower than maternal plasma concentrations.
Liu 2022	Denmark	Cohort	Pregnant women	Continuation of antidepressants throughout pregnancy	Discontinuation of antidepressants prior to, or during, pregnancy	23,189 women	Psychiatric emergency	Moderate risk of bias	Psychiatric emergencies were observed in 76 women who discontinued antidepressants before pregnancy and 91 women who continued. There was no evidence of higher risk of psychiatric emergency among women who discontinued antidepressants before pregnancy (cumulative incidence: 2.9%; 95% CI, 2.3%–3.6% for discontinuation versus 3.4%, 95% CI: 2.8% to 4.2% for continuation; HR, 0.84, 95% CI: 0.61 to 1.16, p = 0.298). Overall, 202 women who discontinued antidepressants during pregnancy and 156 who continued had psychiatric emergencies (cumulative incidence: 5.0%, 95% CI, 4.2%–5.9% versus 3.7%, 95% CI, 3.1%–4.5%). Antidepressant discontinuation during pregnancy was associated with increased risk of psychiatric emergency (HR, 1.25, 95% CI, 1.00–1.55, p=.048). Study limitations include lack of information on indications for antidepressant treatment and reasons for discontinuing antidepressants.

Parpinel 2022	Italy	Cohort	Pregnant women	Untreated depressive disorders or pharmacological therapy	Healthy control	481 women	Age, parity, smoking habit body mass index (BMI), type of depressive disorder, type of psycho-pharmacological treatment, gestational age at delivery, induction of labor, mode of delivery, neonatal weight and Apgar score 5 min after birth	Moderate risk of bias	The women in DG (depressed group) showed higher rates of cesarean section, preterm delivery, induction of labor and SGA babies, and low neonatal weights and 5-min Apgar scores, compared to the untreated patients. Those treated with psychotropic drugs showed lower rates of cesarean section, but lower 5-min Apgar scores, compared to those who were untreated. However, after controlling for confounding variables, the 5-min Apgar scores were linearly associated with neonatal weight and not with the use of psychotropic treatment. No significant differences were observed between the treated and untreated women, regarding the rates of preterm delivery, induction of labor, SGA and low neonatal weight.
Ankarfeldt 2022	Denmark and Sweden	Cohort	Pregnant women	Duloxetine-exposure during early (0–140 days) and late pregnancy (141 days to delivery)	Duloxetine-nonexposure; SSRI-exposure; venlafaxine-exposure; and duloxetine exposure prior to pregnancy	2,083,467 pregnancies	Preterm birth, and small for gestational age	Moderate risk of bias	For small for gestational age, no increased risk was seen for duloxetine across comparators. In the early and late exposure windows, propensity score-matched odds ratios for small for gestational age ranged between 0.64 (95% CI, 0.44–0.95) and 1.48 (95% CI, 0.85–2.57). For preterm birth, the findings differed across comparators and exposure-time windows but trended towards an increased risk for duloxetine-exposed when compared with duloxetine-non-exposed, selective serotonin reuptake inhibitor-exposed, and duloxetine discontinuers in both early exposure and late exposure. The odds ratios ranged between 1.17 and 2.04, of which some did not reach statistical significance. No clear association was observed when compared with venlafaxine exposed, 0.91 (95% CI, 0.73–1.14) for early exposure and 1.26 (95% CI, 0.86–1.86) for late exposure. Most preterm births (79.2%) occurred in weeks 33–36 of gestation.

Stika 2022	United States	Prospective cohort	Pregnant people with MDD to 8 weeks postpartum	Sertraline	Different dosage of sertraline	47 participants	Plasma sertraline and desmethylsertraline concentrations 24 hours post-dose every 4 weeks	Moderate risk of bias	Overall mean sertraline C/D ratios were decreased at study onset and remained consistently low until after delivery. During the last 4weeks of pregnancy the mean sertraline C/D ratio 0.25 (95% CI, 0.19–0.3) ng/mL/dose (mg/day), was smaller than the mean ratio at ≥ 8weeks after delivery, 0.32 (95% CI, 0.27–0.37) ng/mL/dose (mg/day), a 22% difference. Mean sertraline/desmethylsertraline ratios were highest after birth, which confirmed increased sertraline elimination during pregnancy. Sertraline C/D ratios in participants with functional CYP2C19 activity did not change significantly during pregnancy, whereas ratios in participants with poor or intermediate CYP2C19 activity decreased by 51%.
Ankarfeldt 2021A	Denmark and Sweden	Cohort	Pregnant women	Duloxetine-exposure during pregnancy	Duloxetine-nonexposure; SSRI-exposure; venlafaxine-exposure; and duloxetine exposure prior to pregnancy	2,132,163 pregnancies	Risk of major and minor congenital malformations and the risk of stillbirths	Moderate risk of bias	No increased risk for major malformations, minor malformations, or stillbirth was found across comparison groups in adjusted and PS-matched analyses. Duloxetine-exposed versus duloxetine-nonexposed PS-matched analyses showed OR, 0.98 (95% CI, 0.74–1.30; p=.909) for major malformations, OR, 1.09 (95% CI, 0.82–1.45; p=.570) for minor malformation, and 1.18 (95% CI, 0.43–3.19; p=.749) for stillbirths.
Ankarfeldt 2021B	Denmark	Cohort	Pregnant women	Duloxetine-exposure during pregnancy	Duloxetine-nonexposure; SSRI-exposure; venlafaxine-exposure; and duloxetine exposure prior to pregnancy	1,020,288 pregnancies	Risk of Spontaneous and Elective Abortion	Moderate risk of bias	Duloxetine exposed women had an increased HR for spontaneous abortions compared with SSRI-exposed women: propensity score matched HR, 1.25 (95% CI, 1.00–1.57). No increased hazard was observed for duloxetine-exposed women compared with duloxetine non-exposed: 1.08 (95% CI, 0.89–1.31); venlafaxine-exposed: 1.08 (95% CI, 0.82–1.41); and duloxetine discontinuers: 0.99 (95% CI, 0.76–1.30). An increased HR of elective abortions was observed in duloxetine-exposed women compared to duloxetine non-exposed: 1.41 (95% CI, 1.25–1.59); SSRI-exposed: 1.32 (95% CI, 1.15–1.51); and duloxetine discontinuers: 1.46 (95% CI, 1.23–1.75), but not to venlafaxine-exposed women: 1.09 (95% CI, 0.93–1.27)

Galbally 2021	Australia	Cohort	Pregnant women from early pregnancy to 12 months postpartum	Untreated and current depressed, antidepressant use	Healthy control	442 women	Diet and nutritional intake	Moderate risk of bias	This study found that those women with untreated, current depression in pregnancy had higher unhealthy takeaway food intake across the perinatal period compared to those taking antidepressant medication or healthy control women, albeit the overall effects were small and the clinical significance unknown. Higher depressive symptoms in the postpartum were also associated with higher takeaway intake. There was no difference in fruit and vegetable intake between the three groups and intake was highest for all women late in pregnancy and declined in the postpartum period. In all, women's takeaway food intake increased from pregnancy across the postpartum.
Gerbasi 2021	United States	Post hoc analyses	Postpartum women	Brexanolone injection	Placebo	127 patients	Least-squares mean difference in the 17-item Hamilton Rating Scale for Depression (HAMD-17) total score from baseline to 60 h	Moderate risk of bias	Baseline health-related quality of life (HRQoL) of patients with postpartum depression (PPD) was significantly below normative values. Day 7 and day 30 clinical response were associated with large and statistically significant improvements in HRQoL, greater likelihood of meeting SF-36-v2 Health Survey (SF-36v2) responder definitions, and reduced impairment. MCS levels corresponding to those observed in clinical responders were linked to lower HRU and productivity loss relative to non-responders.
Gerbasi 2021	United States	Post hoc analysis	Postpartum women	Brexanolone (BRX) injection	Placebo (PBO)	209 patients	Least-squares mean difference in the 17-item Hamilton Rating Scale for Depression (HAMD-17) total score from baseline to 60 h, Clinical Global Impression of Improvement (CGI-I) response	Moderate risk of bias	The average HAMD-17 MID estimate was -2.1; the least squared mean difference between BRX and PBO exceeded this at hour 60 and day 30. Minimal, moderate, and large MCTs were estimated to be -9, -15, and -20 points, respectively. Significantly more BRX-treated than PBO-treated patients achieved minimal, moderate, and large change (all ps < 0.05) at hour 60 and large meaningful response at day 30 (p < 0.05). BRX-treated patients were more likely to sustain HAMD-17 remission and CGI-I response through day 30 versus PBO. NNTs ranged from 4 to 8, with NNH of 97.

Heinonen 2021	Sweden	Analysis of RCT	Pregnant women with moderate untreated depression	Treatment with sertraline	Placebo	9 mothers and 7 infants	Plasma concentrations, neonatal outcomes	Moderate risk of bias	Median dose-adjusted sertraline concentration in second trimester was 0.15 (ng/mL)/(mg/day), in third trimester and at delivery 0.19 and 1-month postpartum 0.25, with a 67% relative difference between second trimester and postpartum. The interindividual variation was 10-fold. Median concentrations in the infants were 33% and 25% of their mothers', measured in cord blood, and infant plasma, respectively. Only mild and transient adverse effects were seen on the infants.
Rommel 2021	Netherlands	Population-based cohort	Pregnant women and offspring	Antidepressant continuation (use before and during pregnancy)	Antidepressant discontinuation (use before but not during pregnancy)	42,988 singletons	Affective disorders diagnosis in the offspring	Serious risk of bias	To consider confounding by shared environmental or genetic factors, we investigated the effect of paternal antidepressant use on the risk for affective disorders. Affective disorders were diagnosed in 1,538 children. Children whose mothers continued antidepressants during pregnancy had an increased risk of affective disorders (HR, 1.20; 95% CI, 1.08–1.34), compared with children whose mothers discontinued before pregnancy. Similarly, continued paternal antidepressant use during pregnancy was associated with higher risk for offspring affective disorders (HR, 1.29; 95% CI, 1.12–1.49), compared to discontinuation. Based on data from primary and secondary/tertiary care, maternal antidepressant use during pregnancy was associated with an increased risk of affective disorders in the offspring.
Sujan 2021	Sweden	Population-based cohort	Pregnant women	Independent or combined prescriptions of the two medications (opioid analgesic and selective serotonin reuptake inhibitor)	No filled prescriptions for either medication	688,914 births	Preterm birth, small-for-gestational-age	Serious risk of bias	After adjusting for confounders, preterm birth risk was higher among women with opioid analgesic prescriptions only (5.9%; RR, 1.27; 95% CI, 1.22–1.33), SSRIs only (6.2%; RR, 1.34; 95% CI, 1.27–1.42), and both medications (7.8%; RR, 1.70; 95% CI, 1.47–1.96) compared with unexposed women (4.6%). The interaction between the medications on preterm birth was small (risk difference [RD], 0.4%; 95% CI, −0.8%, 1.6%); relative excess risk due to interaction [RERI], 0.09; 95% CI, −0.17, 0.34; RR 1.00; 95% CI, 0.85–1.17). For small for gestational age, risk was approximately 2% across all groups, and there was no interaction between the medications (RD, 0.3%; 95% CI, −0.4%–1.1%); RERI, 0.15; 95% CI, −0.16, 0.47; RR, 1.15; 95% CI, 0.87–1.52).

Wolgast 2021	Sweden	Population-based cohort	Pregnant women	Women diagnosed with MDD and who had redeemed an antidepressant one year before becoming pregnant ("before pregnancy") and women who were diagnosed with MDD and who had redeemed an antidepressant both before and during pregnancy ("before and during pregnancy")	Women who had neither been diagnosed with MDD nor been prescribed antidepressants (population controls)	262,329 women	Obstetric outcomes (hyperemesis, preeclampsia, induced labour, use of epidural analgesia (EDA), mode of childbirth), neonatal outcomes (gestational age, birthweight, small for gestational age, APGAR, admission to NICU)	Serious risk of bias	In comparison to population controls, the "before pregnancy" and the "before and during pregnancy" groups had increased likelihoods of operative childbirth (aOR, 1.19; 95% CI, 1.12–1.27; aOR, 1.38; 95% CI, 1.28–1.48 respectively), and with an increased likelihood for the child being admitted to a neonatal intensive care unit (NICU) (aOR, 1.51; 95% CI, 1.17–1.95; aOR, 1.55; 95% CI, 1.14–2.11). Children born to mothers in the "before and during pregnancy" group had an increased likelihood of preterm birth (aOR, 1.72; 95% CI, 1.52–1.95,), while children to mothers in the "before pregnancy" group had an increased likelihood of low birthweight (aOR, 1.15; 95% CI, 1.00–1.33) compared to population controls. Women in the "before and during pregnancy" group had an increased likelihood for hyperemesis during pregnancy (aOR, 1.93; 95% CI, 1.60–2.32), having an operative childbirth (aOR, 1.17; 95% CI, 1.06–1.29) or a preterm birth (aOR, 1.53, 95% CI, 1.28–1.81) compared to the "before pregnancy" group.
Anderson 2020	United States	Population-based, multicenter case-control	Mothers and infants	Early pregnancy antidepressant-exposed	No antidepressant exposure	30,630 case mothers of infants with birth defects and 11,478 control mothers	Birth defects	Serious risk of bias	Early pregnancy antidepressant use was reported by 1,562 case mothers (5.1%) and 467 control mothers (4.1%), for whom elevated aORs were observed for individual SSRIs and selected congenital heart defects (CHD) (eg, fluoxetine and anomalous pulmonary venous return: aOR, 2.56; 95% CI, 1.10–5.93; this association was attenuated after partially accounting for underlying conditions: aOR, 1.89; 95% CI, 0.56–6.42). This pattern was observed for many SSRI-CHD combinations. Associations between SSRIs and non-CHD birth defects often persisted or strengthened after partially accounting for underlying conditions (eg, citalopram and diaphragmatic hernia: aOR, 5.11; 95% CI, 1.29–20.24). Venlafaxine had elevated associations with multiple defects that persisted after partially accounting for underlying conditions (eg, anencephaly and craniorachischisis: aOR, 9.14; 95% CI, 1.91–43.83).

Bandoli 2020	United States	Retrospective	Pregnant women	Antidepressant use	Depression and no antidepressant use, anxiety and no antidepressant use	226,932 singleton deliveries	Major cardiac malformations, preterm birth, newborn respiratory distress	Serious risk of bias	From 15,041 (6.6%) pregnancies exposed to an antidepressant, use patterns were best described as (1) low use (~10 mg/day) with first-trimester reduction, (2) low sustained use (~20 mg/day), (3) moderate use (~40 mg/day) with first-trimester reduction, (4) moderate sustained use (~40 mg/day), and (5) high sustained use (~75 mg/day). Moderate sustained use increased the risk of major cardiac malformations, although results included the null when compared with depression or anxiety reference groups. Moderate sustained (aRR, 1.31; 95% CI, 1.16–1.49) and high sustained (aRR, 1.78; 95% CI, 1.48–2.14) trajectories were associated with an increased risk of preterm birth. All 4 trajectories increased the risk of neonatal respiratory distress in a dose-response fashion (aRRs, 1.36; 95% CI, 1.20–1.50) to 2.23 (95% CI, 1.83–2.77).
Brouwer 2020	Netherlands	Experience sampling methodology trial	Pregnant women	“Stop” -group received online preventive cognitive therapy (PCT) and tapered antidepressant medication (ADM)	“Go” -group continued the use of ADM as instructed by their prescribing doctor (care as usual)	19 women	Adverse effects on offspring outcomes	Moderate risk of bias	There were no significant differences in positive and negative affect fluctuations, nor recurrence rates between women receiving PCT while tapering ADM vs. women continuing ADM. We found no association between affect fluctuations, pre-natal depressive symptoms, and birth weight (all p>.05).
Colombo 2020	Italy	Prospective	Pregnant women with Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) diagnoses of affective disorders	Selective serotonin reuptake inhibitors and selective serotonin and noradrenaline reuptake inhibitors (SSRIs/SNRIs) use	One dosage versus another, one medication versus another	55 women	Maternal and neonatal outcomes	Serious risk of bias	The pharmacokinetic data were more stable for sertraline, citalopram, and escitalopram compared to other molecules (p=.009). The occurrence of postnatal adaptation syndrome onset was associated with higher plasma levels for sertraline (median at delivery: 16.7 versus 10.5 ng/ml), but not for fluoxetine and venlafaxine. Finally, the subgroup within range plasma concentrations had less blood loss than the below range subgroup (p=0.030).

Cox 2020	United States	Exploratory	Pregnant women with postpartum depression	10 Hz repetitive transcranial magnetic stimulation (rTMS) over the left dorsolateral prefrontal cortex (DLPFC)	-	6 women	Scores on psychiatric rating scales (BDI, EPDS, STATI), cognitive assessments (MMSE, Trails B, List Generation) and breastfeeding practices	Serious risk of bias	Average BDI, EPDS, and STAI scores declined over the 4-week duration of rTMS treatment. Of the six patients, four achieved remission as assessed by EPDS and one achieved remission and two responded as assessed by BDI. Mean BDI and EPDS scores at 3- and 6-months follow-up remained below levels at study entry. No evidence of cognitive changes or breastfeeding disruptions.
Edvinsson 2020	Sweden	Cohort	Pregnant women	Depressive symptoms, SSRI treatment	Control	45 women	Glucocorticoid receptor levels and activation	Moderate risk of bias	There were no differences in levels of the glucocorticoid receptor or activity between groups (control, depressive symptoms, and SSRI treatment; n=45). Similarly, there was no difference in placental glucocorticoid receptor levels or activity dependent upon foetal sex.
Eldar-Lissai 2020	United States	Cost-effectiveness analysis	Mothers	Brexanolone (BRX) treatment	Selective serotonin reuptake inhibitors (SSRIs) treatment	-	Costs, health (quality adjusted life-years [QALYs]	Serious risk of bias	The incremental cost-effectiveness ratio for BRX versus SSRIs was $106,662 per QALY gained over an 11-year time horizon. Drug and administration costs for BRX averaged $38,501, compared with $25 for SSRIs over the studied time horizon. Maternal total direct medical costs averaged $65,908 in the BRX arm, compared with $73,653 in the SSRI arm. BRX-treated women averaged 6.230 QALYs compared with 5.979 QALYs for the SSRI arm. Adding partner costs and utilities in a sensitivity analysis further favored BRX. Results were sensitive to the severity of PPD at baseline and the model time horizon. Probabilistic sensitivity analyses indicated that BRX was cost-effective at the $150,000-per-QALY threshold with 58% probability.
Galbally 2020	Australia	Cohort	Pregnant women	Depressed women taking antidepressants in pregnancy, women with diagnosed depression not taking an antidepressant	Control	485 women	Maternal, parenting and infant outcomes	Serious risk of bias	This study found, for women taking SNRI antidepressant medication there was an elevated rate of pregnancy hypertension. Infants exposed to antidepressants had lower Apgar scores and higher birth weight and this was not associated with dose or class of antidepressant. In contrast, women with higher depressive symptoms had lower maternal antenatal attachment and higher postpartum parenting stress. Both women with depression and those taking antidepressants were less likely to initiate breastfeeding. On the Ages and Stages Questionnaire, there was a significant difference in communication skills in SSRI antidepressant exposed infants at 12 months.

Galbally 2020	Australia	Prospective cohort	Pregnant women	Women with untreated depression in pregnancy, women treated with antidepressants	Control	195 women and children	Child sensorimotor, visuospatial development	Moderate risk of bias	Our study found for sensorimotor development, visuomotor precision completion time was associated with better performance for antidepressant exposed children compared to those with mothers with untreated depression. Yet another measure of sensorimotor development, motor manual sequences, was poorer in those exposed to antidepressants. One subtest for visuospatial processing, block construction, was associated with poorer performance in antidepressant-exposed children who had poor neonatal adaptation and those exposed to a higher dose of antidepressant.
George 2020	United States	Physiologically based pharmacokinetic modeling	Pregnant and nonpregnant women	Sertraline	-	8 subjects in second trimester, 6 subjects in third trimester, 11 non-pregnant subjects	Evaluation of model	Serious risk of bias	The model predicted the pharmacokinetic parameters from a clinical study with eight subjects for the second trimester and six subjects for the third trimester. Based on the model, gestational-dependent changes in physiology and metabolism account for increased clearance of sertraline (up to 143% at 40 weeks gestational age), potentially leading to under-dosing of pregnant women when nonpregnancy doses are used. The PBPK model was converted to a prototype web-based interactive dosing tool to demonstrate how the output of a PBPK model may translate into optimal sertraline dosing in pregnancy.

Huybrechts 2020	United States	Cohort	Pregnant women and their infants	Duloxetine exposure	No exposure to duloxetine, exposure to selective serotonin reuptake inhibitors, exposure to venlafaxine, and exposure to duloxetine before but not during pregnancy	Cohort sizes ranged from 1.3 to 4.1 million, depending on the outcome	Congenital malformations overall, cardiac malformations, preterm birth, small for gestational age infant, pre-eclampsia, and postpartum hemorrhage	Moderate risk of bias	The base risk per 1,000 unexposed women was 36.6 (95% CI, 36.3–36.9) for congenital malformations overall, 13.7 (13.5–13.9) for cardiovascular malformations, 107.8 (107.3–108.3) for preterm birth, 20.4 (20.1–20.6) for small for gestational age infant, 33.6 (33.3–33.9) for pre-eclampsia, and 23.3 (23.1–23.4) for postpartum hemorrhage. After adjustment for measured potential confounding variables, all baseline characteristics were well balanced for all exposure contrasts. In propensity score adjusted analyses versus unexposed pregnancies, the RR was 1.11 (95% CI, 0.93–1.33) for congenital malformations overall and 1.29 (0.99–1.68) for cardiovascular malformations. For preterm birth, the RR was 1.01 (0.92–1.10) for early exposure and 1.19 (1.04–1.37) for late exposure. For small for gestational age infants the RRs were 1.14 (0.92–1.41) and 1.20 (0.83–1.72) for early and late pregnancy exposure, respectively, and for pre-eclampsia they were 1.12 (0.96–1.31) and 1.04 (0.80–1.35). The RR for postpartum hemorrhage was 1.53 (1.08–2.18). Results from sensitivity analyses were generally consistent with the findings from the main analyses.
Molenaar 2020	Netherlands	Prospective cohort	Pregnant women	Serotonin reuptake inhibitor use	-	145 women	Birth weight, gestational age at birth, and being small for gestational age	Serious risk of bias	Maternal SRI dose at 36 weeks of gestation was significantly associated with birth weight (adjusted ß = -180.7, 95%CI -301.1;-60.2, p-value < 0.01) as was mean SRI standardized dose during total pregnancy (adjusted ß = -187.3, 95%CI -322.0;-52.6, p-value < 0.01). No significant associations between maternal SRI dose and gestational age or being small for gestational age were observed.
Park 2020	Canada	Population-based retrospective cohort	Pregnant women and offspring	Exposed to antidepressants, antidepressants use throughout pregnancy	Unexposed, discontinued treatment	94,712 children	Child development	Moderate risk of bias	In all, 3.87% (n=3,661) of children in the overall study population were prenatally exposed to antidepressants. In both analyses, we report increased odds for lower levels of physical independence (HDPS: OR, 1.14; 95% CI, 1.00–1.30; continuers/discontinuers: OR, 1.14; 95% CI, 0.99–1.32), and higher levels of anxious behaviors (HDPS: OR, 1.30; 95% CI, 1.01–1.66; continuers/ discontinuers: OR, 1.32; 95% CI, 1.01–1.72) associated with antidepressant use in pregnancy. All other relationships were not significant using these methods.

