Maternal and neonatal complications of pregnant women with bipolar disorder: a systematic review and meta-analysis

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Summary

Background Confidence in pregnancy outcome data for women with bipolar disorder is compromised by small cohort sizes. However, comprehensive national data have been published over the last decade, but no quantitative synthesis has been established to determine the factors associated with complications in these women. Our goal is to summarise the evidence of population-based data on obstetric complications and neonatal outcomes in women with bipolar disorder compared to women without bipolar disorder.

Methods Following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines, a comprehensive search was conducted of PubMed/MEDLINE, Embase, PsycINFO, Web of Science, and Google Scholar from inception to September 26th, 2024. Thirty-six outcomes were extracted from eligible articles for consideration. The study protocol was registered on PROSPERO (CRD42023369031).

Findings Fourteen population-based retrospective cohort studies from six high-income countries (Australia, Canada, Hong-Kong, Sweden, Taiwan, and USA) involving 47,954 women with bipolar disorder and their newborns compared to 11,896,577 women without bipolar disorder, published between 2005 and 2024, were identified. During pregnancy, women with bipolar disorders seemed to exhibit an increased risk of gestational diabetes OR = 1.46, (95% Confidence Interval [1.06–2.03]; I^2 = 87%), gestational hypertension OR = 1.19 (95% CI [1.02–1.40]; I^2 = 41%), antepartum haemorrhage OR = 2.02 (95% CI [1.30–3.13]; I^2 = 67%), and pre-eclampsia or eclampsia OR = 1.20 (95% CI [1.05–1.36]; I^2 = 67%). At delivery, women with bipolar disorder were observed to face a higher risk of caesarean section OR = 1.35 (95% CI [1.26–1.45]; I^2 = 56%), and postpartum haemorrhage OR = 1.39 (95% CI [1.20–1.62]; I^2 = 0%). Their newborns also appear to be at high risks of very prematurity OR = 1.84 (95% CI [1.32–2.57]; I^2 = 74%), infant death OR = 1.77 (95% CI [1.01–3.13]; I^2 = 41%), low birth weight OR = 1.54 (95% CI [1.19–1.99]; I^2 = 70%), preterm birth OR = 1.49 (95% CI [1.29–1.72]; I^2 = 87%), small for gestational age OR = 1.28 (95% CI [1.14–1.45]; I^2 = 57%), and congenital malformations OR = 1.29 (95% CI [1.09–1.53]; I^2 = 42%). According to the AMSTAR 2 tool, these results correspond to moderate-quality evidence.

Interpretation Despite substantial heterogeneity observed, our findings suggest the presence of a broad spectrum of complications that may affect both pregnant women with bipolar disorder and their newborns. These results can serve as a basis for the development of guidelines for the prevention and management of these complications. We need additional data from other countries, particularly from low-to-moderate income countries.

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Keywords: Bipolar disorder; Pregnancy complications; Delivery complications; Postnatal complication; Meta-analysis

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Research in context

Evidence before this study

Prior to this study, extensive national data on pregnancy in women with bipolar disorder had been published, but no quantitative synthesis existed to identify associated factors for complications in this population. This gap hinders understanding specific risks and developing uniform medical recommendations. Our search strategy was based on MeSH terms in PubMed/Medline and adapted for other databases, focusing on population-based studies of pregnant women with and without bipolar disorder, with quality assessed using the Newcastle–Ottawa scale.

Added value of this study

A total of 14 studies published as of September 26th, 2024, involving 47,954 deliveries by women with bipolar disorder and 11,896,577 deliveries by unexposed women, were included in this analysis. Despite the small number of studies and the resulting substantial heterogeneity, pregnant women with bipolar disorder may face an increased risk of complications during pregnancy and childbirth, including gestational diabetes, hypertension, and a higher likelihood of caesarean delivery, which can lead to postpartum haemorrhage. Their infants are also at an elevated risk of low birth weight, prematurity, and congenital anomalies due to these maternal complications.

Implications of all the available evidence

Care for pregnant women with psychiatric disorders remains underdeveloped. Our analysis of nearly 50,000 cases of pregnant women with bipolar disorder suggest that these women may be at a higher risk of experiencing 12 complications related to pregnancy, delivery, and neonatal outcomes compared to unexposed women. This study presents a range of arguments that may support the development of guidelines aimed at preventing and managing these complications.

Introduction

Bipolar disorder, characterized by alternating episodes of euphoria (mania) and depression, has seen a rising prevalence among women globally, increasing from 13.2 million (95% CI [10.9–15.5]) to 20.7 million (95% CI [17.3–24.6]) between 1990 and 2019.[1] This disorder interacts intricately with the hormonal fluctuations and psychological stressors introduced by pregnancy, potentially exacerbating its symptoms. A brief bibliographic search carried out in June 2023 revealed a series of studies published over the last decade. These studies shed light on the increased prevalence of adverse pregnancy outcomes, such as preterm birth[2] and antepartum hemorrhage,[3] among women diagnosed with bipolar disorder, as evidenced by population-based studies conducted in the USA and Europe.[4,5] Some studies have focused on different outcomes throughout pregnancy,[5] others on outcomes during delivery,[6] while still others have targeted specific problems, such as hypertension and its complications.[7] Literature reviews are available but without quantitative synthesis.[8,9] The lack of quantitative synthesis noted in the literature does not allow us to definitively conclude on the outcomes more frequently observed in bipolar women and to identify potential factors contributing to their variation to guide clinical practice. The current guidelines indeed do not provide specific recommendations for bipolar disorder, although the World Health Organization (WHO) highlighted this urgent need in 2021.[10]

The primary objective is to synthesize the potential evidence on pregnancy, delivery, neonatal complications, and infant mortality among women with bipolar disorder and their newborns compared to women without bipolar disorder.