Paulzen 2020	Germany	Ongoing observational	Pregnant women and newborns	Venlafaxine (VEN) extended release formulation	-	9 mother-infant pairs	Active moiety (AM) as the concentration of VEN + O-desmethylvenlafaxine (ODVEN)	Serious risk of bias	Median daily dosage of venlafaxine was 75 mg (range 37.5–225 mg). There were no significant correlations between daily dose, maternal serum, umbilical cord blood and amniotic fluid concentrations. Median penetration ratio into amniotic fluid was 2.5 (range 0.56–4.48). Median penetration ratio into fetal circulation was 1.05 (range 0.62–2.08). Median concentration of AM was 223.8 ng/mL, range 33.9–338.0 ng/mL (maternal serum), 789.0 ng/mL, range 309-1052.5 ng/mL (amniotic fluid) and 291.0 ng/mL, range 21.1–448.4 ng/mL (cord blood).
Shah 2020	Canada	Prospective comparative cohort	Pregnant women and neonates	Exposed to antidepressants	Unexposed	120 neonates	Gestational age, birth weight, hypoglycemia	Moderate risk of bias	Mean gestational ages were 39 versus 40 weeks (p<.01) and birthweights were 3,250 versus 3,360 g (p=.08) for antidepressant-exposed vs. -unexposed neonates. There were no significant differences between groups in odds of hypoglycemia (4/59: exposed versus 2/61: unexposed; aRR, 1.73; 95% CI, 0.37–8.92) or mean blood glucose levels.
Singal 2020	Canada	Population-based cohort	Mothers who had a mood or anxiety disorder diagnosis between 90 days before pregnancy their children	SSRI or SNRI dispensations during pregnancy	No SSRI or SNRI use	3,048 children	Child developmental health	Moderate risk of bias	21.43% of children in the exposed group were assessed as vulnerable on 2 or more domains versus 16.16% of children in the unexposed group (aOR, 1.43; 95% CI, 1.08–1.90). Children in the exposed group also had a significant risk of being vulnerable in language and/or cognition (aOR, 1.40; 95%, 1.03–1.90).
Sjaarda 2020	United States	Prospective cohort	Women without uncontrolled depression/ anxiety	Exposed to SSRIs while trying to conceive	Unexposed	1,228 women	Fecundability, pregnancy loss	Moderate risk of bias	SSRI exposure was associated with 24% reduced fecundability, and accordingly, a nonsignificant 9% lower live birth incidence, with significantly lower live birth in fluoxetine-exposed women. SSRI exposure was not associated with subsequent pregnancy loss, whether exposure was before pregnancy or at 0, 4, or 8 weeks of gestation, although estimates varied by specific SSRI drug.

Skalkidou 2020	Sweden	Cohort	Pregnant women	Selective serotonin reuptake inhibitor (SSRI) use	No SSRI treatment	31,159 women	Postpartum haemorrhage	Serious risk of bias	Postpartum haemorrhage prevalence was 7.0% among healthy women, 7.6% among women with prior or current psychiatric illness and 9.1% among women treated with SSRI. The unadjusted odds for PPH among women with prior or current psychiatric illness and women on SSRI treatment were increased by 9 and 34%, respectively, compared with healthy unmedicated women without a history of psychiatric illness (OR, 1.09; 95% CI, 1.04–1.14 and OR, 1.34; 95% CI, 1.24–1.44, respectively). The estimates remained unchanged after adjustment for several confounders (such as maternal age, body mass index [BMI], parity, prior caesarean section, smoking, occupation and country of birth) and potential covariates (such as delivery mode, polyhydramnion, preterm delivery, labour dystocia and infant birthweight >4,000 g).
Smearman 2020	United States	Prospective, longitudinal cohort	Mother-child dyads	Serotonin reuptake inhibitor (SRIs) use during pregnancy	Medication-free throughout pregnancy	178 dyads	ASD symptoms and pragmatic language abilities in children	Moderate risk of bias	For the online questionnaire follow-up, no differences emerged between mothers and children who (a) were not eligible for the follow-up, (b) were eligible but did not participate, and (c) were eligible and did participate. For the in-depth laboratory follow-up, children who were eligible and participated had higher expressive language scores than children in the other groups; no other group differences were statistically significant. Among children who were or were not exposed to SRIs, there were no differences on any of the participant demographics examined. As noted above, SRI exposure was significantly associated with higher prenatal maternal depression scores in the questionnaire follow-up, but not in the in-depth laboratory study. In both follow-ups, sertraline and fluoxetine were the most common SRIs used during pregnancy.
van der Veere 2020	Netherlands	Prospective cohort	Pregnant women and their children	Exposure to selective serotonin reuptake inhibitors (SSRIs)	No exposure	111 women and 102 children	Cognitive and motor development and emotional and behavioral problems of children	Moderate risk of bias	SSRI-exposed children had lower scaled scores on cognition and gross motor development than non-SSRI-exposed children: 9.0 ± 1.4 (mean ± SD) versus 9.9 ± 1.7 [P = 0.004], and 7.9 ± 2.2 versus 9.0 ± 2.5 [P = 0.01], respectively. Differences remained significant after adjusting for maternal depression and anxiety and other confounders in various models (mean difference for cognition 0.8 to 0.9 points, for gross motor 1.1 to 1.2 points). Only after adjusting for severity of maternal anxiety, differences in gross motor scores lost significance.

Wall-Wieler 2020	United States	Cohort	Pregnant women	Prepregnancy depression diagnosis, use of antidepressants	No prepregnancy depression diagnosis, no use of antidepressants	1,703,245 pregnancies	Ectopic pregnancy	Serious risk of bias	106,788 (6.3%) women had a prepregnancy depression diagnosis. Among women with a depression diagnosis, 40,287 (37.7%) had an active antidepressant prescription around beginning of pregnacy; the IPT-weighted risk of ectopic pregnancy was similar among women who did and did not fill an antidepressant prescription around beginning of pregnancy (IPT weighted RR, 1.01; 95% CI, 0.93–1.10). Overall, the risk of ectopic pregnancy was higher among women who had a prepregnancy depression diagnosis than women who did not have a prepregnancy depression diagnosis (IPT-weighted RR, 1.09; 95% CI, 1.04–1.15).
Wartko 2020	United States	Retrospective cohort	Pregnant women	Continuation of antidepressant use during pregnancy	Discontinuation of antidepressant use during pregnancy	2,887 births	Maternal gestational weight gain	Serious risk of bias	1,689 (59%) births were to women who continued antidepressants in pregnancy and 1,198 (42%) were to discontinuers. After accounting for confounding, continuers had similar weight gain to those who discontinued (mean difference: 1.3 lbs, 95% CI, -0.1–2.8 lbs) and similar risks of inadequate and excessive GWG (RR, 0.95; 95% CI, 0.80–1.14 and RR, 1.06; 95% CI, 0.98–1.14, respectively). Findings were comparable for specific antidepressants and trimesters of exposure.
Weisskopf 2020	Switzerland and France	Prospective cohort	Pregnant and breastfeeding women	Selective serotonin reuptake inhibitors (SSRI) (escitalopram or racemic citalopram) use	-	33 patients	Drug concentrations in breast milk, model validation	Serious risk of bias	Mean SCIT clearance was 32.3 L/h with a between-subject variability of 31% (CV%) and apparent volume of distribution was 1,590 L. Poor metabolizers of CYP2C19 showed a significant 51% decrease in SCIT clearance compared to other phenotypes. Both parent drug and metabolite were characterized by a MPR of 1.9, while an increased milk fat content was significantly associated with an increased drug transfer into breast milk (+28% for SCIT and +18% for SDCIT when fat amount passes from 3.1 to 6.2 g/100 62 ml). Simulations suggested that an exclusively breastfed infant would ingest daily through breast milk 3.3% of the weight adjusted maternal SCIT dose on average.
Yamamoto-Sasaki 2020	Japan	Retrospective cohort	Mothers and children	Antidepressant use	No use	53,697 pairs of mothers and children	Congenital anomalies	Moderate risk of bias	No increased risk of total congenital anomalies in children whose mothers used antidepressants of any type during the first trimester of pregnancy was found in the analysis (adjusted analysis with confounders, OR, 0.86; 95% CI, 0.52–1.42). In addition, there was no increased risk of organ specific anomalies in the analysis by type of antidepressant.

Adhikari 2019	Canada	Retrospective cohort	Pregnant women	Antidepressant use	No use of antidepressants, with or without depression	158,486 women	Adverse perinatal outcomes	Serious risk of bias	In total, 9.1% women had depression and 2.5% women received antidepressants during pregnancy. The relative risk of severe neonatal morbidity/ mortality was 1.25 (95% CI, 1.17–1.33) times higher for women with depression alone compared to women without depression. The risk of severe neonatal morbidity/mortality was 1.51 (95% CI, 1.36–1.66) times higher for women who used antidepressants compared to women with depression alone—however, the risk differed between the women with and without a history of antidepressant use. A similar risk pattern was observed for preterm birth and neonatal intensive care unit admission.
Adhikari 2019	Canada	Retrospective cohort	Pregnant women	Antidepressant use	One antidepressant class vs another	1,865 women	Medication adherence and persistence, depression symptoms	Serious risk of bias	During pregnancy, 834 (44.7%; 95% CI, 42.4%–47.0%) women discontinued antidepressants. Among those continuing antidepressants, the overall rate of adherence was 62.6% (95% CI, 59.4%–65.7%). The rate differed significantly by medication class (*P*<.0001), with a rate of 75.1% (95% CI, 68.3%–80.9%) for serotonin-norepinephrine inhibitors, 60.9% (95% CI, 57.2%–64.5%) for selective serotonin reuptake inhibitors, 42.8% (95% CI, 19.9%–69.3%) for nonselective monoamine reuptake inhibitors, and 37.5% (95% CI, 22.5% to 55.4%) for atypical antidepressants. Only, 40.7% (95% CI, 37.5–44.1) of women were persistent with antidepressants for the full pregnancy period—the rate differed significantly by medication class (*P*<.0001).

Berard 2019	United States and Canada	Cohort	Pregnant women	Continued antidepressant use	Discontinued antidepressant use	367 women	Depressive symptoms	Moderate risk of bias	Among participants, 149 did not use antidepressants, 38 used antidepressants at the beginning of pregnancy but discontinued before the end of second-trimester, and 180 used antidepressants continuously throughout pregnancy. Among continued users, 46 modified antidepressant dosage before the end of the second trimester, and 134 did not modify dosage. The majority of antidepressant users (150/218, 68.8%) had mild to moderate depression. Thirteen percent (13%) of women who continued antidepressant use throughout pregnancy without dosage modification remained depressed. Adjusting for potential confounders including maternal depression/anxiety before pregnancy, and compared to non-users, discontinued users were 5.95 times (95% CI, 1.54–23.02), and continued users without dosage modification 4.59 times (95% CI, 1.44–14.64) more at risk of depression in the second-half of pregnancy. Those with dosage modifications were at a similar risk of depression during pregnancy than non-users (aOR, 0.58; 95%CI, 0.06–5.52).
Cardenas 2019	United States	Discovery phase of prospective cohort	Pregnant women	Exposure to antidepressants	No exposure	479 women	Depression and anxiety symptoms	Serious risk of bias	In Project Viva, 2.9% (14/479) pregnant women were prescribed antidepressants, 9.0% (40/445) experienced high pregnancy-related anxiety, and 8.2% (33/402) reported symptoms consistent with depression. Newborns exposed to antidepressants in pregnancy had 7.2% lower DNA methylation (95% CI, − 10.4 to − 4.1; P = 1.03 × 10−8) at cg22159528 located in the gene body of ZNF575, and this association replicated in the Generation R Study (β = − 2.5%; 95% CI, − 4.2 to − 0.7; P = 0.006). In Project Viva, the association persisted in early (β = − 6.2%; 95% CI, − 10.7 to − 1.6) but not mid childhood. We observed cohort-specific associations for maternal anxiety and depression in Project Viva that did not replicate.

Cauli 2019	Italy	Cohort	Pregnant and postpartum women	Multidisciplinary psychosocial intervention	Compared between risk groups (low, high, no risk)	318 women	Depression and anxiety scores	Serious risk of bias	Depressive or anxiety symptoms were found in 91 (28.6%) women, 89 (28.0%) had low risk of PPD and 138 (43.4%) had no risk of PPD. The multidisciplinary psychosocial interventions offered to women with clinical symptoms were well accepted, with an uptake of 76/91 (83.5%). Thirty-three women who did not improve with psychotherapy were offered sertraline or paroxetine as a second-line treatment: 7 accepted and 26 (78.8%) refused. Eleven women already on medication at baseline continued their treatment along with the MPI. The MPI interventions had some positive effects in terms of post-partum recovery, symptom reduction, and in preventing a new onset of depression. Among the 227 non-symptomatic during pregnancy, only 5 (2.2%) developed symptoms in the post-partum period. At 12 months post-partum, 84.6% of women who were symptomatic at 2 months postpartum recovered.
Cohen 2019	Norway	Population-based cohort	Mothers, fathers, and their children	Maternal antidepressant use	Paternal antidepressant use as negative control	70,959 families	Gestational age at birth, child anxiety, continuous Z-score	Moderate risk of bias	Antidepressants were used by 1.1% (n=755) of fathers. Paternal antidepressant use was not associated with gestational age at birth (b=0.63 days, 95% CI, –1.56–0.31) whereas it was positively associated with a child anxiety symptom Z-score and high anxiety symptoms (OR, 1.33; 95% CI, 0.90–1.97) in unadjusted analyses. This association was attenuated when controlling for maternal and paternal history of depression and other measured factors (OR, 1.14; 95% CI, 0.76–1.69).
Corti 2019	Italy	Case-control	Pregnant women	Diagnosis of depression and/or anxiety, treated with SSRIs for the whole pregnancy	No psychiatric diagnosis and no exposure to SSRIs during pregnancy	127 women	Neonatal outcomes	Moderate risk of bias	The population was homogenous for demographic, anthropometric, socio-economic and obstetric variables except for smoking and mean hemoglobin values before delivery. Obstetric features were comparable. Newborns exposed to SSRIs during fetal life were significantly more likely to be low birth weight (LBW) (birth weight<2,500 g) (p=0.01), had significantly lower mean Apgar scores at 1' (p=0.006) and at 5' (p=0.023) and worse Apgar distribution at 1' (p=0.017) and at 5' (p=0.013). Fifty-six percent of newborns presented one or more symptoms consistent with poor neonatal adaptation syndrome (PNAS). Pharmacogenetic analysis at delivery did not show significant differences in the frequencies of obstetric or neonatal complications in relation to polymorphisms.

Desai 2019	United States	Retrospective	Mothers	Prenatal exposure to SSRI	One SSRI medication vs another	40 patients	Congenital heart disease	Moderate risk of bias	Seven (18%) out of these 40 were found to have a form of CHD. Two fetuses whose mothers were exposed to fluoxetine during pregnancy had large posteriorly malaligned ventricular septal defect, sub-aortic stenosis and critical coarctation identified on fetal echocardiogram. Exposure to citalopram during pregnancy was found to be associated with a moderate size secundum atrial septal defect on one patient and a moderate size mid muscular ventricular septal defect seen on fetal echocardiogram in another patient. Exposure to venlafaxine during pregnancy showed two small muscular ventricular septal defects on fetal echocardiogram on one patient and ductal constriction with increased ductal velocity on another patient. One of the women on escitalopram had a fetus with a large membranous ventricular septal defect (VSD), secundum atrial septal defect (ASD), and left superior vena cava. None of the women on a combination of drugs had CHD.
Galbally 2019	Australia	Prospective longitudinal cohort	Pregnant women	Nonmedicated depressed, antidepressant-exposed	Healthy control	212 women	Depressive symptoms, initiation and duration of breastfeeding	Moderate risk of bias	Depressed women and antidepressant-exposed women reported a trend toward lower rates of intention, initiation, and duration, but this did not reach statistical significance. There was a statistically significant difference on depressive symptoms for women taking antidepressants during pregnancy, compared with controls, when they continued to breastfeed for 12 months postpartum.
Granstrom 2019	Sweden	Population-based, case–control cohort	Pregnant women	Maternal intake of SSRI during early pregnancy	Control	150 cases and 750 controls	Hirschsprung disease (HSCR)	Serious risk of bias	Five (3.3%) mothers of newborns with HSCR had used SSRI during pregnancy compared to 16 (2.1%) mothers of the controls (p=0.372). The mean age was similar in mothers who had used SSRI compared to those who had not (30.9 (SD +/− 5.1) versus 30.6 (SD +/− 5.0), p = 0.81).
Grieve 2019	United States	Case-control	Pregnant women	Depression, serotonin SSRI medication	Control	77 participants	Rate of occurrence, brush amplitude, oscillation frequency and duration of the bursts from high-density EEGs in infants	Moderate risk of bias	Compared to infants of control mothers, the parameters of delta brush bursts of the offspring of depressed and SSRI-using mothers are significantly altered: burst amplitude is decreased; the oscillation frequency increased, and the duration increased (SSRI only). These significant differences were found during both sleep states.

Hutchison 2019	Canada	Longitudinal prospective cohort	Pregnant women and their children	Selective serotonin reuptake inhibitor (SSRI) antidepressant treatment exposure	Non-exposed	139 children	Developing executive function (EF) in child	Serious risk of bias	Higher levels of maternal depressive symptoms (MDS), especially at 3 years, were associated with poorer maternal reports of EF skills at 6 years. Associations between prenatal SSRI exposure and EF outcomes were not significant, even when controlling for maternal education and MDS at 3 years.
Hutchison 2019	Canada	Longitudinal cohort	Pregnant women	Prenatal exposure to selective serotonin reuptake inhibitor (SSRI) antidepressants and maternal depression	Non-exposed	116 mothers and their children	Maternal depression symptoms, physical activity, dietary total intake, markers of adiposity in children	Serious risk of bias	Children with SSRI exposure had lower levels of PA than children without SSRI exposure. Total dietary energy intakes did not vary between exposure groups. SSRI exposure was not associated with BMI or WC z-scores of the children. Importantly, although lower birth weight was observed in SSRI-exposed children, differences did not remain, accounting for gestational age.
McLean 2019	Canada	Retrospective cohort	Pregnant women with history of depression	Antidepressant use	No use	205 women	Fetal growth, gestational age at delivery, neonatal abstinence syndrome (NAS)	Serious risk of bias	There were no significant differences in umbilical artery pulsatility index (PI), gestational age at delivery, or birth weight when comparing women based on antidepressant use. A small proportion (18%) of neonates had mild withdrawal symptoms; one baby had a score (≥ 8) consistent with severe NAS. In women with a history of depression, there was no difference in uteroplacental hemodynamics as measured by third trimester Doppler ultrasonography when comparing women who took antidepressant medication versus those who did not. The large majority of babies who were exposed to antidepressants in utero did not show withdrawal symptoms.
Molenaar 2019	Netherlands	Observational cohort	Pregnant women with a history of depression	Antidepressants use (e.g. selective serotonin reuptake inhibitors or serotonin and noradrenaline reuptake inhibitors or tricyclic antidepressant (TCA))	No intervention	85 women	Recurrence of depression	Serious risk of bias	Eight women (9.4%) experienced a recurrence of depression; two during pregnancy and six in the first 12 weeks postpartum. All women with recurrence of depression had first onset of depression during childhood or adolescence and had at least 2 psychiatric co-morbidities. Identification of vulnerability markers associated with recurrence of depression yielded associations with depressive symptoms around 16 weeks of pregnancy (OR, 1.28; 95% CI, 1.08–1.52), number of psychiatric co-morbidities (OR, 1.89; 95% CI, 1.16–3.09), and duration of antidepressant use (OR, 1.01; 95% CI 1.00–1.02).

Perrotta 2019	Italy	Disproportionality analysis of individual case study reports	Pregnant women	Use of selective serotonin reuptake inhibitors (SSRIs) or the serotonin and norepinephrine reuptake inhibitor (SNRI) venlafaxine	Comparisons between therapeutic thresholds	43 cases	Postpartum hemorrhage (PPH)	Serious risk of bias	Only 43 Individual Case Safety Reports (ICSRs) reported at least one SSRIs or venlafaxine as suspect drug in 14 years (database analyses). Forty-three women were enrolled in the study population (observational study). In 24 patients (55.8%) the plasma drug concentration was below the therapeutic threshold. Unexpectedly, the mean blood loss in the below-range group was significantly higher than that in the in-range group. PPH occurred in 30% of women: in 9.3% and in 20.7% of patients in the in range and below-range groups, respectively.
Pogliani 2019	Italy	Prospective observational	Pregnant and lactating women	Selective serotonin reuptake inhibitors (SSRIs) use	-	19 women	Passage of SSRIs into human milk, neonatal outcomes	Serious risk of bias	Human milk-to-plasma ratios ranged from 51.1% to 703.4%. The patients had a median relative infant dose (RID) of 1.5%, with differences among the selective serotonin reuptake inhibitors. All newborns had been breastfed from birth up to day three of life. At 1 week follow up, 58% of infants were breastfed, 37% were complementary fed, and 5% were formula fed. No side effects due to passage of selective serotonin reuptake inhibitors into human milk were found.
Richardson 2019	United Kingdom	Prospective observational comparative cohort	Pregnant women	Venlafaxine exposed	Unexposed, selective serotonin reuptake inhibitors (SSRIs) exposed	2,529 women	Spontaneous abortion risks	Serious risk of bias	After correction for variation in competing outcome rates and the stage of pregnancy at reporting, no statistically significant differences in the hazard of spontaneous abortion were observed following gestational venlafaxine use compared with either antidepressant unexposed (HR, 1.28; 95% CI, 0.850–1.94) or SSRI exposed (HR, 1.03; 95% CI, 0.681–1.57) pregnancies.
Rotem-Kohavi 2019	Canada	Cohort	Pregnant women and their infants	Depressed selective serotonin reuptake inhibitors (SSRIs)-treated, depressed-only	Control	53 infants	Neonatal functional brain organization	Moderate risk of bias	Modularity was similar across all groups. The depressed-only group showed higher connector hub values in the left anterior-cingulate, insula, and caudate as well as higher provincial hub values in the amygdala compared to the control group. The SSRI group showed higher provincial hub values in Heschl's gyrus relative to the depressed-only group. PLSR showed that newborns' hub values predicted 10% of the variability in infant temperament at 6 months, suggesting different developmental patterns between groups.
Rotem-Kohavi 2019	Canada	Cohort	Depressed pregnant women	Selective serotonin reuptake inhibitors (SSRIs)-exposed	Without SSRI exposure, control	84 women and their infants	Neonatal resting-state networks (RSNs) functional organization	Serious risk of bias	SSRI-exposed neonates had higher connectivity in a putative auditory RSN compared with depressed only (p=.01) and control (p=.02) infants (corrected for multiple comparisons), controlling for sex, age at the magnetic resonance imaging, and Pregnancy Experiences Scale score.

Schoretsaniti s 2019	Germany	Prospective	Pregnant women	Antidepressant s (sertraline, citalopram, or venlafaxine)	One medication vs another	17 women	Antidepressan t serum concentrations in breast milk	Serious risk of bias	Serum concentration of citalopram and daily dosage correlated positively while daily dosage and mother milk concentration did not (rho = 0.939, p = 0.005, and rho = 0.772, p > 0.05 respectively). A significant correlation was also found between serum and milk concentrations (rho = 0.812, p = 0.05). Venlafaxine daily dosage correlated positively with the active moiety milk concentration (rho = 0.949, p = 0.014). No significant correlations were reported for sertraline. The amount of antidepressant concentrations to which neonates may be exposed, assessed as absolute infant dose (AID), was particularly low with the highest median AID being 0.16 mg/kg/day for venlafaxine. No significant difference was detected for the M/P ratios between different drugs (p > 0.05), whereas the comparison of C/D ratios revealed lower values in the sertraline group, with the highest values reported for citalopram group (p = 0.007 for serum concentrations and p = 0.008 for mother milk).
Stuebe 2019	United States	Longitudinal cohort	Pregnant women	Current or past depression or anxiety	No history of depression or anxiety	222 mother-infant dyads	Infant feeding outcomes	Moderate risk of bias	In multivariable-adjusted analyses, baseline diagnosis was not associated with breastfeeding outcome, but baseline symptoms of depression (Beck Depression Inventory $\geq$11) or anxiety (Spielberger State Anxiety $\geq$40) were associated with earlier introduction of formula (depression: aHR, 1.52; 95% CI, 1.01–2.30; anxiety: 1.70; 95% CI 1.01–2.87); and any cessation of breastfeeding (depression: aHR, 2.02; 95% CI, 1.23–3.31; anxiety: 1.83; 95% CI, 1.00–3.33), as were depression symptoms among women who were being treated with antidepressants, compared with untreated asymptomatic women (formula: aHR, 2.27; 95% CI 1.29–4.02; cessation: 2.32; 95% CI, 1.17–4.61). History of childhood trauma (aHR 1.34, 95% CI 1.12–1.61), disordered eating symptoms (aHR, 1.22; 95% CI, 1.02–1.46), and poor sleep quality in pregnancy (aHR, 1.32; 95% CI, 1.09–1.60) were independently associated with earlier introduction of formula.

Sun 2019	Denmark	Case-time-control and cohort	Mothers and their children	Maternal antidepressant use; mothers redeemed at least one antidepressant (AD) prescription in the first three months of pregnancy	Nondiseased control; two other groups including the unexposed children with maternal AD prescriptions in the 12 months before pregnancy	792,685 singletons	Congenital heart defect	Serious risk of bias	The case-time-control OR for any congenital heart defect were 1.03 (95% CI, 0.61–1.73), which was similar to the OR (1.09; 95% CI, 0.88–1.35) from the cohort design when we compared the exposed children with the unexposed children with maternal AD use before pregnancy.
Thombre Kulkarni 2019	United States	Case-control	Women with singleton live birth pregnancies	ICD-9CM codes for chronic hypertension (CH), pre-eclampsia (PE), and gestational hypertension (GH) or unspecified hypertension	No hypertension as control	12,647 women	Depression and/or anxiety diagnoses (ICD-9CM codes) and anti-depressant and/or anxiolytic prescriptions	Moderate risk of bias	Among women with hypertension disorders of pregnancy, 59% had PE or GH, referred to here as pregnancy hypertension (PH). PH was associated with anti-depressant use prior to LMP only, (aOR, 1.2; 95% CI 1.0–1.5), continued use, (aOR, 1.4; 95% CI, 1.1–1.7), and initiation of anxiolytic medication during pregnancy, (aOR, 2.5; 95% CI, 1.6–4.2). In this latter group, 96% started medication before PH diagnosis. CH and PH were not associated with depression or anxiety in the absence of anti-depressants/anxiolytics.
Uguz 2019	Turkey	Retrospective	Women from pregnancy to postpartum period	Postpartum prophylaxis (sertraline, paroxetine, or escitalopram)	-	33 patients	Efficacy of antidepressant treatment prophylactically	Serious risk of bias	Statistical analyses indicated that the mean Hamilton Rating Scale for Depression (HAM-D) and Hamilton Rating Scale for Anxiety (HAM-A) scores before (9.45 ± 7.01 and 10.09 ± 6.42, respectively) and after (9.09 ± 6.65 and 9.54 ± 5.97, respectively) the delivery were not significant.
Wartko 2019	United States	Retrospective cohort	Pregnant women	Continuers (antidepressant fill during pregnancy)	Discontinuers (without a fill)	2,845 women	Gestational diabetes (GDM), blood glucose levels	Serious risk of bias	Compared with discontinuers, antidepressant continuers had comparable risk of GDM (RR: 1.10, 95% CI: 0.84–1.44) and screening blood glucose levels (mean difference: 2.3 mg/dL, 95% CI: −1.5 to 6.1 mg/dL). We observed generally similar results for specific antidepressants, with the potential exceptions of risk of GDM associated with sertraline (RR: 1.30, 95% CI: 0.90–1.88) and venlafaxine (RR: 1.52, 95% CI: 0.87–2.68), but neither association was statistically significant.

Yamamoto-Sasaki 2019	Japan	Retrospective cohort	Pregnant women and their offspring	Antidepressant use (selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and all other types)	No use	26,925 mother-child pairs	Autism spectrum disorder (ASD) in children	Serious risk of bias	Crude analysis showed that the ASD prevalence in children was significantly higher with any antidepressant use than with non-use (OR, 2.32; 95% CI, 1.08–4.95). However, when the analysis was adjusted for the confounding effect of maternal depression during pregnancy, statistical significance was lost (OR, 0.76; 95% CI, 0.27–2.18).
Benard-Laribiere 2018	France	Population-based cohort	Pregnant women	Antidepressant usage	-	755,519 women	Changes in usage, changes in medication, resumption	Serious risk of bias	Antidepressant use during pregnancy was 25.7 per 1,000 (95% CI, 25.3–26.0). New use concerned 3.9 per 1,000 (95% CI, 3.7–4.0); the most initiated class during pregnancy was selective serotonin reuptake inhibitors (SSRIs), while the most prescribed individual drug in second and third trimesters was amitriptyline, a tricyclic. Most changes were observed before pregnancy and during the first trimester: 63% of ongoing treatments in the year before pregnancy were discontinued before pregnancy; 68% of treatments maintained after the start of pregnancy were discontinued during the first trimester; switches or antidepressant associations mostly occurred during the prepregnancy period or during the initial weeks of pregnacy. Regardless of initial antidepressant, switches to sertraline were the most frequent. Associations mainly consisted of a prescription of tri-/tetracyclic or mirtazapine/ mianserin in addition to an SSRI. Discontinuation during pregnancy led to treatment resumption in 22% of pregnancies.
Delaney 2018	Canada	Prospective	Lactating women	Use of escitalopram	Quality control	18 women	Drug concentration in breast milk	Moderate risk of bias	Escitalopram concentrations in milk were 50±17 ng/mL (mean ± standard deviation). The simulated infant plasma AUC following escitalopram exposure through breast milk was low, with a median of 1.7% (range 0.5–5.9%) of the corresponding maternal plasma AUC indicating no substantial exposure.

Galbally 2018	Australia	Cohort	Pregnant and postpartum women	Structured Clinical Interview for the DSM-IV, Edinburgh Postnatal Depression Scale (EPDS), Female Sexual Functioning Inventory (FSFI), antidepressant use	Control	211 women	Female sexual function, maternal mental health,	Moderate risk of bias	Women showed a decline in sexual functioning over pregnancy and the first 6 months postpartum, which recovered by 12 months. For women with depression sexual functioning was lower throughout pregnancy and continued to be lower at six months postpartum than those without depression. Ongoing depressive symptoms at 12 months were also associated with lower sexual functioning. Sexual functioning was not predicted by mode of delivery, antidepressant use or childhood trauma. Breastfeeding predicted lower sexual functioning only at 6 months. Higher partner support predicted higher female sexual functioning.
Galbally 2018	Australia	Prospective cohort	Pregnant and postpartum women	Antidepressant medication use	No use, control	264 women	Infant sleep outcomes	Serious risk of bias	Maternal antepartum depression and antidepressant use were not significant predictors of infant sleep problems. Likewise, infant sleep problems were not significant predictors of postpartum maternal depression. However, maternal cognitions about infant sleep, characterised by maternal expectations to immediately attend to their crying child, did demonstrate positive reciprocal effects with infant nocturnal waking between six and 12 months postpartum.
Giardinelli 2018	Italy	Consecutive series	Pregnant women diagnosed with major depression	Combination of pharmacotherapy and psychological support	Psychological support only, healthy control group	72 women	Fetal growth, neonatal outcomes	Serious risk of bias	The infants of both treatment groups showed significant alterations in fetal biometry and a higher rate of low birth weight with respect to controls. The infants of the patients treated with psychological support showed only a significantly higher rate of head circumference, <10th percentile with respect to controls. No significant difference was found between the two patient groups when fetal growth characteristics and neonatal outcomes were taken into account.
Grzeskowiak 2018	Australia	Retrospective cohort	Women who have given birth to preterm infants	Exposure to serotonin reuptake inhibitor (SRI) antidepressants	Non-exposed	3,024 women	Postnatal domperidone use	Moderate risk of bias	Compared with non-exposed women, nonmedicated psychiatric illness (aRR, 1.64; 95% CI, 1.16–2.30) but not late pregnancy SRI use (aRR, 1.00; 95% CI 0.59–1.70) was associated with an increased risk of domperidone use, indicative of low milk supply.

Gustafsson 2018	United States	Prospective longitudinal	Pregnant women	Serotonin reuptake inhibitor (SRI) Only; SRI + Non-SRI; or Non-SRI	No Medication	161 women	Fetal development, fetal heart rate	Moderate risk of bias	On average fetuses showed the expected development over gestation. In contrast, infant average Bayley psychomotor and mental development scores were low (M = 84.10 and M = 89.92, range of normal limits 85–114) with rates of delay more than 2–3 times what would be expected based on this measure's normative data. Controlling for prenatal and postnatal depressive symptoms, prenatal medication effects on neurobehavioral development were largely undetected in the fetus and infant.
Kronenfeld 2018	Israel	Prospective	Lactating mothers and their infants	Chronic use of psychotropic medications	Use of antibiotics	280 infants	Adverse effects, physical measures and gross motor developmental milestone achievements of the infant	Serious risk of bias	At follow-up, no significant differences between infants in the two groups were observed with regard to height, weight, head circumference and weight-length ratio percentile (p=0.339, p=0.223, p=0.738, p=0.926, respectively). Children in both groups were, according to their parents, within the normal developmental range for all milestones, according to the Denver Developmental Scale. Use of psychotropic medications during breastfeeding was not significantly associated with adverse reactions. After propensity score matching (n=120 pairs) to control for differences in baseline characteristics and the length of lactation, only one significant difference was reported, sleepiness in infants in the study group (7/120) and none in the comparison group (p=0.008).
Lugo-Candelas 2018	United States	Cohort	Mothers and their infants	Selective serotonin reuptake inhibitor (SSRI) exposure	Untreated maternal depression exposure	98 mother-infant dyads	Gray matter volume estimates, white matter structural connectivity (connectome)	Moderate risk of bias	The sample included 98 mother (31 [32%] white, 26 [27%] Hispanic/Latina, 26 [27%] black/African American, 15 [15%] other) and infant (46 [47%] boys, 52 [53%] girls) dyads. Mean (SD) age of the infants at the time of the scan was 3.43 (1.50) weeks. Voxel-based morphometry showed significant gray matter volume expansion in the right amygdala (Cohen d = 0.65; 95% CI, 0.06–1.23) and right insula (Cohen d = 0.86; 95% CI, 0.26–1.14) in SSRI-exposed infants compared with both healthy controls and infants exposed to untreated maternal depression (*P*<.05; whole-brain correction). In connectome-level analysis of white matter structural connectivity, the SSRI group showed a significant increase in connectivity between the right amygdala and the right insula with a large effect size (Cohen d = 0.99; 95% CI, 0.40–1.57) compared with healthy controls and untreated depression (*P*<.05; whole connectome correction).

Lupattelli 2018	France, Italy, Switzerland, United Kingdom, Finland, Norway, Sweden, Croatia, Poland, Russia, Serbia, Slovenia	Cross-sectional	Pregnant women	Edinburgh Postnatal Depression Scale (EPDS), antidepressant treatment	Non medicated	8,069 women	Postnatal depressive symptom severity	Serious risk of bias	The period prevalence of moderate-to-very severe depressive symptoms was higher in the western and eastern regions relative to the northern region, both in the antenatal period (6.8%–7.5% versus 4.3%) and in the postnatal period (7.6% versus 4.7%). One in two mothers with psychiatric disorders used an antidepressant in pregnancy (86 of 173). In the association analysis, women medicated at any time during pregnancy (adjusted β=−0.34; 95% CI, −0.66 to −0.02) had a significant postnatal symptom severity reduction compared with the nonmedicated counterpart. This effect was larger (β=−0.74; 95% CI, −1.24 to −0.24) when the analysis was restricted to mothers within 6 months after childbirth.
Magnus 2018	Norway	Cohort	Pregnant women and their children	Measures of maternal psychosocial stress	Paternal psychosocial stress as a negative control	63,626 children	Asthma	Serious risk of bias	Childhood asthma was associated with maternal lifetime major depressive symptoms (aRR, 1.19; 95% CI, 1.09–1.30), in addition to symptoms of anxiety/ depression during pregnancy (aRR, 1.17; 95% CI, 1.06–1.29) and 6 months after delivery (aRR, 1.17, 95% CI, 1.07–1.28). Maternal negative life events during pregnancy (aRR, 1.10; 95% CI, 1.06–1.13) and 6 months after delivery (aRR, 1.14; 95% CI, 1.11–1.18) were also associated with asthma.
Petersen 2018	United Kingdom	Cohort	Women who have given live birth	Clinical and prescribing records	-	206,517 women	Prevalence of postnatal depression, depression diagnoses, depressive symptoms, antidepressant and nonpharmacological treatment within a year after birth	Serious risk of bias	23,623 (11%) had a record of depressive diagnosis or symptoms in the year after delivery and more than one in eight women received antidepressant treatment. Recording and treatment peaked 6–8 weeks after delivery. Initiation of SSRI treatment has become earlier in the more recent years. Thus, the initiation rate of SSRI treatment per 100 pregnancies (95% CI) at 8 weeks were 2.6 (2.5 to 2.8) in 2000–2004, increasing to 3.0 (2.9 to 3.1) in 2005–2009 and 3.8 (3.6 to 3.9) in 2010–2013. The overall rate of initiation of SSRI within the year after delivery, however, has not changed noticeably. A third of the women had at least one record suggestive of depression at any time prior to delivery and of these one in four received SSRI treatment in the year after delivery. Younger women were most likely to have records of depression and depressive symptoms. (Relative risk for postnatal depression: age 15–19: 1.92 (1.76 to 2.10), age 20–24: 1.49 (1.39 to 1.59) versus age 30–34). The risk of depression, postnatal depression and depressive symptoms increased with increasing social deprivation.

Pope 2018	Canada	Longitudinal prospective	Women with major depressive disorder (MDD)	Edinburgh Postnatal Depression Scale (EPDS), Hamilton Depression Rating Scale, (HDRS), antidepressant treatment	-	130 women	Postpartum recurrence rates of depression	Serious risk of bias	Over half of women (56.9%) were not receiving medication during pregnancy to treat their mood disorder, with the rate of medication use increasing over the 1-year postpartum period. When comparing women being treated with antidepressant medication (monotherapy or combination therapy) to women receiving no psychotropic medication, no significant differences in recurrence rates were observed during the postpartum period. However, we did observe that the occurrence of depression in our sample fluctuated between rates comparable to general population estimates to rates that were at times more than twofold higher, regardless of treatment with antidepressant medication.
Shulman 2018	Canada	Non-equivalent control group quasi-experimental	Women with diagnosis of postpartum depression/ anxiety within the first year following childbirth	Mindfulness-based cognitive therapy (MBCT) intervention	Treatment-as-usual control	30 women	Depression and anxiety levels	Serious risk of bias	Multivariate analyses demonstrated that depression and anxiety levels decreased, and mindfulness levels increased, in the MBCT group, but not in the control group. Many of the between-group and over time comparisons displayed trends towards significance, although these differences were not always statistically significant. Additionally, the effect sizes for anxiety, depression, and mindfulness were frequently large, indicating that the MBCT intervention may have had a clinically significant effect on participants.
Zakiyah 2018	Netherlands	Retrospective cohort	Pregnant women	Use of antidepressants	Non-exposed	28,000 women	Gestational hypertension	Serious risk of bias	539 (1.92%) used antidepressants. The risk of gestational hypertension was doubled for women using antidepressant (aOR, 2.00; 95% CI, 1.28–3.13). Significant associations were also found for the subgroup SSRIs (aOR, 2.07; 95% CI, 1.25–3.44), ≥30 DDDs (aOR, 2.50; 95% CI, 1.55–3.99) and maternal age of 30–34 years (aOR, 2.59; 95% CI, 1.35–4.98). Varying the theoretical gestational age showed comparable results.
Yang 2017	United States	Secondary analysis of two observational studies	Pregnant women	Serotonin reuptake inhibitor (SRI) antidepressants exposure or exposure to a DSM-IVTR–defined mood disorder	Unexposed	214 mothers	Neonatal discontinuation signs	Serious risk of bias	The rates of sign presence (defined as a score ≥ 2 on the Finnegan Scale) in the SRI, Mood Disorder, and Comparison groups were similar at 34.1%, 35.1%, and 30.4%, respectively. Women in the SRI group had a significantly higher preterm birth rate (24.4%) compared to the other 2 groups (7.4% and 8.9% in the Mood Disorder and Comparison groups, respectively; *P*=.012). Preterm newborns had a significantly higher sign rate compared to full-term newborns (54% versus 31%, *P*=.020). We observed a significant relationship between Finnegan signs and preterm birth.

Almedia 2016	Canada	Historical cohort	Pregnant women	Women prescribed antidepressants in the first trimester and with a recorded diagnosis of depression before pregnancy	Women with neither antidepressant use nor a depression diagnosis before or during pregnancy; women with a depression diagnosis before pregnancy, but no antidepressants prescribed in the first trimester; and women prescribed hypothyroid medication in the first trimester, but not antidepressants	41,964 women	Miscarriage risk	Serious risk of bias	The miscarriage risk uncorrected for induced abortions was 16%, 10%, and 9% for depressed women exposed to antidepressants; unexposed depressed women; and unexposed, nondepressed women, respectively. These decreased to 11%, 8%, and 7% after correction for induced abortions. In multivariable analysis, the corrected risk of miscarriage relative to unexposed, nondepressed women was 1.3 (1.1–1.5) for antidepressant-exposed women and 1.1 (1.0–1.2) for unexposed depressed women. The miscarriage relative risk for antidepressant users compared with unexposed depressed women was thus 1.2 (1.0–1.4).
Huybrechts 2015	United States	Cohort	Pregnant women with a depression diagnosis	SSRI and non-SSRI monotherapy use during the 90 days before delivery	No use	3,789,330 pregnancies	Recorded diagnosis of PPHN during the first 30 days after delivery	Moderate risk of bias	A total of 128,950 women (3.4%) filled at least 1 prescription for antidepressants late in pregnancy: 102,179 (2.7%) used an SSRI and 26,771 (0.7%) a non-SSRI. Overall, 7,630 infants not exposed to antidepressants were diagnosed with PPHN (20.8; 95% CI, 20.4–21.3 per 10,000 births) compared with 322 infants exposed to SSRIs (31.5; 95% CI, 28.3–35.2 per 10,000 births), and 78 infants exposed to non-SSRIs (29.1; 95% CI, 23.3–36.4 per 10 000 births). Associations between antidepressant use and PPHN were attenuated with increasing levels of confounding adjustment. For SSRIs, odds ratios were 1.51 (95% CI, 1.35–1.69) unadjusted and 1.10 (95% CI, 0.94–1.29) after restricting to women with depression and adjusting for the high-dimensional propensity score. For non-SSRIs, the odds ratios were 1.40 (95% CI, 1.12–1.75) and 1.02 (95% CI, 0.77–1.35), respectively. Upon restriction of the outcome to primary PPHN, the adjusted odds ratio for SSRIs was 1.28 (95% CI, 1.01–1.64) and for non-SSRIs 1.14 (95% CI, 0.74–1.74).

Kieviet 2015	Netherlands	Cohort	Pregnant women and infants	Exposure to an antidepressant during the last trimester of fetal life	Type of antidepressant versus another	247 infants	Poor neonatal adaptation (PNA)	Serious risk of bias	247 infants included in the study and 157 (64%) developed PNA. Formula feeding was associated with an increased risk of PNA compared to breastfeeding or mixed feeding (OR, 3.16; 95% CI, 1.40–7.13; p=0.003). Selective serotonin reuptake inhibitors (SSRIs) were associated with an increased risk of PNA compared to serotonin and noradrenaline reuptake inhibitors (OR, 2.52; 95% CI, 1.07–5.95; p=0.04). Dosage did not influence the risk of PNA (OR, 1.50; 95% CI, 0.89–2.52; p=0.13).
Palmsten 2013	United States	Cohort	Pregnant women with depression	Exposure to selective serotonin reuptake inhibitor (SSRI), serotonin-norepinephrine reuptake inhibitor (SNRI), tricyclic, bupropion, other antidepressant monotherapy or polytherapy, and specific antidepressants	Unexposed	100,942 women	Preeclampsia	Serious risk of bias	The risk of preeclampsia was 5.4% among women with depression and no antidepressant exposure. Compared with these women, the risk for preeclampsia was higher among those receiving SNRI (RR, 1.52; 95% CI, 1.26–1.83) and tricyclic monotherapy (RR, 1.62; 95% CI, 1.23–2.12), but not SSRI monotherapy (RR, 1.00; 95% CI, 0.93–1.07) or other antidepressants. Compared with women receiving SSRI monotherapy, preeclampsia risk was higher among women with SNRI (RR, 1.54; 95% CI, 1.28–1.86) and tricyclic (RR, 1.64; 95% CI = 1.25-2.16) monotherapy. None of the specific SSRIs was associated with preeclampsia. The RR with venlafaxine was 1.57 (95% CI, 1.29–1.91) and with amitriptyline 1.72 (95% CI, 1.24–2.40).
Palmsten 2012	United States	Cohort	Pregnant women	Antidepressant use/exposure	No antidepressant use, discontinued antidepressant use	306,831 pregnancies from 224,827 women	Preeclampsia	Moderate risk of bias	The risk of preeclampsia in depressed women not treated with antidepressants (2.4%) was similar to that in women without depression (2.3%). Compared with women with untreated depression, women treated with SSRI, SNRI, and tricyclic antidepressants (TCAs) monotherapy had adjusted relative risks of 1.22 (95% CI, 0.97–1.54), 1.95 (95% CI, 1.25–3.03), and 3.23 (95% CI, 1.87–5.59), respectively. Within prepregnancy antidepressant users, the relative risk for preeclampsia among continuers compared with discontinuers was 1.32 (95% CI, 0.95–1.84) for SSRI, 3.43 (95% CI, 1.77–6.65) for SNRI, and 3.26 (95% CI, 1.04–10.24) for TCA monotherapy.

Ko 2012	United States	Cross-sectional survey data analysis	Pregnant women	Survey assessing major depressive episode (MDE) and mental health treatment, pregnant women	Survey assessing major depressive episode (MDE) and mental health treatment, non-pregnant women	375 pregnant women (8,657 nonpregnant women)	Prevalence, diagnosis, treatment, mental health treatment, treatment barriers	Serious risk of bias	MDE in pregnant women (65.9%) went undiagnosed more often than in nonpregnant women (58.6%) (adjusted prevalence ratio [aPR], 1.1; 95% CI, 1.0–1.3). Half of depressed pregnant (49.6%) and nonpregnant (53.7%) women received treatment (aPR, 1.0; 95% CI, 0.90–1.1), with prescription medication the most common form for both pregnant (39.6%) and nonpregnant (47.4%) women. Treatment barriers did not differ by pregnancy status and were cost (54.8%), opposition to treatment (41.7%), and stigma (26.3%).
Warburton 2010	Canada	Retrospective	Pregnant women	SSRI-exposed in the last 14 days of gestation (L14)	Gestational exposure, but not during the last 14 days (NL14)	119,547 birth records	Adverse neonatal outcomes	Moderate risk of bias	Increased risk for neonatal respiratory distress was present where L14 exposure occurred compared with risk where exposure stopped before L14. However, controlling for potential maternal and neonatal confounders, differences disappeared.
Chambers 2006	United States	Retrospective cohort	Women whose infants had persistent pulmonary hypertension of the newborn (PPHN)	SSRI exposure	Control	377 women and 836 matched controls	Risk of PPHN	Moderate risk of bias	Fourteen infants with PPHN had been exposed to an SSRI after the completion of the 20th week of gestation, as compared with six control infants (aOR, 6.1; 95% CI, 2.2–16.8). In contrast, neither the use of SSRIs before the 20th week of gestation nor the use of non-SSRI antidepressant drugs at any time during pregnancy was associated with an increased risk of PPHN.
Avram 2016	Global	Review, future study	Pregnant women	SSRIs treatment	-	-	Adverse outcomes, drug efficacy	-	The physiological changes of pregnancy can affect the pharmacokinetics of a drug, thereby affecting its dose requirements. Because pharmacokinetic (PK) studies in pregnant women have rarely been conducted, evidence-based dosing adjustments are seldom available. In particular, despite the fact that the use of antidepressants has become increasingly common, pregnancy-associated PK changes of the selective serotonin reuptake inhibitors (SSRIs) are largely unknown.

Yonkers 2009	Global	Review	Pregnant women	Depression and antidepressant exposure	No exposure	-	Fetal and neonatal outcomes	-	Both depressive symptoms and antidepressant exposure are associated with fetal growth changes and shorter gestations, but the majority of studies that evaluated antidepressant risks were unable to control for the possible effects of a depressive disorder. Short-term neonatal irritability and neurobehavioral changes are also linked with maternal depression and antidepressant treatment. Several studies report fetal malformations in association with first trimester antidepressant exposure but there is no specific pattern of defects for individual medications or class of agents. The association between paroxetine and cardiac defects is more often found in studies that included all malformations rather than clinically significant malformations. Late gestational use of selective serotonin reuptake inhibitor antidepressants is associated with transitory neonatal signs and a low risk for persistent pulmonary hypertension in the newborn. Psychotherapy alone is an appropriate treatment for some pregnant women; however, others prefer pharmacotherapy or may require pharmacological treatment.
Moses-Kolko 2005	Global	Literature review	Pregnant women	In utero SRI exposure	No exposure	13 case reports and 9 cohort studies	Neonatal behavioral syndrome	-	Compared with early gestational SRI exposure or no exposure, late SRI exposure carries an overall risk ratio of 3.0 (95% CI, 2.0–4.4) for a neonatal behavioral syndrome. The most SRI-related neonatal case reports involved fluoxetine and paroxetine exposures. Neonates primarily display central nervous system, motor, respiratory, and gastrointestinal signs that are usually mild and disappear by 2 weeks of age. Medical management has consisted primarily of supportive care in special care nurseries. A severe syndrome that consists of seizures, dehydration, excessive weight loss, hyperpyrexia, or intubation is rare in term infants (1/313 quantifiable cases). There have been no reported neonatal deaths attributable to neonatal SRI exposure.

Safety and Efficacy of Pharmacologic Interventions for Perinatal Anxiety Disorders

Author, year	*Setting*	*Design/ approach*	*Subjects*	*Intervention*	*Comparator*	*Sample size*	*Outcomes*	*Quality Assessment*	*Results*

Kautzky 2022	Global	Systematic Review and meta-analysis	Neonates	Continuous SRI-treatment of the mother during pregnancy until birth	Unexposed mothers without psychoactive medication	33 studies	Any biological or psychological symptoms; odds ratios and mean differences	High quality review	Single studies showed increased risks for deficits in neurological functioning and autonomous adaptation in SRI exposed infants. Meta-analytical evaluation showed increased symptom occurrence or severity in exposed neonates for low APGAR scores, birth weight, size for gestational age, preterm delivery, neuromuscular and autonomous regulation, and higher rates of admission to specialized care. Mostly, increased risk after SRI exposure was supported by comparison to unexposed infants born to mothers diagnosed with depression.
Viswanathan 2021	Global	Systematic review and meta-analysis	Pregnant and postpartum women	Treatment	Placebo, one treatment vs another, no treatment	164 studies (131 studies included in analyses)	Symptoms, functional capacity, quality of life, peripartum events, adherence to treatment/care, suicidal events	High quality review	Brexanolone for depression onset in the third trimester or in the postpartum period probably improves depressive symptoms at 30 days (least square mean difference in the Hamilton Rating Scale for Depression, -2.6; p=0.02; N=209) when compared with placebo. Sertraline for postpartum depression may improve response (calculated RR, 2.24; 95% CI, 0.95–5.24; N=36), remission (calculated RR, 2.51; 95% CI, 0.94–6.70; N=36), and depressive symptoms (p-values ranging from 0.01 to 0.05) when compared with placebo. Discontinuing use of mood stabilizers during pregnancy may increase recurrence (aHR, 2.2; 95% CI, 1.2–4.2; N=89) and reduce time to recurrence of mood disorders (2 versus 28 weeks, aHR, 12.1; 95% CI, 1.6–91; N=26) for bipolar disorder when compared with continued use. Brexanolone for depression onset in the third trimester or in the postpartum period may increase the risk of sedation or somnolence, leading to dose interruption or reduction when compared with placebo (5% versus 0%). More than 95 percent of studies reporting on harms were observational in design and unable to fully account for confounding. These studies suggested some associations between benzodiazepine exposure before pregnancy and ectopic pregnancy; between specific antidepressants during pregnancy and adverse maternal outcomes such as postpartum hemorrhage, preeclampsia, and spontaneous abortion, and child outcomes such as respiratory issues, low Apgar scores, persistent pulmonary hypertension of the newborn, depression in children, and autism spectrum disorder; between quetiapine or olanzapine and gestational diabetes; and between benzodiazepine and neonatal intensive care admissions. Causality cannot be inferred from these studies. We found insufficient evidence on benefits and harms from comparative effectiveness studies, with one exception: one study suggested a higher risk of overall congenital anomalies (aRR, 1.85; 95% CI, 1.23–2.78; N=2,608) and cardiac anomalies (aRR, 2.25; 95% CI, 1.17–4.34; N=2,608) for lithium compared with lamotrigine during first trimester exposure.

Leshem 2021	Global	Systematic review and meta-analysis	Pregnant women and offspring	Exposure to SSRIs and SNRIs	Not exposed	18 studies	Risk for ASD and ADHD	High quality review	Found an association between SSRIs/SNRIs prenatal use and the risk for ASD and ADHD (OR, 1.42; 95% CI, 1.23–1.65; I2=58%; OR, 1.26; 95% CI, 1.07–1.49; I2=48%, respectively). Similar findings were obtained in women who were exposed to SSRIs/SNRIs before pregnancy, representing statistically significant association with ASD (OR, 1.39; 95% CI, 1.24–1.56; I^2=33%) and ADHD (OR, 1.63; 95% CI, 1.50–1.78; I^2=0%) in the Offspring, although they were not exposed to those medications in utero.
Grigoriadis 2020	Global	Systematic review and meta-analysis	Pregnant women	Benzodiazepines exposure	Unexposed	14 studies	Delivery outcomes	High quality review	There were 9 outcomes with sufficient data for meta-analysis. Antenatal BZD exposure was significantly associated with increased risk of 6 outcomes initially: spontaneous abortion (pooled OR, 1.86; 95% CI, 1.43–2.42), preterm birth (1.96; 95% CI, 1.25–3.08), low birth weight (2.24; 95% CI, 1.41–3.88), low Apgar score (2.19; 95% CI, 1.94–2.47), Neonatal Intensive Care Unit (NICU) admission (2.61; 95% CI, 1.64–4.14), and induced abortion (2.04; 95% CI, 1.23–3.40). There was significant heterogeneity between studies for most outcomes without consistent moderators. Birth weight (mean difference [MD]: -151.35 g; 95% CI, -329.73 to 27.03), gestational age (-0.49 weeks; 95% CI, -1.18 to 0.19), and small for gestational age (SGA; 1.42; 95% CI, 1.00 to 2.01) did not show significant associations although after adjusting for publication bias, gestational age, and SGA became significant, totaling 8 significant outcomes.
Salameh 2020	Global	Systematic review	Pregnant women	Treatment	-	28 articles	Depression, anxiety, substance use disorders, treatment receipt	Critically low quality review	Two trend studies showed that illicit drug use disorder increased in pregnant women over the past decade, particularly opioid and marijuana use disorders. Three studies reported an increase in treatment admissions for these disorders from 1992 to 2012; however, the overall treatment admission rate for pregnant women remained relatively stable at 4%. Three studies identified an increase in antidepressant use from 1995 to 2010 in pregnant women. Nine of 19 population-based studies revealed that White ethnicity, older reproductive age, college education, and health insurance coverage were associated with mental health and substance use treatment receipt among pregnant women.

Grigoriadis 2019	Global	Systematic review and meta-analysis	Pregnant women and their offspring	Antenatal benzodiazepine exposure as monotherapy and in combination with antidepressants	Not exposed	8 studies	Risk of congenital malformations	High quality review	Prenatal benzodiazepine use was not associated with an increased risk of congenital malformations (OR, 1.13; 95% CI, 0.99–1.30, 8 studies, n = 222/5,195 exposed and 64,335/2,082,467 unexposed), including with first trimester exposure specifically (OR, 1.08; 95% CI, 0.93–1.25, *P*=.33; 5 studies, n=181/4,331 exposed and 64,308/2,081,463 unexposed). There was no significant association with cardiac malformation following exposure (OR=1.27; 95% CI, 0.98–1.65, *P*=.07; 4 studies, n=61/4,414 exposed and 19,260/2,033,402 unexposed). However, concurrent use of benzodiazepine and antidepressants during pregnancy was associated with a significantly increased risk of congenital malformations (OR, 1.40; 95% CI, 1.09–1.80, *P*=.008; 3 studies).
Loughnan 2018	Global	Systematic review	Pregnant or postpartum women	Psychological interventions for clinical anxiety	One intervention vs another	5 studies	Mother-infant outcomes	Critically low quality review	Of the five studies included, four were open trials and one was a randomised controlled trial. Three studies evaluated group-based interventions; one study evaluated an online-delivered intervention; and one study a combined pharmacologic-psychological intervention. All participants demonstrated significant reductions in anxiety symptom severity from pre- to post-treatment. However, this review was limited to published literature evaluating treatments for clinical anxiety in perinatal women, which may have excluded important intervention studies and prevention programs, and unpublished literature.
Nillni 2018	Global	Systematic review	Pregnant and postpartum women	Treatment of depression, anxiety, and trauma-related disorders	One treatment vs another, placebo	78 studies	Treatment efficacy	Low quality review	The majority of studies focused on perinatal depression (n=73). Of the five studies focused on anxiety or trauma-related disorders, only one was a randomized controlled trial (RCT). The most studied treatment was cognitive behavioral therapy (CBT; n=22), followed by interpersonal psychotherapy (IPT; n=13). Other interventions reviewed include other talk therapies (n=5), collaborative care models (n=2), complementary and alternative medicine approaches (n=18), light therapy (n=3), brain stimulation (n=2), and psychopharmacological interventions (n=13). Eleven studies focused specifically on treatment for low-income and/or minority women. Both CBT and IPT demonstrated a significant benefit over control conditions. However, findings were mixed when these interventions were examined in low income and/or minority samples. There is some support for complementary and alternative medicine approaches (e.g., exercise). Although scarce, SSRIs demonstrated good efficacy when compared to a placebo. However, SSRIs did not outperform another active treatment condition (e.g., CBT).

Stika 2022	United States	Prospective cohort	Pregnant people with MDD to 8 weeks postpartum	Sertraline	Different dosage of sertraline	47 participants	Plasma sertraline and desmethylsertraline concentrations 24 hours post-dose every 4 weeks	Moderate risk of bias	Overall mean sertraline C/D ratios were decreased at study onset and remained consistently low until after delivery. During the last 4weeks of pregnancy the mean sertraline C/D ratio (95% CI, 0.25 (95% CI, 0.19–0.3) ng/mL/dose (mg/day), was smaller than the mean ratio at ≥8weeks after delivery, 0.32 (95% CI, 0.27–0.37) ng/mL/dose (mg/day), a 22% difference. Mean sertraline/desmethylsertraline ratios were highest after birth, which confirmed increased sertraline elimination during pregnancy. Sertraline C/D ratios in participants with functional CYP2C19 activity did not change significantly during pregnancy, whereas ratios in participants with poor or intermediate CYP2C19 activity decreased by 51%.
Bais 2020	Denmark	Population-based cohort	Women in the peripartum period	Psychiatric history, use of prescription drug	No psychiatric history, no use of prescription drug	1,154,817 pregnancies	Medication continuation/discontinuation	Moderate risk of bias	A population-based study of 1,154,817 pregnancies between 1997 and 2015 in Denmark, of which 205,406 (17.8%) pregnancies in women with a psychiatric history. Prescription drugs starting with Anatomical Therapeutic Chemical codes N05BA, N05CD, and N05CF from 12 months before pregnancy to 12 months following pregnancy were identified. We used generalised estimating equations to estimate the adjusted 5-year risk difference in the proportion of women redeeming benzodiazepines from 1 year to 5 years after. Logistic regression was used to analyze the association between characteristics and discontinuation of benzodiazepines during pregnancy. The prevalence of benzodiazepine prescriptions was 1.9% before pregnancy, 0.6% during pregnancy, and 1.3% after pregnancy. In women with a psychiatric history, the prevalence was 5–6 times higher. A significant decrease in prescriptions to women with a psychiatric history was observed, which was less profound among women with no psychiatric history. Approximately 90% of women discontinue benzodiazepines during pregnancy, with a higher percentage of women discontinuing from 1997 to 2015.

Huitfeldt 2020	Norway	Cohort	Pregnant women	Exposure to benzodiazepines or z-hypnotics	No exposure	82,038 singleton pregnancies among 69,434 women	Gestational age at delivery, risk of preterm delivery, birth weight, birth weight relative to gestational age and sex, risk of being small for gestational age, head circumference, Apgar score less than 7 at 5 minutes, and risk of neonatal respiratory distress	Moderate risk of bias	Mean (SD) maternal age was 30.2 (4.5) years, and 37,641 pregnancies (45.9%) were in primiparous women. Exposure to benzodiazepines or z-hypnotics was reported in 679 pregnancies (0.8%). After adjusting for all measured baseline and postbaseline confounders, benzodiazepine or z-hypnotic use during pregnancy was associated with lower birth weight (mean difference, −79.3 [95% CI, −126.7 to −31.9] g), lower gestational age at birth (mean difference, −2.1 [95% CI, −3.3 to −0.9] days), and higher risk of preterm birth (risk ratio, 1.41 [95% CI, 1.03–1.94]).We found no significant association of exposure to benzodiazepines or z-hypnotics with the child's birth weight relative to gestational age and sex (z score), or any of the other immediate birth outcomes.
Wall-Wieler 2020	United States	Cohort	Pregnant women	Filled prescription for benzodiazepine in the 90 days before pregnancy	Did not fill prescription for benzodiazepine in the 90 days before pregnancy	1,691,366 pregnancies	Ectopic pregnancy	Serious risk of bias	1.06% filled at least two benzodiazepine prescriptions totaling at least 10 days' supply in the 90 days before pregnancy. Among women with a benzodiazepine prescription, there was an excess of 80 ectopic pregnancies per 10,000 pregnancies, and their IPT-weighted risk of ectopic pregnancies was 1.47 (95% CI, 1.32–1.63) times greater relative to women without benzodiazepine prescriptions before pregnancy. The IPT-weighted RR between ectopic pregnancy and benzodiazepine use was 1.34 (95% CI, 1.18–1.53) among women with anxiety disorder diagnoses and 1.28 (95% CI, 0.99–1.68) among women with an insomnia diagnosis.
Cardenas 2019	United States	Discovery phase of prospective cohort	Pregnant women	Exposure to antidepressants	No exposure	479 women	Depression and anxiety symptoms	Serious risk of bias	In Project Viva, 2.9% (14/479) pregnant women were prescribed antidepressants, 9.0% (40/445) experienced high pregnancy-related anxiety, and 8.2% (33/402) reported symptoms consistent with depression. Newborns exposed to antidepressants in pregnancy had 7.2% lower DNA methylation (95% CI, − 10.4, − 4.1; P = 1.03 × 10−8) at cg22159528 located in the gene body of ZNF575, and this association replicated in the Generation R Study (β = − 2.5%; 95% CI − 4.2, − 0.7; P = 0.006). In Project Viva, the association persisted in early (β = − 6.2%; 95% CI − 10.7, − 1.6) but not mid childhood. We observed cohort-specific associations for maternal anxiety and depression in Project Viva that did not replicate.

Cauli 2019	Italy	Cohort	Pregnant and postpartum women	Multidisciplinary psychosocial intervention, scores	Compared between risk groups (low, high, no risk)	318 women	Depression and anxiety scores	Serious risk of bias	Depressive or anxiety symptoms were found in 91 (28.6%) women, 89 (28.0%) had low risk of PPD and 138 (43.4%) had no risk of PPD. The multidisciplinary psychosocial interventions offered to women with clinical symptoms were well accepted, with an uptake of 76/91 (83.5%). Thirty-three women who did not improve with psychotherapy were offered sertraline or paroxetine as a second-line treatment: 7 accepted and 26 (78.8%) refused. Eleven women already on medication at baseline continued their treatment along with the MPI. The MPI interventions had some positive effects in terms of post-partum recovery, symptom reduction, and in preventing a new onset of depression. Among the 227 non-symptomatic during pregnancy, only 5 (2.2%) developed symptoms in the post-partum period. At 12 months post-partum, 84.6% of women who were symptomatic at 2 months post-partum recovered.
Lupattelli 2019	Norway	Cohort	Pregnant women, children	Children exposed to benzodiazepines /z-hypnotics in midpregnancy (weeks 17–28) or late pregnancy (week 29 or later)	Children born to nonmedicated women	36086 children	Motor and communication skills, ADHD symptoms	Serious risk of bias	283 (0.8%) were prenatally exposed to benzodiazepines/z-hypnotics (134 in the depressive/anxiety, 60 in the sleeping, and 89 in the pain-related disorders). There was no increased risk for greater ADHD symptoms or fine motor deficits after intrauterine benzodiazepine/z-hypnotic exposure at different time points. Children born to women with depressive/anxiety disorders who took benzodiazepines/z-hypnotics in late pregnancy had greater gross motor (weighted β, 0.67; 95% CI, 0.21–1.13) and communication (weighted β, 0.35; 95% CI, 0.04–0.65) deficits than unexposed children. There was no evidence for substantial duration or coexposure associations.
Sheehy 2019	Canada	Case-control	Pregnant women	Benzodiazepine exposure	Control	442,066 pregnancies	Spontaneous abortion	Moderate risk of bias	27,149 (6.1%) ended with SA, with a mean (SD) maternal age of 24.2 (6.5) years. Among pregnancies ending with SA, 375 (1.4%) were among women exposed to benzodiazepines in early pregnancy compared with 788 (0.6%) of the 134,305 matched control pregnancies (crude OR, 2.39; 95% CI, 2.10–2.73). Adjusting for potential confounders, including maternal mood and anxiety disorders before pregnancy, and compared with nonuse, benzodiazepine exposure in early pregnancy was associated with an increased risk of SA (aOR, 1.85; 95% CI, 1.61–2.12). The risk was similar among pregnancies exposed to short-acting (284 exposed cases; aOR, 1.81; 95% CI, 1.55–2.12) and long-acting (98 exposed cases; aOR, 1.73; 95% CI, 1.31–2.28) benzodiazepines during early pregnancy. All benzodiazepine agents were independently associated with an increased risk of SA (range of aORs, 1.13–3.43).

Sundbak k 2019	Norway	Cohort	Pregnant women, children	Prenatal exposure to benzodiazepines (BZDs) and z-hypnotics	No exposure	36,401 children	Externalizing and internalizing behavior problems	Serious risk of bias	The main, IPTW and censoring weighted analyses showed that prenatal exposure to BZD and/or z-hypnotics increased the risks of internalizing behavioral problems (RR, 1.35; 95% CI, 0.73–2.49) and externalizing behavioral problems (RR, 1.51; 95% CI, 0.86–2.64).
Thombre Kulkarni 2019	United States	Case-control	Women with singleton live birth pregnanc ies	ICD-9CM codes for chronic hypertension (CH), pre-eclampsia (PE), and gestational hypertension (GH) or unspecified hypertension	No hypertension as control	12,647 women	Depression and/or anxiety diagnoses (ICD-9CM codes) and anti-depressant and/or anxiolytic prescriptions	Moderat e risk of bias	Among women with hypertension disorders of pregnancy, 59% had PE or GH, referred to here as pregnancy hypertension (PH). PH was associated with anti-depressant use prior to LMP only, (aOR, 1.2; 95% CI, 1.0–1.5), continued use, (aOR, 1.4; 95% CI, 1.1–1.7), and initiation of anxiolytic medication during pregnancy, (aOR, 2.5; 95% CI, 1.6–4.2). In this latter group, 96% started medication before PH diagnosis. CH and PH were not associated with depression or anxiety in the absence of anti-depressants/anxiolytics.
Tinker 2019	United States	Case-control	Pregnant women	BZD use in pregnancy	Control	11,614 women	Specific birth defects	Serious risk of bias	Exposure to benzodiazepines during pregnancy was rare (N = 93/11,614; 0.8%). Benzodiazepine use was more common among control mothers who were ≥30 years, non-Hispanic white, had more education, smoked, and took antidepressant medication. We observed significantly elevated ORs for any benzodiazepine and Dandy–Walker malformation (cOR, 3.1; 95% CI, 1.1–8.6); for alprazolam and anophthalmia or microphthalmia (cOR, 4.0; 95% CI, 1.2–13.1) and esophageal atresia or stenosis (aOR, 2.7; 95% CI, 1.2–5.9); and lorazepam and pulmonary valve stenosis (cOR, 4.1; 95% CI, 1.2–14.2), but sample sizes were limited and therefore CIs were wide.
Uguz 2019	Turkey	Retrospective	Women from pregnanc y to postpartu m period	Postpartum prophylaxis (sertraline, paroxetine, or escitalopram)	-	33 patients	Efficacy of antidepressant treatment prophylactically	Serious risk of bias	Statistical analyses indicated that the mean Hamilton Rating Scale for Depression (HAM-D) and Hamilton Rating Scale for Anxiety (HAM-A) scores before (9.45 ± 7.01 and 10.09 ± 6.42, respectively) and after (9.09 ± 6.65 and 9.54 ± 5.97, respectively) the delivery were not significant.
Grzesko wiak 2018	Australia	Retrospective cohort	Women who have given birth to preterm infants	Exposure to serotonin reuptake inhibitor (SRI) antidepressants	Non-exposed	3,024 women	Postnatal domperidone use	Moderat e risk of bias	Compared with non-exposed women, nonmedicated psychiatric illness (aRR, 1.64; 95% CI, 1.16–2.30) but not late pregnancy SRI use (aRR, 1.00; 95% CI, 0.59– 1.70) was associated with an increased risk of domperidone use, indicative of low milk supply.

Magnus 2018	Norway	Cohort	Pregnant women and children	Maternal psychosocial stress	Paternal psychosocial stress	83,767 children, (63,626 maternal stress info, 47,619 paternal stress info)	Asthma development	Serious risk of bias	Measures of psychosocial stress included lifetime major depressive symptoms, current anxiety/ depression symptoms, use of antidepressants, anxiolytics, and/or hypnotics, life satisfaction, relationship satisfaction, work stress, and social support. Childhood asthma was associated with maternal lifetime major depressive symptoms (aRR, 1.19; 95% CI, 1.09–1.30), in addition to symptoms of anxiety/depression during pregnancy (aRR, 1.17; 95% CI, 1.06–1.29) and 6 months after delivery (aRR, 1.17; 95% CI, 1.07–1.28). Maternal negative life events during pregnancy (aRR, 1.10; 95% CI: 1.06–1.13) and 6 months after delivery (aRR, 1.14; 95% CI, 1.11–1.18) were also associated with asthma. These associations were not replicated when evaluated within sibling groups. There were no associations with paternal psychosocial stress.
Ogawa 2018	Japan	Case-control	Mothers who had given birth to preterm and/or LBW infants	Use of BZDs	Control	42,058 births	Preterm birth, low birth weight	Serious risk of bias	The maternal use of benzodiazepines was significantly associated with an increased risk of preterm birth (aOR, 2.03; 95% CI, 1.11–3.69; *P*<.05), while the maternal use of benzodiazepines was not significantly associated with LBW (aOR, 1.55; 95% CI, 0.96–2.50). The use of antidepressants was not significantly associated with both preterm deliveries (aOR, 0.57; 95% CI, 0.08–4.16), and LBW (aOR, 0.56; 95% CI 0.14–2.29).
Shulman 2018	Canada	Non-equivalent control group quasi-experimental	Women with diagnosis of postpartum depression/anxiety within the first year following childbirth	Mindfulness-based cognitive therapy (MBCT) intervention	Treatment-as-usual control	30 women	Depression and anxiety levels	Serious risk of bias	Multivariate analyses demonstrated that depression and anxiety levels decreased, and mindfulness levels increased, in the MBCT group, but not in the control group. Many of the between-group and over time comparisons displayed trends towards significance, although these differences were not always statistically significant. Additionally, the effect sizes for anxiety, depression, and mindfulness were frequently large, indicating that the MBCT intervention may have had a clinically significant effect on participants.
Uguz 2018	Turkey	Case-control	Pregnant women with panic disorder	Pharmacotherapy	No treatment, healthy control	146 women	Birth outcomes (preterm, low birth weight, neonatal care unit, gestational age at birth, birth weight)	Moderate risk of bias	The highest proportions of preterm birth (28.8%), low birthweight (34.6%) and requirement of neonatal care (25.0%) were observed in infants of untreated patients. Pharmacotherapy group and control subjects had similar neonatal outcomes. Compared with infants of healthy subjects and the pharmacotherapy group, infants of untreated patients had significantly lower birth weight and gestational age at delivery. In addition, newborns of untreated patients had higher rate of hospitalization at the neonatal care unit.

Wikner 2007	Sweden	Retrospective cohort	Mothers	Use of BZD and/or hypnotic benzodiazepine receptor agonists (HBRA) in early pregnancy	Use of BZD and/or hypnotic benzodiazepine receptor agonists (HBRA) in late pregnancy	1,944 mothers with 1,979 infants in early pregnancy, 390 mothers with 401 infants in late pregnancy	Neonatal outcome, congenital malformations	Serious risk of bias	An increased risk for preterm birth and low birth weight was detected in the exposed population. The rate of relatively major congenital malformations was moderately increased among infants exposed in early pregnancy (aOR, 1.24; 95% CI, 1.00–1.55), not explained by known teratogenic maternal co-medication. A higher-than-expected number of infants with pylorostenosis or alimentary tract atresia (especially small gut) was found. This was, however, based on only seven infants for each group of malformation without association to any specific BZD or HBRA. The earlier proposed increased risk for orofacial clefts was not confirmed in our study.
Thorsness 2018	Global	Narrative review	Women during the perinatal period	Management for anxiety	-	-	Adverse outcomes	-	Clear understanding of the role of the obstetric provider in the identification, stabilization, and initiation of medication and/or referral to psychotherapy for women with perinatal anxiety disorders is critical to maternal and neonatal wellbeing. Informed by our clinical practice as perinatal psychiatric providers, we have provided a concise summary of current research on the approach to the treatment of perinatal anxiety disorders in the obstetric setting that includes psychotherapy and supportive interventions, primary and adjuvant psychiatric medication, and general prescribing pearls. Medications that we examined include antidepressants, benzodiazepines, sedative-hypnotics, antihistamines, quetiapine, buspirone, propranolol, and melatonin.

Safety and Efficacy of Pharmacologic Interventions for Bipolar Disorder during the Perinatal Period

Author, year	*Setting*	*Design/ approach*	*Subjects*	*Intervention*	*Comparator*	*Sample size*	*Outcomes*	*Quality Assessment*	*Results*

American College of Obstetricians and Gynecologists (ACOG) 2017: Practice Bulletin 187	United States	Guideline	Pregnant women	Prevention and management of neural tube defects	-	Systematic review/meta-analyses, randomized controlled trials (RCTs), observational studies, literature reviews	Maternal and fetal outcomes	5.07 out of 7	All women planning a pregnancy or capable of becoming pregnant should take 400 micrograms of folic acid supplementation daily. Supplementation should begin at least 1 month before pregnancy and continue through the first 12 weeks of pregnancy.
Wilson 2022	Global	Systematic review and meta-analysis	Pregnant women	Prepregnancy mental disorders	-	22 studies	Gestational diabetes (GDM)	Low quality review	There was evidence for an increased risk of GDM in women with schizophrenia (pooled OR 2.44; 95% CI 1.17–5.1; 5 studies) and a reduced risk of GDM in women with anorexia nervosa (pooled OR 0.63; 95% CI 0.49–0.80; 5 studies). There was some limited evidence of an increased risk in women with bipolar disorder. There was no evidence for an association with prepregnancy depression or bulimia nervosa on meta-analysis. There were insufficient studies on anxiety disorders for meta-analysis.

Viswanathan 2021	Global	Systematic review and meta-analysis	Pregnant and postpartum women	Treatment	Placebo, one treatment vs another, no treatment	164 studies (131 studies included in analyses)	Symptoms, functional capacity, quality of life, peripartum events, adherence to treatment/care, suicidal events	High quality review	Brexanolone for depression onset in the third trimester or in the postpartum period probably improves depressive symptoms at 30 days (least square mean difference in the Hamilton Rating Scale for Depression, -2.6; p=0.02; N=209) when compared with placebo. Sertraline for postpartum depression may improve response (calculated RR, 2.24; 95% CI, 0.95–5.24; N=36), remission (calculated RR, 2.51; 95% CI, 0.94–6.70; N=36), and depressive symptoms (p-values ranging from 0.01 to 0.05) when compared with placebo. Discontinuing use of mood stabilizers during pregnancy may increase recurrence (aHR, 2.2; 95% CI, 1.2–4.2; N=89) and reduce time to recurrence of mood disorders (2 versus 28 weeks, aHR, 12.1; 95% CI, 1.6–91; N=26) for bipolar disorder when compared with continued use. Brexanolone for depression onset in the third trimester or in the postpartum period may increase the risk of sedation or somnolence, leading to dose interruption or reduction when compared with placebo (5% versus 0%). More than 95 percent of studies reporting on harms were observational in design and unable to fully account for confounding. These studies suggested some associations between benzodiazepine exposure before pregnancy and ectopic pregnancy; between specific antidepressants during pregnancy and adverse maternal outcomes such as postpartum hemorrhage, preeclampsia, and spontaneous abortion, and child outcomes such as respiratory issues, low Apgar scores, persistent pulmonary hypertension of the newborn, depression in children, and autism spectrum disorder; between quetiapine or olanzapine and gestational diabetes; and between benzodiazepine and neonatal intensive care admissions. Causality cannot be inferred from these studies. We found insufficient evidence on benefits and harms from comparative effectiveness studies, with one exception: one study suggested a higher risk of overall congenital anomalies (aRR, 1.85; 95% CI, 1.23–2.78; N=2,608) and cardiac anomalies (aRR, 2.25; 95% CI, 1.17–4.34; N=2,608) for lithium compared with lamotrigine during first trimester exposure.
Wang 2021	Global	Systematic review and meta-analysis	Pregnant women	Antipsychotic agent exposure	Unexposed	10 studies	Gestational diabetes mellitus (GDM)	High quality review	In total 10 cohort studies met the inclusion criteria in our systematic review with 6,642 exposed and 1,860 290 unexposed pregnancies. Six studies were included in the meta-analysis with a pooled aRR of 1.24 overall (95% CI, 1.09–1.42). The I^2 result suggested low heterogeneity between studies (I^2 = 6.7%, p=0.373).

Fornaro 2020	Global	Systematic review and meta-analysis	Pregnant and postpartum women	Exposure to lithium treatment	No lithium treatment	29 studies	Any congenital anomaly, mood relapse prevention	Low quality review	20 studies were of good quality, and six were of poor quality; one study had an unclear risk of bias, and two had a high risk of bias. Thirteen of the 29 studies could be included in the quantitative analysis. Lithium prescribed during pregnancy was associated with higher odds of any congenital anomaly (N=23,300, k=11; prevalence=4.1%, k=11; OR, 1.81; 95% CI, 1.35–2.41; number needed to harm (NNH)=33, 95% CI, 22–77) and of cardiac anomalies (N=1,348,475, k=12; prevalence=1.2%, k=9; OR=1.86, 95% CI, 1.16–2.96; NNH=71, 95% CI, 48–167). Lithium exposure during the first trimester was associated with higher odds of spontaneous abortion (N=1,289, k=3, prevalence=8.1%; OR, 3.77; 95% CI, 1.15–12.39; NNH=15; 95% CI, 8–111). Comparing lithium-exposed with unexposed pregnancies, significance remained for any malformation (exposure during any pregnancy period or the first trimester) and cardiac malformations (exposure during the first trimester), but not for spontaneous abortion (exposure during the first trimester) and cardiac malformations (exposure during any pregnancy period). Lithium was more effective than no lithium in preventing postpartum relapse (N=48, k=2; OR=0.16; 95% CI, 0.03–0.89; number needed to treat=3; 95% CI, 1–12). The qualitative synthesis showed that mothers with serum lithium levels, 0.64 mEq/L and dosages, 600 mg/day had more reactive newborns without an increased risk of cardiac malformations.
Gilden 2020	Global	Systematic review and meta-analysis	Postpartum	First-onset postpartum psychosis (PP)	-	6 studies	Recurrence	Moderate quality review	Six studies and 645 patients could be included in the quantitative analyses; follow-up periods were 11–26 years. Of these patients, 279 did not experience subsequent severe episodes outside the postpartum period. Meta-analysis using random-effect estimation resulted in a weighted estimate of 43.5% (95% CI, 37.7%–49.4%).

Uguz 2020	Global	Systematic review	Pregnant and postpartum women	Pharmacologic al treatment	One treatment versus another	256 patients	Recurrence rates, adverse maternal and fetal outcomes	Critically low quality review	The present report included patients using lithium (n=143), lamotrigine (n=73), valproate (n=17), olanzapine (n=17), quetiapine (n=4), and haloperidol (n=1) during pregnancy or the postpartum period. Recurrence rates in pregnant patients using lithium (n=79) and lamotrigine (n=17) were 22.7% and 41.2%, respectively. According to very limited data, none of the patients using valproate (n=2), quetiapine (n=3), or olanzapine (n=6) experienced a new episode during pregnancy. A recurrence was reported in 12 (70.6%) of 17 patients using valproate during the postpartum period. The same recurrence rates in patients using lithium (n=123), lamotrigine (n=63), olanzapine (n=17), and quetiapine (n=3) were 20.3%, 7.9%, 11.7%, and 33.3%, respectively.
Gimenez 2019	Global	Systematic review	Pregnant women with bipolar disorder (BD) or schizoaffect ive disorder (SAD)	Use of antiepileptic drugs (AEDs)	No use of AEDs, one treatment vs another	9 studies	Adverse outcomes in pregnancy, major congenital malformations (MCM)	Critically low quality review	The AEDs evaluated were lamotrigine (LTG), valproate (VPA), carbamazepine (CBZ), oxcarbazepine (OXC), topiramate (TPR), and gabapentin (GBP). VPA and CBZ were the AED most commonly associated to MCM. LTG showed the best safety profile. Higher rates of complications during pregnancy were observed in treated and untreated women with BD compared to healthy controls.
Stevens 2019	Global	Systematic review	Patients diagnosed with bipolar disorder (BD) or major depressive disorder (MDD) prior to pregnancy	Medication	One medication vs another	22 studies	Recurrence (medication continuation/di scontinuation)	Critically low quality review	Included studies reported a wide variation in the recurrence rate of bipolar disorder and major depressive disorder during pregnancy (BD: mean=19%, range=4%–73%; MDD: mean=8%, range=1%–75%). Observational data showed a relative risk reduction of maintenance therapy during pregnancy of 66% in women with BD and 54% for women with MDD, a significant difference (95% CI, 9.4–14.6; p<0.001).
Cuomo 2018	Global	Systematic review	Women in pregnancy, peripartum and lactation	Aripiprazole use	-	93 studies	Major malformations -adverse events, perinatal complications	Critically low quality review	Antipsychotic drugs are increasingly used for both bipolar disorder and schizophrenia and it is not uncommon for a woman to find out that she is pregnant while taking an antipsychotic. Data safety literature concerning SGA is still limited, with clozapine, olanzapine, quetiapine, and risperidone being the most-studied medications until recently. However, relatively large prospective studies, large database studies, and several case reports describing the use of aripiprazole during pregnancy are now published and pregnancy outcome data in exposed children are quite reassuring. Nonetheless, published data do not provide final evidence about aripiprazole safety during pregnancy and the peripartum period.

Poels 2018	Global	Systematic review and meta-analysis	Pregnant women (includes animal studies)	Use of antipsychotics and lithium	No use of medication, one medication vs another	73 studies	Fetal/newborn neurodevelopmental consequences	Moderate quality review	Of preclinical studies, 93% found one or more adverse effects of prenatal exposure to antipsychotics or lithium on neurodevelopment or behaviour. Only three clinical cohort studies have investigated the consequences of lithium exposure, all of which reported normal development. In 66% of clinical studies regarding antipsychotic exposure, a transient delay in neurodevelopment was observed. The relative risk for neuromotor deficits after in utero exposure to antipsychotics was estimated to be 1.63 (95% CI. 1.22–2.19; I^2 = 0%). Preclinical studies suggest long-term adverse neurodevelopmental consequences of intrauterine exposure to either lithium or antipsychotics. However, there is a lack of high-quality clinical studies.
Uguz 2016	Global	Systematic review	Lactating women	Use of mood stabilizers	No use	26 reports	Adverse events, infant/maternal ratio of serum drug concentration	Critically low quality review	These reports included lamotrigine (122 cases in 12 reports), lithium (26 cases in five reports), carbamazepine (64 cases in five reports), valproate (nine cases in three reports), and oxcarbazepine (two cases in two reports). Of 26 reports, one report included both carbamazepine and valproate. The reports suggest that a considerable amount of lithium and lamotrigine are excreted into breast milk. There is a paucity of data on valproate and oxcarbazepine; however, the infant/maternal ratio of serum drug concentration seems to be lower in valproate exposure compared to other mood stabilizers. The incidence of adverse events in infants exposed to mood stabilizers is reported to be very low.
Bak 2014	Global	Systematic review and meta-analysis	Adults age 18 or older	Duration of antipsychotic (AP)-use stratified as ≤ 6 weeks, 6–16 weeks, 16–38 weeks, and >38 weeks	Different durations	307 studies	Body weight change, change in body mass index (BMI) and clinically relevant weight change	Moderate quality review	The majority were AP switch studies. Almost all AP showed a degree of weight gain after prolonged use, except for amisulpride, aripiprazole, and ziprasidone, for which prolonged exposure resulted in negligible weight change. The level of weight gain per AP varied from discrete to severe. Contrary to expectations, switch of AP did not result in weight loss for amisulpride, aripiprazole, or ziprasidone. In AP-naive patients, weight gain was much more pronounced for all AP.

Jentink 2010	Global	Systematic review and case-control	Pregnant women	Exposure to carbamazepine monotherapy	Control groups (no antiepileptic drug exposure, valproic acid monotherapy, and other antiepileptic drug monotherapy (excluding valproic acid)	8 cohort studies (2,680 pregnancies)	Overall prevalence for a major congenital malformation	SR: Critically low quality review; Case-control: moderate risk of bias	The literature review yielded an overall prevalence for a major congenital malformation of 3.3% (95% CI, 2.7–4.2) after exposure to carbamazepine monotherapy in the first trimester. In 131 registrations of malformations, the fetus had been exposed to carbamazepine monotherapy. Spina bifida was the only specific major congenital malformation significantly associated with exposure to carbamazepine monotherapy (OR, 2.6; 95% CI, 1.2– 5.3) compared with no antiepileptic drug), but the risk was smaller for carbamazepine than for valproic acid (0.2, 0.1–0.6). There was no evidence for an association with total anomalous pulmonary venous return (no cases with carbamazepine exposure), cleft lip (with or without palate) (0.2, 0.0–1.3), diaphragmatic hernia (0.9, 0.1–6.6), or hypospadias (0.7, 0.3–1.6) compared with no exposure to antiepileptic drugs. Further exploratory analysis suggested a higher risk of single ventricle and atrioventricular septal defect.
Clark 2022	United States	Prospective cohort	Perinatal patients	Lithium	-	4 participants	Change in Serum concentration/ elimination	Serious risk of bias	Three women treated with lithium for bipolar disorder completed serial blood sampling protocols during each trimester of pregnancy and at least once postpartum. The trajectory of lithium elimination clearance, creatinine clearance, and serum lithium concentrations were determined. Manic, depressive, and anxiety symptoms were also assessed at each study visit. Compared to the nonpregnant state, lithium elimination clearance increased an average of 63.5% by the third trimester. Lithium elimination clearance was inversely related to changes in serum lithium concentration. Mood symptoms worsened with declines in serum lithium concentration. Lithium elimination clearance returned to baseline at 4 to 9 weeks postpartum.
Poels 2021	Netherlands	Retrospective cohort	Women with singleton pregnancies	Exposure to lithium	No exposure to lithium	119 women (8,184 non-exposed controls)	Ultrasound measurements	Serious risk of bias	Lithium use during pregnancy was associated with an average increase in head circumference of 1.77 mm (95% CI, 0.53–3.01), in abdominal circumference of 5.54 mm (95% CI, 3.95–7.12), and in femur length of 0.59 mm (95% CI, 0.22–0.96) at 18–22 weeks gestation. Furthermore, lithium use during pregnancy was associated with an average increase in birth weight of 142.43 grams (95% CI, 58.01–226.89), whereas it was associated with an average decrease of 1.41 weeks in gestational duration (95% CI, −1.78 to −1.05).

Uguz 2021	Turkey	Prospective	Postpartum women with bipolar disorder	Use of olanzapine or quetiapine	-	23 patients	Recurrent mood disorders	Serious risk of bias	The mean follow-up period was 33.95612.07 weeks. Six (26.1%) of 23 patients experienced recurrent mood episodes during the postpartum period. Four of these six patients were taking olanzapine and two were taking quetiapine. Patients with recurrent mood episodes had a significantly stronger family history of bipolar disorder, higher number of past episodes, and earlier onset and longer duration of illness compared to patients without recurrent mood episodes.
Taylor 2019	United Kingdom	Historical cohort	Women with history of serious mental illness (SMI) who delivered babies	Exposed to regular medication	Unexposed to regular medication	452 pregnancies	Relapse of SMI in first 3 months postpartum, medication exposure	Serious risk of bias	128 (28.3%) pregnancies were associated with relapse in the first 3 months postpartum, with recent relapse an independent predictor (aOR; 95% CI, 1.30–2.27). There was no evidence of a prophylactic effect of medication (crude OR, 0.65; 95% CI, 0.34–1.25) (aOR, 0.99; 95% CI, 0.54–1.83), in women with non-affective or affective psychoses (interaction test p = 0.453).
Wisner 2019	United States	Prospective	Women with bipolar disorder (BD)	Psychotropic treatment (BD-P)	Without psychotropic exposure (BD-NP), control with no BD or psychotropic exposure (Comp)	174 mother-infant dyads	Method of delivery, gestational age of newborn, birth weight, length, head circumference, Apgar score at 5 min, admission to a neonatal intensive care unit (NICU), and neonatal complication signs	Moderate risk of bias	The BP-P, BP-NP and Comp groups varied significantly on sociodemographic characteristics. Women with BD were more likely to be less educated, unemployed, single, and use tobacco and illicit drugs than women in the Comp group. Compared to women with BD-NP, women with BD-P were more likely to be older and educated. Approximately 10% of all infants were delivered preterm. No significant differences in outcome occurred for Apgar scores < 8, NICU admissions, sex or infant length. Infants of mothers with BD-NP had significantly smaller head circumferences (HC) than the other groups, adjustment for confounding variables mitigated this association.
Byatt 2018	United States	Descriptive exploratory	Pregnant and postpartum women	Structured, in-depth interview	-	25 women	Clinical diagnosis of bipolar disorder, referral, treatment	Serious risk of bias	Most participants (n=19, 79.17%) did not have a clinical diagnosis of bipolar disorder documented in their medical records nor had received referral for treatment during pregnancy (n=15, 60%). Of participants receiving pharmacotherapy (n=14, 58.33%), most were treated with an antidepressant alone (n=10, 71.42%). Most medication was prescribed by an obstetric (n=4, 28.57%) or primary care provider (n=7, 50%). Qualitative interviews indicated that participants want their obstetric practices to proactively screen for, discuss, and help them obtain mental health treatment.

Elkjaer 2018	Denmark	Prospective cohort	Children with prenatal exposure to valproate sodium and other antiepileptic drugs	Valproate-exposed children	Unexposed children and children exposed to another AED (lamotrigine)	479,027 children	Performance in Danish national tests	Serious risk of bias	Children who participated in the national tests were evaluated, including children exposed to the following AEDs in monotherapy: valproate, 253; phenobarbital, 86; oxcarbazepine, 236; lamotrigine, 396; clonazepam, 188; and carbamazepine, 294. The mean (SD) age of the 244,095 children completing the sixth-grade Danish test was 12.9 (0.39) years; 122,774 (50.3%; 95% CI, 50.1%–50.5%) were boys and 121,321 (49.7%; 95% CI, 49.5%–49.9%) were girls. Valproate-exposed children scored worse on the sixth-grade Danish tests (adjusted difference, −0.27 SD; 95% CI, −0.42 to −0.12) and sixth-grade mathematics tests (adjusted difference, −0.33 SD; (95% CI, −0.47 to −0.19) compared with unexposed children and children exposed to lamotrigine (adjusted difference, −0.33 SD; 95% CI, −0.60 to −0.06). Also, children exposed to clonazepam scored worse in the sixth-grade Danish tests (adjusted difference, −0.07 SD; 95% CI, −0.12 to −0.02). Carbamazepine, lamotrigine, phenobarbital, and oxcarbazepine were not linked to poor school performance compared with unexposed children.
Forsberg 2018	Sweden	Retrospective	Women with and without mood disorders and their children	Lithium and maternal mood disorder (MMD) exposure during pregnancy	No MMD	24 women with 27 pregnancies and 28 children; 11 mother–child pairs in control group	Neonatal health, cognition of children	Moderate risk of bias	20 were exposed to lithium and MMD during pregnancy, eight were exposed to MMD but not lithium and 11 were not exposed to MMD or lithium. The children's full scale intelligence quotient (IQ), performance IQ and verbal IQ results did not differ significantly between the groups. The processing speed quotient was significantly lower in children exposed to mood disorders, but there was a high level of missing data for this subtest.
Frayne 2018	Australia	Cohort	Women with severe mental illness, who were prescribed lithium at any time during the pregnancy	Continuation of lithium	Discontinuation of lithium	33 women	Delivery, maternal, and neonatal outcomes	Moderate risk of bias	Women who were prescribed lithium, irrespective of whether they continued or discontinued the medication represented a high-risk group obstetrically, with high rates of smoking overall (33%), medical comorbidities (54%), and antenatal complications (88%). Prepregnancy counseling occurred in 33% of the cohort but increased the likelihood of continuing lithium in pregnancy (p=.007). Compared to those who ceased lithium, women who remained on lithium through the pregnancy had increased rates of fetal ultrasound abnormalities such as abdominal circumference >90th% (p=.005). Psychiatric relapses through the antenatal and immediate postpartum period appeared to be due to a combination of factors.

Hernandez-Diaz 2018	United States	Population-based cohort	Pregnant women	Exposure to topiramate (filling ≥1 prescriptions during the first trimester of pregnancy)	No exposure to topiramate, exposure to lamotrigine	136,0101 women	Oral cleft	Moderate risk of bias	The risk of oral clefts at birth was 4.1 per 1,000 in the 2,425 infants born to women exposed to topiramate compared with 1.1 per 1,000 in the unexposed group (RR, 2.90; 95% CI, 1.56–5.40). The RR among women with epilepsy was 8.30 (95% CI, 2.65–26.07); among women with other indications such as bipolar disorder, it was 1.45 (95% CI, 0.54–3.86). The median daily dose for the first prescription filled during the first trimester was 200 mg for women with epilepsy and 100 mg for women without epilepsy. For topiramate monotherapy, the RR for oral clefts associated with doses ≤100 mg was 1.64 (95% CI, 0.53–5.07) and for doses >100 mg it was 5.16 (95% CI, 1.94–13.73). Results were similar when lamotrigine was used as a reference group.
Karanam 2018	United States	Observational	Pregnant women with epilepsy	Lamotrigine (LTG)	Differences in lamotrigine clearance (LTG-CL/F)	Twenty-five pregnancies (22 participants)	Changes in LTG-CL/F	Serious risk of bias	Increases in LTG-CL/F were present at 5 weeks gestational age. Both estradiol and gestational week were highly correlated with LTG-CL/F changes; LTG-CL/F increased at the rate of 0.115l/h for every gestational week and 0.844l/h for every 1ng/ml of estradiol, with women in the high LTG-CL/F percentage change group changing at a faster rate ($p<0.001$). Models using gestational week performed better than models using estradiol.
Munk-Olsen 2018	Denmark, Canada, Netherlands, Sweden, United Kingdom, United States	Cohort studies using meta-analysis	Pregnant women	Lithium exposed pregnancies	Reference pregnancies in mothers with a mood disorder, but unexposed to lithium	727 exposed, 21,397 unexposed	Pregnancy complications, delivery outcomes, neonatal readmission to hospital within 28 days of birth, congenital malformations	Serious risk of bias	Lithium exposure was not associated with any of the pre-defined pregnancy complications or delivery outcomes. There was an increased risk for neonatal readmission in lithium exposed (27·5%) versus reference group (14·3%) (Pooled aOR1·62; 95% CI, 1·12–2·33). Lithium exposure during first trimester was associated with increased risk of major malformations (7·4% versus 4·3%; pooled aOR 1·71; 95% CI, 1·07–2·72). Similarly, more lithium exposed children had major cardiac malformations, albeit not statistically significant (2·1% versus 1·6%; pooled aOR, 1·54; 95% CI, 0·64–3·70). Limitations in our study include serum lithium levels were not available, hence no analyses related to dose-response effects could be performed, and residual confounding from e.g. substance abuse cannot be ruled out.

Taylor 2018	United Kingdom	Historical cohort	Pregnant women with a history of serious mental illness	Medication continuation	No medication, change in medication	454 pregnancies (389 women)	Severe relapse, medication exposure	Serious risk of bias	There were 58 (24%) relapses in women with non-affective psychoses and 25 (12%) in women with affective psychotic or bipolar disorders. Independent predictors of relapse included non-affective psychosis (aOR=2.03; 95% CI, 1.16–3.54), number of recent admissions (1.37; 1.03–1.84), recent self-harm (2.24; 1.15–4.34), substance use (2.15; 1.13–4.08), smoking (2.52; 1.26–5.02) and non-white ethnicity (black ethnicity: 2.37; 1.23–4.57, mixed/other ethnicity: 2.94; 1.32–6.56). Women on no regular medication throughout first trimester were also at greater risk of relapse in pregnancy (1.99; 1.05–3.75). There was no interaction between severity of illness and medication status as relapse predictors. Therefore, women with non-affective psychosis and higher number of recent acute admissions are at significant risk of severe relapse in pregnancy.
Santucci 2017	United States	Prospective cohort	Pregnant women with bipolar disorder	Bipolar disorder with psychotropic exposure	Prenatal maternal bipolar disorder without psychotropic treatment	197 mother-infant dyads	Infant outcomes	Serious risk of bias	Neither prenatal exposure to BD− or BD+ significantly impacted overall Psychomotor Development Index (PDI) (*P* =.2449), Mental Development Index (MDI) (*P*=.7886), or BRS (*P*=.6072) scores. However, we observed a significant effect of BD+ exposure-by-time interaction for the Behavioral Rating Scale (BRS) Motor Quality index (F245 = 3.16, *P*=.0441), with BD+ exposed infants less likely to be above the 75th percentile at the 52-week assessment (mean = 11.5%) compared with BD− (mean = 40.0%) and nonexposed infants (mean = 48.4%).
Cohen 2016	United States	Prospective	Pregnant and postpartum women	Second-generation antipsychotics use	Control	487 women	Congenital malformations	Serious risk of bias	Medical records were obtained for 82% of participants. A total of 303 women had completed the study and were eligible for inclusion in the analysis. Of 214 live births with first-trimester exposure to second-generation antipsychotics, three major malformations were confirmed. In the control group (N=89), one major malformation was confirmed. The absolute risk of major malformations was 1.4% for exposed infants and 1.1% for unexposed infants. The odds ratio for major malformations comparing exposed infants with unexposed infants was 1.25 (95% CI, 0.13–12.19).

Polepally 2014	United States	Prospective observational	Pregnant and postpartum women or women planning pregnancy	LTG therapy	Differences in gestational age	60 women (64 pregnancies)	LTG clearance	Serious risk of bias	The baseline LTG CL/F was 2.16 L/h with a between-subject variability of 40.6%. The influence of pregnancy on CL/F was described by gestational week. Two subpopulations of women emerged based on the rate of increase of LTG CL/F during pregnancy. The gestational age-associated increase in CL/F displayed a ten-fold higher rate in 77% of the women (0.118 L/h/week) compared to 23% (0.0115 L/h/week). The between-subject variability in these slopes was 43.0%. The increased CL/F at delivery declined to baseline values with a half-life of 0.55 weeks.
Toh 2014	United States	Population-based	Pregnant women	Prenatal use of atypical and typical antipsychotics	No exposure to antipsychotics	585,615 deliveries	Prevalence of prenatal use of atypical and typical antipsychotics, mental health diagnosis	Serious risk of bias	4,223 (0.72%) deliveries were to women who received an atypical antipsychotic and 548 (0.09%) were to women receiving a typical antipsychotic any time from 60 days before pregnancy through delivery. There was a 2.5-fold increase in atypical antipsychotic use during the study period, from 0.33% (95% CI, 0.29%–0.37%) in 2001 to 0.82% (0.76%–0.88%) in 2007, while the use of typical antipsychotics remained stable. Depression was the most common mental health diagnosis among deliveries to women with atypical antipsychotic use (63%), followed by bipolar disorder (43%) and schizophrenia (13%).
Newport 2007	United States	Prospective	Pregnant women	Atypical antipsychotic or haloperidol	-	54 women	Placental passage, obstetrical outcome	Serious risk of bias	Complete maternal-infant sample pairs were available for 50 participants. Placental passage ratio was highest for olanzapine (mean=72.1%, SD=42.0%), followed by haloperidol (mean=65.5%, SD=40.3%), risperidone (mean=49.2%, SD=33.9%), and quetiapine (mean=23.8%, SD=11.0%). There were tendencies toward higher rates of low birth weight (30.8%) and neonatal intensive care unit admission (30.8%) among neonates exposed to olanzapine.
Jablensky 2005	Australia	Population-based cohort	Women who had given birth	Schizophrenia or major affective disorders	Control	3,174 births (3,129 controls)	Incidence of complications during pregnancy, labor, and delivery and the neonatal characteristics of infants	Serious risk of bias	Both schizophrenic and affective disorder patients had increased risks of pregnancy, birth, and neonatal complications, including placental abnormalities, antepartum hemorrhages, and fetal distress. Women with schizophrenia were significantly more likely to have placental abruption, to give birth to infants in the lowest weight/growth population decile, and to have children with cardiovascular congenital anomalies. Neonatal complications were significantly more likely to occur in winter; low birth weight peaked in spring. Complications other than low birth weight and congenital anomalies were higher in pregnancies after psychiatric illness than in pregnancies preceding the diagnosis.

Newport 2005	United States	Prospective and literature review	Pregnant women	Lithium	-	10 participants in study and 32 cases from review	Obstetrical outcome	Serious risk of bias	The ratio of lithium concentrations in umbilical cord blood to maternal blood (mean=1.05, SD=0.13) was uniform across a wide range of maternal concentrations (0.2–2.6 meq/liter). Significantly lower Apgar scores, longer hospital stays, and higher rates of CNS and neuromuscular complications were observed in infants with higher lithium concentrations (>0.64 meq/liter) at delivery. Withholding lithium therapy for 24–48 hours before delivery resulted in a 0.28 meq/liter reduction in maternal lithium concentration.
Pennell 2004	United States	Prospective	Pregnant women	Lamotrigine (LTG) monotherapy	Comparisons between trimesters	14 women	LTG clearance	Serious risk of bias	LTG apparent clearance, weight-adjusted relative clearance, and percentages of baseline clearance significantly differed between prepregnancy baseline and each trimester and between trimesters. LTG clearance progressively increased until 32 weeks' gestational age, reaching a peak of >330% of baseline, and then began to decline.
Tran 2002	United States	Prospective	Patients before, during, and after pregnancy	LTG	Different time points	Twelve pregnancies	Drug clearance	Serious risk of bias	An increase in apparent clearance (>65%) was observed between prepregnancy and the second and third trimesters ($p<0.05$). Eleven pregnancies required higher doses of LTG to maintain therapeutic levels during pregnancy. There was no significant change in apparent clearance between each trimester. A decrease in apparent clearance was observed between the last two trimesters and postpartum ($p<0.05$). In the postpartum period, apparent clearances returned to the prepregnancy baseline, and LTG doses needed to be reduced.
Adab 2001	United Kingdom	Retrospective survey analysis	Pregnant women	Antiepileptic drug (AED) monotherapy	AED polytherapy	721 women	Additional educational needs (AENs)	Serious risk of bias	721 (57%) women of the 1,267 approached returned an adequately completed questionnaire; 330 (46%) had given birth to at least one live-born child. Information was collected on 594 children, 400 of whom were of school age (4–18). 150 (37.5%) had been exposed to monotherapy in utero, 74 (18.5%) were exposed to polytherapy, and 176 were not exposed to any AEDs. The OR of AENs for all children exposed to AEDs in utero compared with those unexposed was 1.49 (95% CI, 0.83–2.67). Odds ratios for AENs for each therapy subgroup compared with those unexposed were also calculated for all children. Those exposed to valproate monotherapy had an odds ratio of 3.4 (95% CI, 1.63–7.10) by contrast with an odds ratio of 0.26 (95% CI, 0.06–1.15) for carbamazepine. Polytherapy including valproate had similarly high OR for AENs compared with those unexposed of 2.51 (95% CI, 1.04–6.07) versus the OR of 1.51 (95% CI, 0.56–4.07) for polytherapy excluding valproate.

Ebbesen 2000	Denmark	Cohort	Epileptic women	Valproate, valproate and carbamazepine	-	22 women and infants	Neonatal hypoglycaemia, withdrawal symptoms	Moderate risk of bias	Thirteen of the 22 infants became hypoglycaemic. One infant had eight episodes of hypoglycaemia, one had three episodes, two had two episodes, and nine had one episode each. The lowest blood glucose concentration was 1.0 mmol/l. All episodes were asymptomatic. The maternal mean plasma concentration of total valproate during the third trimester correlated negatively with blood glucose concentration one hour after delivery ($p<0.0003$) and with the development of hypoglycaemia ($p<0.0001$). There was no evidence for hyperinsulinaemia as the cause of hypoglycaemia. Ten infants developed withdrawal symptoms, which correlated positively with the mean dose of valproate in the third trimester and the concentration of the free fraction of valproate in maternal plasma at delivery ($p<0.02$).
Moore 2000	United Kingdom	Cohort	Mothers and their children	Exposure to anticonvulsants	One medication versus another	57 children	Behavioral problems, autistic features, learning difficulties, facial features	Moderate risk of bias	Thirty-four (60%) were exposed in utero to valproate alone, four (7%) to carbamazepine alone, four (7%) to phenytoin alone, and 15 (26%) to more than one anticonvulsant. Forty-six (81%) reported behavioural problems, 22 (39%) with hyperactivity or poor concentration of whom four (7%) had a diagnosis of attention deficit and hyperactivity disorder. Thirty-four (60%) reported two or more autistic features, of whom four had a diagnosis of autism and two of Asperger's syndrome. Forty-four (77%) had learning difficulties, 46 (81%) had speech delay, 34 (60%) had gross motor delay, and 24 (42%) had fine motor delay. Nineteen (33%) had glue ear and 40 (70%) had joint laxity involving all sizes of joints. Of 46 who had formal ophthalmic evaluation, 16 (34%) had myopia.

Rodriguez-Pinilla 2000	Spain	Case-control	Pregnant women and infants	Exposure to valproic acid (VPA)	Control	22,294 consecutive malformed infants and 21,937 control infants	Presence of limb deficiencies in newborn infants	Moderate risk of bias	Of the total of malformed infants exposed to VPA, 36.8% (21/57) presented with congenital limb defects of different types (including overlapping digits, talipes, clubfoot, clinodactyly, arachnodactyly, hip dislocation, pre- and postaxial polydactyly, etc.), three of them having limb deficiencies. The result of the case-control analysis shows a risk for limb deficiencies of OR, 6.17; 95% CI, 1.28–29.66; *P*=0.023, after controlling for potential confounder factors. If we consider that in our population the prevalence at birth of this type of defect is 6.88 per 10,000 livebirths (95% CI, 6.43–7.36) we can estimate that the risk for women treated with VPA of having a baby with limb deficiencies would be around 0.42%. The limb deficiencies in the three patients exposed to VPA were the following: the first case was a newborn infant with hypoplasia of the left hand, the second patient was a newborn infant with unilateral forearm defect and hypoplastic first metacarpal bone in the left hand, and the third patient presented with short hands with hypoplastic first metacarpal bone, absent and hypoplastic phalanges, retrognathia, facial asymmetry, hypospadias, teleangiectatic angioma in skull, and hypotonia.
Canger 1999	Italy	Prospective	Mothers with epilepsy	Antiepileptic drug (AED) treatment	One treatment vs another, monotherapy vs two AEDs vs 3 AEDs	517 pregnancies	Malformations, pregnancy outcome	Serious risk of bias	The overall rate of malformations was 9.7%: of these, 5.3% were structurally severe, 2.2% were mild, 0.4% were chromosomic-genetic, and 1.8% were deformities. No malformation was detected in the 25 untreated patients.
Kaneko 1999	Japan, Italy, Canada	Prospective	Mothers being treated for epilepsy	AEDs treatment	One AED treatment vs another	983 offspring	Relative teratogenic risk of AEDs	Moderate risk of bias	The incidence of congenital malformations in offspring without drug exposure was 3.1%, versus an incidence with drug exposure of 9.0%. The highest incidence in offspring exposed to a single AED occurred with primidone (PRM; 14.3%), which was followed by valproate (VPA; 11.1%), phenytoin (PHT; 9.1%), carbamazepine (CBZ; 5.7%), and phenobarbital (PB; 5.1%). The VPA dose and level positively correlated with the incidence of malformations. This study first determined a cut-off value of VPA dose and level at 1000 mg/day and 70 microg/ml, respectively, to avoid the occurrence of malformations. The incidence of malformations increases as the number of drugs increases, and as the total daily dose increases. Specific combinations of AEDs such as VPA + CBZ and PHT + PRM + PB produced a higher incidence of congenital malformations. The incidence of malformations was not associated with any background factors studied except for the presence of malformations in siblings.

Samren 1999	Netherlands	Retrospective cohort	Mothers with epilepsy	AED use	Control	1,411 children and 2,000 nonepileptic matched controls	Major congenital abnormalities	Serious risk of bias	We found significantly increased risks of major congenital abnormalities for carbamazepine and valproate monotherapy, with evidence for a significant dose-response relationship for valproate. The risk of major congenital abnormalities was nonsignificantly increased for phenobarbital monotherapy when caffeine comedication was excluded, but a significant increase in risk was found when caffeine was included. Phenytoin monotherapy was not associated with an increased risk of major congenital abnormalities. Regarding polytherapy regimens, increased risks were found for several antiepileptic drug combinations. Clonazepam, in combination with other antiepileptic drugs, showed a significantly increased relative risk. Furthermore, there were significantly increased relative risks for the combination of carbamazepine and valproate and the combination of phenobarbital and caffeine with other antiepileptic drugs.
Samren 1997	Finland, Germany, Netherlands	Reanalysis of prospective studies	Women with epilepsy treated AEDs	Exposure to AED during pregnancy	Unexposed control pregnancies	896 women with epilepsy treated with AEDs and 1,221 children born to these subjects, and 158 children born to nonepileptic control subjects	Major congenital malformations (MCA)	Moderate risk of bias	There was an increased risk of MCA in children exposed to AED during gestation (RR, 2.3; 95% CI, 1.2–4.7). A significant increase in risk was found for children exposed to valproate (VPA) (RR, 4.9; 95% CI, 1.6–15.0) or carbamazepine (CBZ) (RR, 4.9; 95% CI, 1.3–18.0) in monotherapy. When comparing different AED regimens during all 1,221 pregnancies, risks of MCA were significantly increased for the combination of phenobarbital (PB) and ethosuximide (RR, 9.8; 95% CI, 1.4–67.3) and the combination of phenytoin, PB, CBZ, and VPA (RR, 11.0; 95% CI, 2.1–57.6). Offspring of mothers using > 1,000 mg VPA/day were at a significantly increased risk of MCA, especially neural tube defects, compared to offspring exposed < or =600 mg VPA/day (RR, 6.8; 95% CI, 1.4–32.7). No difference in risk of MCA was found between the offspring exposed to 601–1,000 mg/day and < or =600 mg/day.

Omtzigt 1993	Netherlands	Prospective cohort	Pregnant epileptic patients	Carbamazepine (CBZ) alone	CBZ in combination with other antiepileptic drugs	100 pregnancies	Congenital malformation	Serious risk of bias	In 100 pregnancies with first trimester CBZ exposure (including 7 with malformed outcome), parent drug and metabolite concentrations in maternal serum were evaluated. CBZ-10,11-epoxide concentrations increased with increasing dose. Comedication with phenobarbital led to lower 10,11-epoxide concentrations in maternal serum and a higher percentage of the dose recovered in urine as 10,11-diol. Valproate comedication led to slightly higher 10,11-epoxide concentrations in maternal serum, in combination with lower CBZ concentrations and a lower percentage of the dose recovered in the urine as 10,11-diol. In amniotic fluid, concentrations of CBZ and its main metabolites in most patients were 2 to 2.5 times higher than the free concentrations in maternal serum. Metabolites and parent drug concentrations in amniotic fluid correlated with their free concentration in maternal serum, but stronger with each other in amniotic fluid. No significant differences in levels of CBZ and its metabolites were observed between pregnancies with normal and malformed outcome.
Gaily 1990	FinaInd	Cohort	Epileptic mothers and children	Exposure to antiepileptic drug(s)	Control	104 children with epileptic mothers (105 controls)	Specific cognitive abilities and motor function	Serious risk of bias	The majority (89%) of the children of epileptic mothers had been exposed to anti-epileptic drugs during pregnancy, most commonly phenytoin (69%). Maternal seizures had occurred during pregnancy in 52%. A significant difference, with poorer performance in the study group, was found in block design (Wechsler Preschool and Primary Scale of Intelligence) and auditory closure (Illinois Test of Psycholinguistic Abilities). Significantly more study than control children had some type of specific cognitive dysfunction. Within the study group, increased risk was associated with maternal partial seizures, with seizures occurring during pregnancy, and with low paternal education, but not with exposure to anti-epileptic drugs.

Martinez-Frias 1990	Spain	Case-control	Pregnant women and their infants	Exposed only to Valproic acid (VPA) (monotherapy)	VPA plus other anticonvulsant drugs (polytherapy)	28 patients	Clinical manifestation of major congenital defects	Serious risk of bias	Among the 28 malformed infants prenatally exposed VPA, in 15 (53.6%) the exposure was to VPA only and in 13 (46.4%) to VPA plus other anticonvulsant drugs. In 8 children in which the exposure was to VPA only, the drug was used throughout pregnancy, while in the remaining 5, it was used at least in the first trimester. The total doses range from 200 to 2,500 mg. In cases that were exposed to VPA plus other anticonvulsants, the exposure was throughout pregnancy in all but 3 children who were exposed only in the first trimester. The daily doses ranged from 200 to 2,000 mg. Six cases (21.4%) had spina bifida (SB), 3 (20%) among the 15 cases exposed to VPA only and 3 (23.1%) among the 13 cases exposed to VPA plus other anticonvulsant drugs. Microcephaly and other central nervous system anomalies were only observed in cases with prenatal exposure to VPA polytherapy. Hydrocephaly, on the other hand, was observed in 3 children exposed to VPA monotherapy. Of the 3 observed cases, only one had SB.
Jager-Roman 1986	Germany	Prospective	Women with epilepsy and their infants	VPA monotherapy, VPA in combination with other anticonvulsant drugs	Matched-pair controls, controls	26 infants of mothers	Fetal and neonatal distress, birth measurements, major malformations, and minor anomalies	Moderate risk of bias	During the first trimester, total VPA serum concentrations were well above therapeutic levels (100 to 184 micrograms/ml) in two women receiving high VPA doses (2,000 and 1,500 mg daily). Although dosage remained the same, serum concentrations decreased during pregnancy to therapeutic levels (33.9 to 57.0 micrograms/ml). The VPA percent free fraction increased in the third trimester and was threefold higher at birth. Almost half of the infants exposed to VPA monotherapy were distressed during labor, and 28% had low Apgar scores. Fetal and neonatal distress may be caused by the high VPA percent free fraction during labor and at birth. Mean body measurements at birth after VPA monotherapy were comparable to those in the matched control group but were reduced in the group of infants receiving VPA combination therapy. Four infants exposed to VPA monotherapy were born with major malformations. The median number of minor anomalies was four times higher in infants whose mothers received VPA alone or VPA combination therapy than in controls. Seven infants had a pattern of craniofacial and digital anomalies that was distinctly different from that observed after in utero exposure to other anticonvulsant medications.

Lindhout 1986	United Kingdom	Questionnaire analysis	Pregnant women with epilepsy	VPA	Other anticonvulsant drugs	13 groups	Neural tube defects (NTD)	Serious risk of bias	Of a total of 2,111 infants exposed to any anticonvulsant drug, 12 had an NTD (11 SB and anencephaly). The frequency of NTD among infants exposed to VPA with or without other anticonvulsants (6/393 or 1.5%) or to VPA alone (3/120 or 2.5%) is significantly higher than that among infants exposed to other anticonvulsant drugs (6/1,718 or 0.35%).
Mountain 1970	Australia	Prospective	Epileptic mothers	Anticonvulsant drug therapy	-	16 mothers and neonates	Neonatal coagulation defect	Serious risk of bias	Two of the neonates had clinical evidence of a bleeding tendency. A coagulation defect similar to that in vitamin-K deficiency was found in 8 neonates and was severe in 7. The mothers of the 8 affected neonates had been treated with a barbiturate or with a drug metabolised to a barbiturate and with phenytoin. It is suggested that anticonvulsant drug therapy during pregnancy, especially treatment with barbiturates, frequently causes a coagulation defect which may result in bleeding during the early neonatal period. The prophylactic use of vitamin K_1 is especially important in this situation.
Montiel 2022	United States	Case study	Primiparous woman	Lurasidone	-	1 woman	Symptoms, quality of life, illness exacerbation	-	This case report presents perinatal changes in the concentration of lurasidone and the implications for bipolar disorder (BD) illness course in a primiparous woman. Monitoring of lurasidone serum concentrations and recurrence of BD symptoms after the second trimester of pregnancy until the third postpartum month was completed. Lurasidone serum concentrations ranged from 0 to 4.7 ng/mL during pregnancy and increased to 10 to 12 ng/mL postpartum. The subject presented with worsening anxiety and depressive symptoms during the second trimester of pregnancy which resulted in a 40 mg daily dose increase during the second half of her pregnancy. Despite the decrease in lurasidone to the prepregnancy dose post-delivery, the concentrations were higher postpartum compared to pregnancy.
Clark 2018	Global	Literature review	Pregnant and postpartum women	Treatment for bipolar disorder	-	-	Congenital malformation, infant outcomes, management during pregnancy and postpartum, breastfeeding	-	Pharmacotherapy is the most effective treatment for most women with BD, and the risks and benefits of exposure to medication versus untreated illness during pregnancy must be considered for each woman. Women with BD who continue medication in pregnancy and postpartum reduce their risk for episode recurrence as well as the onset of postpartum depression and postpartum psychosis. If available and indicated, medication combined with bright light therapy optimizes treatment for women with bipolar depression. When psychiatric services are limited, use of professional and patient mental health resources are advised.

Gentile 2014	Italy	Expert opinion	Pregnant women	Second-generation antipsychotic (SGAs) treatment	Different SGAs	-	Metabolic safety, gestational diabetes mellitus (GDM)	-	Among studies assessing the metabolic safety of specific SGAs, we have 18 cases of GDM overall: 5 cases involve clozapine (CLO), 9 olanzapine (OLA) - the SGA agent that shows the highest number of reported cases of pregnancy exposure - and 2 each for quetiapine and risperidone. Four of these cases, 2 involving CLO and 2 OLA, were complicated by serious fetal and/or neonatal consequences. Such reports of SGA-associated GDM, together with preliminary data coming from retrospective and prospective studies, may represent signals of a potential safety issue.
Bescoby-Chambers 2001	United Kingdom	Case report	Two patients with features of fetal valproate syndrome (FVS)	CBZ, valproate	-	2 patients	Features of FVS, ICD-10 diagnosis, features of pervasive develop-mental disorders (PDD)	-	Both patients exhibited features of FVS. One patient was diagnosed with childhood autism, and one patient was diagnosed with Asperger syndrome and Tourette Syndrome.
Kozma 2001	United States	Case report and literature review	Pregnant patient and offspring	VPA	-	2 siblings	Phenotypic abnormalities	-	Both children had craniofacial findings, multiple systemic and orthopedic abnormalities, an overgrowth pattern, and developmental deficits. The literature from 1978–2000 is reviewed. A total of 69 cases that were solely exposed to VPA with adequate phenotypic description were identified. The clinical manifestations of FVS encompass a wide spectrum of abnormalities including consistent facial phenotype, multiple systemic and orthopedic involvement, central nervous system dysfunction, and altered physical growth. The facial appearance is characterized by a small broad nose, small ears, flat philtrum, a long upper lip with shallow philtrum, and micro/retrognathia. In this review, 62% of the patients had musculoskeletal abnormalities, 30% had minor skin defects, 26% had cardiovascular abnormalities, 22% had genital abnormalities, and 16% had pulmonary abnormalities. Less frequently encountered abnormalities included brain, eye, kidney, and hearing defects. Neural tube defects were seen in 3% of the sample. Twelve percent of affected children died in infancy and 29% of surviving patients had developmental deficits/mental retardation. Although 15% of patients had growth retardation, an overgrowth pattern was seen in 9%.

Sodhi 2001	India	Case report	Epileptic mother and infant	Phenobarbitone and sodium valproate	-		1 mother and 1 infant	Major congenital cardiac malformation	-	A term male baby was born to a 28-year-old third gravida mother, a known epileptic from 2-4 years of age, poorly controlled and on irregular treatment. Her previous two pregnancies had resulted in a fresh still born baby the first time and a second malformed baby with cleft lip who died within a few hours after birth. During this pregnancy she was on regular follow-up in the hospital, received phenobarbitone (120 mg/day) and sodium valproate (800rag/day) for seizure control, and had an uneventful antenatal period. Antenatal foetal ultrasound of around 18 weeks gestation was normal. Baby was born by emergency caesarean section for non-progress of labour. His birth weight was 2.7 kg and he had mild asphyxia. Soon after birth, he developed central cyanosis with oxygen saturation ranging between 60–70% for which he was intubated and bag and tube ventilation with 100% oxygen started. Inspite of this, his saturation did not improve, and the baby remained blue indicating a cardiac cause.
Williams 2001	United States	Case report	5 patients	VPA, CBZ	-		5 patients	Cognitive deficits, manifestations of autism, and typical phenotypic characteristics of FVS	-	VPA was used alone during pregnancy in two of the patients and in combination with another anticonvulsant in three patients. While these children were seen at different institutions, each had an intensive neurodevelopmental evaluation that involved a pediatrician with expertise in autism. Diagnosis of autism was based on markedly impaired development in social interaction and communication and significantly restricted range of activities and interests. None of our patients had evidence of growth deficiency or microcephaly, consistent with previous studies which have indicated no specific pattern of pre- or postnatal growth with exposure to VPA alone.

Kennedy 1998	Global	Literature review	Women of reproductive age	VPA	-	-	Teratogenic effects, prenatal issues	-	Because of the demographics of the population affected by such psychiatric conditions, more women of childbearing age are likely to be exposed to this teratogenic drug. Neural tube defects (NTD) are the most common of the major anomalies associated with in utero valproic acid exposure and are estimated to occur in 1–2% of exposed fetuses. Other teratogenic effects include facial dysmorphism, congenital cardiac defects, limb reduction defects and other skeletal anomalies. Prenatal diagnosis, in particular maternal serum ax-fetoprotein screening and targeted ultrasonography, should be offered to all pregnant women exposed to valproic acid and couples need to be aware of the prenatal diagnostic options available to them. The pregnancy and prophylaxis with high doses of folic acid is recommended for all women on valproic acid and counselling should also emphasize planning pregnancy to optimize folic acid supplementation. Psychiatrists should be aware of the teratogenic potential of valproic acid and know how to counsel their patients of reproductive age.
Williams 1997	United States	Case report	Patient	Valproate	-	One patient	FVS	-	Case reports on a patient who has a clinical phenotype compatible with both FVS and autism. The presence of an autistic disorder in a previously reported case of FVS and similar findings in our patient suggest that a relation between this known teratogen and autism may exist.
Thisted 1993	Denmark	Case series	Epileptic mothers	Sodium valproate	-	17 infants and mothers	Malformations, withdrawal manifestations, hypoglycemia	-	Nine infants had minor abnormalities and of these infants five also had major malformations, described as the 'fetal valproate syndrome'. The most frequent malformation was congenital heart disease. Nine of the infants had manifestations of withdrawal, such as irritability, jitteriness, abnormalities of tone, seizures, and feeding problems. Four of these infants had an unrelated hypoglycaemia. The frequency of withdrawal symptoms was significantly related to the dose of valproate given to the mothers in the third trimester, and there was a tendency for both the frequency of the minor abnormalities and the major malformations to be related to the valproate dosage in the first trimester.

Ardinger 1988	United States	Case series	Pregnant women and their children	VPA	-	19 children	Infant outcomes	-	The study found no consistent alterations of pre- or postnatal growth with exposure to VPA monotherapy. Postnatal growth deficiency and microcephaly were present however, in two thirds of children exposed to VPA in combination with other anticonvulsants. Developmental delay or neurologic abnormality was found in 71% of those exposed to VPA monotherapy, and in 90% of those exposed to VPA and other anticonvulsants. Craniofacial anomalies, which can be seen with other anticonvulsant exposures, including midface hypoplasia, short nose with a broad and/or flat bridge, epicanthal folds, minor abnormalities of the ear, philtrum or lip, and micrognathia were also found in infants whose mothers used VPA. Prominent metopic ridge and outer orbital ridge deficiency or bifrontal narrowing and certain major anomalies such as tracheomalacia, talipes equinovarus (with intact spine) and lumbosacral meningomyelocele seem to be peculiar to infants with VPA exposure. Other defects such as urogenital anomalies, inguinal or umbilical hernias, and minor digital anomalies that are common to other prenatal anticonvulsant exposures are also occasionally found in those exposed to VPA. Heart defects have been found in infants exposed to nearly every class of anticonvulsant although the types of defects associated with maternal VPA use may be clarified when classified by pathogenetic mechanism.
Winter 1987	England	Case series	Pregnant women and their infants	Sodium valproate or VPA	-	4 infants	Facial features	-	Common facial features in the three surviving infants include epicanthic folds, a flat nasal bridge, a broad nasal base, anteverted nostrils, a shallow philtrum, and a thin upper lip with a thick lower lip. Ridging of the metopic suture, congenital heart defect, postaxial polydactyly, and hypospadias were additional features in individual cases.

Koch 1983	Germany	Prospective case series	Epileptic women and their infants	Valproate monotherapy	-	14 infants	Infant outcomes, major and minor malformations	-	The daily doses of valproate ranged from 300 to 2,000 mg. All the women had primary generalized epilepsy. Five women had grand real seizures during pregnancy. Three infants (including twins) were prematurely born. One infant with multiple malformations was small for date and microeephalic. All other infants had birth measurements within the normal range (weight 3,363 _+ 527 gm; length 51.8 _+ 2.7 cm; head circumference 35.4 _+ 1.4 cm). Five of the infants had a pattern of minor anomalies of the face and digits that had been partially described before. 1,2 The most prominent features were brachycephaly with high forehead, shallow orbits, small nose, microstomy, thin lips, low-set and rotated ears, arachnodactyly, overlapping fingers and toes, and hyperconvex fingernails. We suggest that there is a typical pattern of minor anomalies that differs from the pattern in infants exposed to phenytoin and barbiturates. Major malformations were present in three of the five affected infants. One infant with myelomeningocele, congenital heart defect, and multiple skeletal abnormalities died at the age of 7 weeks. The two other infants had premature stenosis of the metopic suture and aplasia of both first ribs, respectively
Paulson 1981	Global	Literature review	Pregnant women	Anticonvulsants	One treatment vs another, different drug dosages	Animal studies, human studies	Incidence of malformations	-	The incidence of malformations in fetal mice exposed to phenytoin depends on drug dosage and the strain of mice. Animal research also suggests that most anticonvulsants are teratogenic in experimental animals when large doses are used, but the effect of valproate sodium on the fetus is poorly known. Cleft lip and palatal defects have been most extensively studied, but defects have also been noted in eyes, heart, and limb buds. Data from humans are less clear than the animal data, but human maternal exposure to anticonvulsants may increase infant clefting by threefold to tenfold. If a woman at risk for childbearing is given anticonvulsants for the first time, carbamazepine may be given first. Before pregnancy, the true need for anticonvulsants should be reassessed, but abrupt discontinuation of anticonvulsants during pregnancy is not now recommended.

Dalens 1980	France	Case report	Pregnant woman and infant	VPA	-	1 woman and 1 infant	Teratogenicity, infant malformations	-	A healthy young woman bad a short, generalized seizure at the onset of her pregnancy (second week) and received 1,000 mg VPA daily, without any other drug, for the duration of gestation. Two other grand real seizures occurred about the sixth and seventh months; treatment was continued. Delivery at term produced a dysmorphic female. The major clinical findings are summarized in the Table. The infant died suddenly at 19 days of age. Other examinations demonstrated levocardia and partial right bundle branch block, and electroencephalographic alterations. Two karyotypes were normal and postmortem examination did not show new features, especially as regards cardiac morphology.

Safety and Efficacy of Pharmacologic Interventions for Postpartum Psychosis

Author, year	*Setting*	*Design/ approach*	*Subjects*	*Intervention*	*Comparator*	*Sample size*	*Outcomes*	*Quality Assessment*	*Results*
Viswanathan 2021	Global	Systematic review and meta-analysis	Pregnant and postpartum women	Treatment	Placebo, one treatment vs another, no treatment	164 studies (131 studies included in analyses)	Symptoms, functional capacity, quality of life, peripartum events, adherence to treatment/care, suicidal events	High quality review	Brexanolone for depression onset in the third trimester or in the postpartum period probably improves depressive symptoms at 30 days (least square mean difference in the Hamilton Rating Scale for Depression, -2.6; p=0.02; N=209) when compared with placebo. Sertraline for postpartum depression may improve response (RR, 2.24; 95% CI, 0.95– 5.24; N=36), remission (calculated RR, 2.51; 95% CI, 0.94–6.70; N=36), and depressive symptoms (p-values ranging from 0.01 to 0.05) when compared with placebo. Discontinuing use of mood stabilizers during pregnancy may increase recurrence (aHR, 2.2; 95% CI, 1.2–4.2; N=89) and reduce time to recurrence of mood disorders (2 versus 28 weeks, aHR, 12.1; 95% CI, 1.6–91; N=26) for bipolar disorder when compared with continued use. Brexanolone for depression onset in the third trimester or in the postpartum period may increase the risk of sedation or somnolence, leading to dose interruption or reduction when compared with placebo (5% versus 0%). More than 95 percent of studies reporting on harms were observational in design and unable to fully account for confounding. These studies suggested some associations between benzodiazepine exposure before pregnancy and ectopic pregnancy; between specific antidepressants during pregnancy and adverse maternal outcomes such as postpartum hemorrhage, preeclampsia, and spontaneous abortion, and child outcomes such as respiratory issues, low Apgar scores, persistent pulmonary hypertension of the newborn, depression in children, and autism spectrum disorder; between quetiapine or olanzapine and gestational diabetes; and between benzodiazepine and neonatal intensive care admissions. Causality cannot be inferred from these studies. We found insufficient evidence on benefits and harms from comparative effectiveness studies, with one exception: one study suggested a higher risk of overall congenital anomalies (aRR, 1.85; 95% CI, 1.23–2.78; N=2,608) and cardiac anomalies (aRR, 2.25; 95% CI, 1.17–4.34; N=2,608) for lithium compared with lamotrigine during first trimester exposure.

Liu 2022	Denmark	Cohort	Pregnant women	Continuation of antidepressants throughout pregnancy	Discontinuation of antidepressants prior to, or during, pregnancy	23,189 women	Psychiatric emergency	Moderate risk of bias	Psychiatric emergencies were observed in 76 women who discontinued antidepressants before pregnancy and 91 women who continued. There was no evidence of higher risk of psychiatric emergency among women who discontinued antidepressants before pregnancy (cumulative incidence: 2.9%, 95% CI, 2.3%–3.6% for discontinuation versus 3.4%, 95% CI, 2.8%–4.2% for continuation; HR = 0.84, 95% CI, 0.61–1.16, p=0.298). Overall, 202 women who discontinued antidepressants during pregnancy and 156 who continued had psychiatric emergencies (cumulative incidence: 5.0%, 95% CI: 4.2%–5.9% versus 3.7%, 95% CI: 3.1%–4.5%). Antidepressant discontinuation during pregnancy was associated with increased risk of psychiatric emergency (HR, 1.25, 95% CI, 1.00–1.55, p=0.048). Study limitations include lack of information on indications for antidepressant treatment and reasons for discontinuing antidepressants.
Wang 2021	Hong Kong	Population-based cohort	Mother-child pairs	Gestationally exposed to antipsychotics	Gestationally nonexposed; past exposure; never exposed	411,251 mother-child pairs	ADHD, ASD, preterm birth, and small for gestational age	Moderate risk of bias	There were 13,196 children (3.95%) with a diagnosis of ADHD, 8,715 (2.12%) with ASD, 33,891 (8.24%) preterm, and 7,009 (1.70%) who were small for gestational age. The weighted hazard ratio (wHR) was 1.16 (95% CI, 0.83–1.61) for ADHD and 1.06 (95% CI, 0.70–1.60) for ASD, while the weighted odds ratio (wOR) was 1.40 (95% CI, 1.13–1.75) for preterm birth and 1.36 (95% CI, 0.86–2.14) for small for gestational age when comparing gestationally exposed with gestationally nonexposed individuals. Additional analyses showed no association when comparing gestationally exposed individuals with those with past exposure (ADHD: wHR, 0.99; 95% CI, 0.60–1.61; ASD: wHR, 1.10; 95% CI, 0.58–2.08; preterm birth: wOR, 0.93; 95% CI, 0.70–1.24; small for gestational age: wOR, 1.21; 95% CI, 0.66–2.20) and in a sibling-matched analysis (ADHD: wHR, 0.41; 95% CI, 0.04–4.93; ASD: wHR, 0.90; 95% CI, 0.40–2.01; preterm birth: wOR, 1.25; 95% CI, 0.85–1.82; small for gestational age: wOR, 0.86; 95% CI, 0.32–2.31).
Vallee 2020	Norway, Europe, North and South America, Australia	Cross sectional	Mothers in five weeks to one year postpartum period	Antidepressant treatment, survey questions	-	187 women	Reported thoughts of self-harm	Serious risk of bias	Overall, 52.9% of women took an antidepressant during pregnancy. Frequent self-harm ideation (SHI) postpartum was reported by 15.2% of non-medicated women and 22.0% of women on past antidepressant treatment in pregnancy; this proportion was higher following a single trimester treatment compared to three trimesters (36.3% versus 18.0%). There was no preventative association of antidepressant treatment in pregnancy on reporting frequent SHI postpartum (weighted RR, 1.90; 95% CI, 0.79–4.56), relative to never/hardly ever SHI.

Garriga 2019	Spain	Cohort	Patients with weight gain after initiating antipsychotics	Olanzapine cohort	Clozapine cohort	47 patients	Weight gain, birth weight	Serious risk of bias	Only in naïve patients, weight gain due to antipsychotics was significantly associated with birth weight, while male gender and body mass index at baseline were associated in both cohorts of patients. Treatment-resistant psychotic patients under clozapine were older, had previous antipsychotic treatment and more years of disease, confounders that might have influence a non-significant association
Hill 2019	Australia	Retrospective	Mothers with postpartum psychosis and their babies admitted to a mother-baby unit	Biopsychosocial package of care	-	25 dyads	Maternal illness and treatment, infant outcomes	Serious risk of bias	Affected women were found to be severely ill with a high rate of involuntary status (64%). They waited an average 4.7 days for a bed in the mother-baby unit. All received an atypical antipsychotic, with 16% receiving lithium augmentation. Infants were found to have generally normative growth and development, with relationship concerns noted in 5. A total of 36% of the cohort maintained some breastfeeding, and all had their infants in their care at discharge.
Schaffer 2019	Australia	Population-based cohort	Women who gave birth in specified time period	Antipsychotic use	No antipsychotic use	137,993 women	Mental health diagnoses and hospitalisations, use of psychotropic medicines and birth outcomes	Moderate risk of bias	2,741 (2.0%) were exposed to antipsychotics prior to or during pregnancy. We identified six trajectories of antipsychotic use: two involved short-term use of low daily doses prior to pregnancy (51.1%), while three involved long-term use of low (20.9%), moderate (11.0%) and high (2.0%) daily doses throughout pregnancy. One trajectory (15.0%) involved increasing use during pregnancy. Women with long-term use were more likely to have a schizophrenia or bipolar disorder diagnosis, to have used multiple psychotropics and to have a mental health hospitalisation during pregnancy. Overall, women using antipsychotics had elevated rates of adverse birth outcomes compared to unexposed women. Women with the greatest antipsychotic exposure had the highest rates of gestational diabetes and gestational hypertension.
Taylor 2019	United Kingdom	Historical cohort	Women with history of serious mental illness (SMI) who delivered babies	Exposed to regular medication	Unexposed to regular medication	452 pregnancies	Relapse of SMI in first 3 months postpartum, medication exposure	Serious risk of bias	128 (28.3%) pregnancies were associated with relapse in the first 3 months postpartum, with recent relapse an independent predictor (aOR; 95% CI, 1.30–2.27). There was no evidence of a prophylactic effect of medication (crude OR, 0.65; 95% CI, 0.34–1.25) (aOR, 0.99; 95% CI, 0.54–1.83), in women with non-affective or affective psychoses (interaction test p=.453).

Freeman 2018	United States	Prospective	Pregnant women	Exposed to second-generation antipsychotics (SGAs)	Control	403 participants	Gestational weight gain	Serious risk of bias	The mean pre-pregnancy weight, body mass index (BMI), and likelihood to begin pregnancy with an obese BMI were significantly higher in the exposed group compared to controls (p=.0003, p<0.0001 and p<.0001 respectively), as were the mean weight and BMI at delivery (p < 0.0001). The mean weight gain did not differ significantly between groups. Across pre-pregnancy BMI categories, both groups gained more than the recommended amount of weight during pregnancy.
Park 2018	United States	Cohort	Women who during the 3 months before their last menstrual period filled a prescription for atypical antipsychotics	Continuers of medication (aripiprazole, olanzapine, quetiapine, risperidone, or ziprasidone) exposure that occurred during the first 140 days of pregnancy	Discontinuers	1,924 women	Gestational diabetes	Moderate risk of bias	Women who continued antipsychotic treatment during pregnancy generally had higher comorbidity and longer baseline antipsychotic use. The crude risk of developing gestational diabetes among continuers compared with discontinuers, respectively, was 4.8% and 4.5% for aripiprazole, 4.2% and 3.8% for ziprasidone, 7.1% and 4.1% for quetiapine, 6.4% and 4.1% for risperidone, and 12.0% and 4.7% for olanzapine. The adjusted relative risks were 0.82 (95% CI, 0.50–1.33) for aripiprazole, 0.76 (95% CI, 0.29–2.00) for ziprasidone, 1.28 (95% CI, 1.01–1.62) for quetiapine, 1.09 (95% CI, 0.70–1.70) for risperidone, and 1.61 (95% CI, 1.13–2.29) for olanzapine.
Luykx 2019	Global	Review	Postpartum women	Assessment for postpartum psychosis (PP)	-	-	Prevention, management	-	For women with acute PP, 3 types of prevention can be distinguished. These are (1) prevention of PP in women at high risk (primary prevention); (2) early detection of PP (in women without a previous psychiatric history, secondary prevention); and (3) prompt and adequate treatment and management of PP, ensuring the safety of both mother and child (tertiary prevention).

Bergink 2016	Literature review	Global	Postpartum women	Screening for psychosis/ mania	-	-	Diagnostic recommendations, treatment options, and strategies for prevention	-	The incidence of first-lifetime onset postpartum psychosis/mania from population-based register studies of psychiatric admissions varies from 0.25 to 0.6 per 1,000 births. After an incipient episode, 20%–50% of women have isolated postpartum psychosis. The remaining women have episodes outside the perinatal period, usually within the bipolar spectrum. Presumably, the mechanism of onset is related to physiological changes after birth (e.g., hormonal, immunological, circadian), which precipitate disease in genetically vulnerable women. Some women have treatable causes and comorbidities, such as autoimmune thyroiditis or infections. N-methyl-D-aspartate-encephalitis or inborn errors of metabolism may present after birth with psychosis. Inpatient care is usually required to ensure safety, complete the diagnostic evaluation, and initiate treatment. The relapse risk after a subsequent pregnancy for women with isolated postpartum psychoses is 31% (95% CI, 22–42). Strategies for prevention of postpartum psychosis include lithium prophylaxis immediately postpartum and proactive safety monitoring.

Health Equity

Author, year	*Setting*	*Design/ approach*	*Subjects*	*Intervention*	*Comparator*	*Sample size*	*Outcomes*	*Quality Assessment*	*Results*

Rojas 2007	Chile	Randomized controlled trial	Mothers with major depression	Multicomponent intervention (psychoeducational group, treatment adherence support, and pharmacotherapy if needed)	Usual care	230 mothers	Edinburgh Postnatal Depression Scale (EPDS) score	High risk of bias	208 (90%) of women randomly assigned to treatment groups completed assessments. The crude mean EPDS score was lower for the multicomponent intervention group than for the usual care group at 3 months (8·5 [95% CI, 7·2–9·7] versus 12·8 [11·3–14·1]). Although these differences between groups decreased by 6 months, EPDS score remained better in multicomponent intervention group than in usual care group (10·9 [9·6–12·2] versus 12·5 [11·1–13·8]). The adjusted difference in mean EPDS between the two groups at 3 months was –4·5 (95% CI –6·3 to –2·7; p<0·0001). The decrease in the number of women taking antidepressants after 3 months was greater in the intervention group than in the usual care group (multicomponent intervention from 60/101 [59%; 95% CI, 49–69%] to 38/106 [36%; 27–46%]; usual care from 18/108 [17%; 10–25%] to 11/102 [11%; 6–19%]).
Snowber 2022	United States	Retrospective cohort	Pregnant and postpartum people who self-identified as either Black or White, and received prenatal care at academic faculty offices affiliated with an urban quaternary medical center	Implementation of the perinatal collaborative care model	Epochs of implementation	4,710 individuals	Frequency of depression screening, frequency of provision of a treatment recommendation for those with a positive depression screen	Moderate risk of bias	4,135 (87.8%) self-identified as White and 575 (12.2%) self-identified as Black. Before implementation, Black individuals were more likely to receive screening (aOR, 2.44) but less likely to have a treatment recommended when a positive screen was identified (aOR, 0.05). In multivariable models, race-by-epoch interaction terms were significant for both antenatal screening (*P*<.001) and antenatal treatment recommendation (*P*=.045), demonstrating that implementation of the perinatal collaborative care model was associated with reductions in extant racial disparities. After implementation, there were no significant differences by race (referent=White) in screening for antenatal depression (aOR, 1.22, 95% CI, 0.89–1.68) or treatment recommendations for those who screened positive (aOR, 0.64; 95% CI, 0.27–1.53). Race-by-epoch interaction terms were not significant in multivariable models for either postpartum screening or treatment recommendation.

Petersen 2021	United States	Database cohort and analysis	Commercially insured pregnant women	Selective serotonin reuptake inhibitor (SSRI) use	No SSRI use	1,061,023 women	Patterns of selective serotonin reuptake inhibitor (SSRI) use	Serious risk of bias	A total of 46,087 of women (4.34%) were dispensed SSRIs during the estimated pregnancy period. Sertraline was the most common overall and had the highest initial use after trimester 1, including women who switched from another SSRI, although dispensing for > 1 SSRI during pregnancy was uncommon. Use of vilazodone was rare and had the highest discontinuation after trimester 1, followed by paroxetine. SSRI use was more common among women who were older, White, college-educated, higher income (≥ $100,000), or resided in the Midwest. Paroxetine and dispensings for > 1 SSRI were more common in lower education subgroups. White women had the highest proportion of use in all trimesters of pregnancy, whereas Hispanic women had the lowest.
Hanley 2018	Canada	Retrospective population-based cohort	Postpartum women	Depression	Without depression	305,683 pregnancies among 217,721 women	Health service use	Moderate risk of bias	Women in the highest income quintile were significantly more likely to see a psychiatrist for depression during pregnancy and to fill prescriptions for serotonin reuptake inhibitor (SRI) antidepressants than women in the lowest income quintile. Women at the lower end of the income distribution were more likely to have a GP visit for depression. Women at the low end of the income distribution were more likely to end up in hospital for depression or a mental health condition during pregnancy and more likely to receive a benzodiazepine and/or an antipsychotic medication.

Sherman 2018	United States	Database analysis	Women of reproductive age with record of live birth	Medicaid	Private insurance	131,067 women	Days to diagnosis, postpartum depression, days to treatment initiation, and number of therapy sessions	Moderate risk of bias	After childbirth, 7% of privately insured women and 13% with Medicaid were newly diagnosed with depression (h = 0.22). Those with Medicaid were diagnosed earlier (median 43 days versus 78 days for private), but treatment initiation occurred later (h = 0.38) and at a lower rate (54% with Medicaid received some treatment versus 71% with private insurance, h = 0.35). Many women received medication without therapy (44% with Medicaid versus 51% with private insurance). Therapy was used more commonly by private enrollees (20% versus 10% of Medicaid; h = 0.28). Among those who received therapy, the median was three sessions.
Bhat 2017	United States	Analysis of randomized controlled trial	Medicaid-enrolled pregnant women	MOMCare (choice of brief interpersonal psychotherapy, pharmacotherapy, or both)	Intensive maternity support services (MSS-Plus)	160 women	Postpartum depression scores, functional impairment, adverse birth event	Moderate risk of bias	For women who received MOMCare, postpartum depression scores (measured with the Symptom Checklist–20) did not differ by whether or not they experienced an adverse birth event (mean6SD scores of .866.51 for mothers with an adverse birth event and .836.56 for mothers with no event; p=.78). For women who received MSS-Plus, having an adverse birth event was associated with persisting depression in the postpartum period (mean scores of 1.20 $\pm$ 0.61 for mothers with an adverse birth event and .93 $\pm$.52 for mothers without adverse birth event; p=.04). Similar results were seen for depression response rates and functioning.
Grote 2017	United States	Analysis of randomized controlled trial	Medicaid-enrolled pregnant women	MOMCare (choice of brief interpersonal psychotherapy, pharmacotherapy, or both)	Intensive maternity support services (MSS-Plus)	164 women	Depression severity	Moderate risk of bias	When the analysis controlled for baseline depression severity, women with probable depression and PTSD in MOMCare had 68 more depression-free days over 18 months than those in MSS-Plus (p<.05). The additional depression care cost per MOMCare participant with comorbid PTSD was $1,312. The incremental net benefit of MOMCare was positive if a depression free day (DFD) was valued at $\geq$$20.
Ncube 2017	United States	Prospective cohort	Women who received prenatal care	Patient Health Questionnaire-9 and self-reported antenatal antidepressant medication use	-	2,073 participants	Preterm birth, antenatal depression	Serious risk of bias	Non-Hispanic (NH) black (RR, 1.89; 95% CI, 0.94–3.80), NH white (RR, 1.58; 95% CI, 1.04–2.39), and Asian (RR, 2.06; 95% CI, 0.69–6.13) women with antenatal depression were at increased risk for delivering preterm infants, compared with women without antenatal depression, although the associations were statistically significant only among NH white women. There was no evidence of an association between antenatal depression and risk of PTB among Hispanic women (RR, 0.96; 95% CI, 0.28–3.25); p-value for interaction = 0.81.

Prady 2016	United Kingdom	Cohort analysis	Pregnant women	Diagnoses, symptoms, signs, referrals for treatment, non-pharmacological and pharmacological treatment, monitoring	-	2,234 women	Rates and types of treatment during pregnancy	Serious risk of bias	Most women were discontinued from pharmacological treatment early in pregnancy, but this was accompanied by recorded access to non-drug treatments in only 15% at the time of delivery. Fewer minority ethnic women accessed treatments compared to White British women despite minority ethnic women being 55–70% more likely than White British women to have been identified with anxiety in their medical record.
Yamamoto 2015	United States	Survey and analysis	Pregnant women	Antidepressant use	No use, one medication vs another	18,262,000	Disparities	Moderate risk of bias	Antidepressant use was reported during 2.2% of all outpatient visits for pregnant women. Providers indicated a depression diagnosis in 4.5% of visits. Among visits for depressed pregnant women, providers reported antidepressant use 25.4% of the time for all visits. Antidepressant use during pregnancy varied significantly by race/ethnicity. Among visits for non-Hispanic White women, 3.1% included a code for antidepressant use vs just 1.0% for non-White women (P<0.0001). After adjustment for age, insurance status and region of the country, this association persisted with non-Hispanic White (vs non-White) pregnant women having higher odds of antidepressant use (aOR, 3.3; 95% CI 2.1–5.3).
Lara-Cinisomo 2014	United States	Data from focus groups	Prenatal and postpartum Latinas at risk for depression	Focus group interview	-	22 women	Perinatal depression coping strategies, preferred approaches to treating perinatal depression, and recommendations for engaging perinatal Latinas in treatment	Serious risk of bias	The results suggest that Latinas' treatment preferences consist of a pathway (i.e., hierarchical) approach that begins with the use of one's own resources, followed by the use of formal support systems (e.g., home-visiting nurse), and supplemented with the use of behavioral therapy. Antidepressant use was judged to be acceptable only in severe cases or after delivery.

Wu 2014	United States	Retrospective cohort	Pregnant women diagnosed with major depression	Initiated antidepressant medications during pregnancy	-	804 women	Treatment nonpersistence to antidepressant therapy during pregnancy	Serious risk of bias	Nearly 45% of this cohort did not continue to use antidepressant pharmacotherapy, showing a gap ≥15 days between 2 prescriptions, after initiating antidepressant therapy during pregnancy. Women reporting nonwhite race were 36% more likely to show a gap in antidepressant medication use during pregnancy than white women. Women with a history of antidepressant use before pregnancy were 44% more likely to discontinue the antidepressant therapy during pregnancy.

Palmsten 2013	United States	Cohort	Pregnant women with a diagnosis of mood or anxiety disorder	Current pharmacy use (delivery date), recent (1–30 days before delivery date), past (1–5 months before delivery date)	No exposure (reference group)	106,000 women	Risk of postpartum hemorrhage by timing of exposure and by serotonin or non-serotonin reuptake inhibitors, classes of antidepressant, and antidepressant types	Moderate risk of bias	12,710 (12%) women had current exposure to serotonin reuptake inhibitor monotherapy, and 1,495 (1.4%) women had current exposure to non-serotonin reuptake inhibitor monotherapy. The risk of postpartum hemorrhage was 2.8% among women with mood/anxiety disorders but no exposure to antidepressants, 4.0% in the current users of serotonin reuptake inhibitors, 3.8% in the current users of non-serotonin reuptake inhibitors, 3.2% in the recent users of serotonin reuptake inhibitors, 3.1% in the recent users of non-serotonin reuptake inhibitors, 2.5% in the past users of serotonin reuptake inhibitors, and 3.4% in the past users of non-serotonin reuptake inhibitors. Compared with no exposure, women with current exposure to serotonin reuptake inhibitors had a 1.47-fold increased risk of postpartum hemorrhage (95% CI, 1.33–1.62) and women with current non-serotonin reuptake inhibitor exposure had a 1.39-fold increased risk (1.07–1.81). Results were similar with hdPS adjustment. Women with current exposure to serotonin reuptake inhibitors had an adjusted excess risk of 1.26% (0.90%–1.62%), with a number needed to harm of 80, and for women with current exposure to non-serotonin reuptake inhibitors the excess risk was 1.03% (0.07%–1.99%), with a number needed to harm of 97. For exposure to serotonin reuptake inhibitors the relative risk was 1.19 (1.03–1.38) for recent exposure and 0.93 (0.82–1.06) for past exposure; for non-serotonin reuptake inhibitors the figures were 1.17 (0.80–1.70) and 1.26 (1.00–1.59), respectively. Current exposure to selective serotonin reuptake inhibitor monotherapy was also associated with postpartum hemorrhage (1.42, 1.27–1.57), as was current serotonin norepinephrine (noradrenaline) reuptake inhibitor (1.90, 1.37 to 2.63) and tricyclic monotherapy (1.77, 0.90–3.47). All types of selective serotonin reuptake inhibitors available for analysis and venlafaxine, a serotonin norepinephrine reuptake inhibitor, were significantly associated with postpartum hemorrhage.

Kozhimannil 2011	United States	Retrospective cohort	Postpartum women	Black women and Latinas enrolled in Medicaid	Statistical analyses used white women as a comparison group for both black women and Latinas	29,601 women	Postpartum mental health treatment initiation, follow-up, and receipt of continued care	Serious risk of bias	Nine percent (N=1,120) of white women initiated postpartum mental health care, compared with 4% (N=568) of black women and 5% (N=162) of Latinas. With analyses controlling for clinical factors, the odds of initiating treatment after delivery were significantly (p<.001) lower for blacks (aOR, .43) and Latinas (aOR, .59) compared with whites. Among those who initiated treatment, blacks and Latinas were less likely than whites to receive follow-up treatment (blacks, aOR, .66; p<.001; Latinas, aOR, .67; p<.05) or continued care (blacks, aOR, .81; p=.069; Latinas, aOR, .67; p<.05). Among those who initiated antidepressant treatment, black women and Latinas were less likely than whites to refill a prescription.
Sleath 2005	United States	Questionnaire analysis	Pregnant women	Questionnaire/interview	-	73 women	Depression, treatment preference	Serious risk of bias	Nineteen percent of women had symptoms of moderate or severe depression. Women with moderate or severe symptoms of depression were more likely to believe that antidepressants were an acceptable treatment than those without symptoms or with only minor depression symptoms. There were only small differences among the three ethnic groups for antidepressant use preference, but most women found them to be unacceptable. In contrast, approximately half of the White women felt that herbal medicines were acceptable compared with 16% and 22% for African Americans and Hispanics, respectively. Only 44% of African American women felt that counseling from a mental health professional was an acceptable treatment for depression compared to 68% for White and 61% for Hispanic women. Similarly, African American women were less likely to believe that waiting and getting over depression symptoms naturally was acceptable compared to Hispanic and White women.