Methods

Search strategy and selection criteria

The reporting of this study adhered to the established guidelines outlined in the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020.[11] To ensure transparency and consistency, a detailed protocol outlining predefined eligibility criteria was registered with PROSPERO, a prospective register of systematic reviews (CRD42023369031) on June 6th, 2023.

The search paradigm was based on the Mesh terminology of the PubMed/Medline database and adapted for Embase, Web of science [clarivate], PsycINFO and Google Scholar[12] ("bipolar disorder" [All Fields] OR "affective psychosis" [All Fields]) AND ("pregnancy" [All Fields] OR "pregnan*" [All Fields] OR "newborn disease" [All Fields] OR "labor complication" [All Fields] OR "delivery complication" [All Fields] OR "pregnancy disorder" [All Fields] OR "neonatal" [All Fields]). This search was carried out from inception to September 26th, 2024, with no language or date restrictions. The reference lists and bibliographies of relevant reviews and articles collected from the database searches, were hand searched for other relevant articles collection. The corresponding authors were requested to supply any unpublished results as well as any other data not included in the original articles, if necessary.

The eligibility criteria were: (i) Only population-based studies with unmatched retrospective cohorts (ii) Any language and date of publication; (iii) Original research papers; (iv) Exposed group: pregnant women with a diagnosis of bipolar disorder. The bipolar diagnosis may not necessarily be reported before delivery; (v) Unexposed group: pregnant women without bipolar disorder

or without psychiatric disorder; (vi) At least one pregnancy, delivery, neonatal or infant mortality outcome reported in the exposed and unexposed groups. The exclusion criteria were single-center studies (i.e., studies based on a single department or hospital except if this hospital covered the whole geographical population area), reviews, meta-analyses and overlapping datasets for dates. If two studies analysed the same database, the article with the highest number of participants, was preferred. If an outcome was only found in the article with the lowest number of participants, it was also included in the meta-analysis. DEE and GF carried out the inclusion of studies. In the case of a non-consensus for the inclusion of a study, a third author (LB) made the final decision.

Variations in clinical and methodological aspects among studies may not always be evident through statistical differences, so assessing the similarity of studies should be based on the population studied, the specific questions and outcomes under consideration,[13,14] as investigated in this study.

Data extraction and quality assessment

All the data extracted were binary variables. The following pregnancy outcomes (15) were extracted: gestational diabetes, gestational hypertension, thromboembolism, urinary infection, anaemia, pre-eclampsia or eclampsia, placental abruption, antepartum haemorrhage, chorioamnionitis, threatened preterm labour, premature rupture of membrane, placental complication, oligohydramnios, polyhydramnios, and general infection during pregnancy. The following delivery outcomes (7) were extracted: C-section, labour induction, instrumental delivery, postpartum haemorrhage, foetal distress, breech presentation, and maternal death. The following newborn outcomes (14) were extracted: congenital malformations, asphyxia, Apgar score at 5 min <7, intensive care, small for gestational age, large for gestational age, low birth weight, high birth weight, preterm birth (gestational age between 32 and 37 weeks), very preterm birth (gestational age <32 weeks), stillbirths, neonatal mortality (between 0 and 28 days of life), post-neonatal mortality (between 29 and 365 days of life), and infant death during the first year of life (0–365 days of life).

The following study characteristics were extracted: author, year of publication, year of first birth inclusion, year of last birth inclusion, country, database used, exposed definition (time for psychiatric diagnosis, diagnosis period covering the period before pregnancy, inclusion of post-delivery bipolar disorder diagnoses, and ICD or DSM codes), and unexposed definition (women without bipolar disorder or without psychiatric disorder). Sociodemographic variables, comorbidities, treatments, and follow-up variables that could potentially affect pregnancy, delivery, neonatal, and child outcomes were also extracted: i.e., age, parity, absence of a partner in supportive environment (single, divorced, or widowed), low socioeconomic level, ethnicity, primiparous pregnancy, child sex, smoking, alcohol, illicit drug, obesity, hypertension before pregnancy, diabetes before pregnancy, dysthyroid disorder, epilepsy, infection by human immunodeficiency virus, mood stabilizer treatments, and the number of prenatal visits. Quality of included studies was assessed using Newcastle–Ottawa scale for cohort studies.[15] Studies were classified as good, fair or poor quality according to Agency for Health Research and Quality (AHRQ) standards: Good quality: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain; Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain; Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain.[16] To assess the quality of the obtained results, we followed the AMSTAR 2 recommendations.[17] Two investigators (DEE and GF) independently performed the screening and extracted data from included trials using a predesigned extraction form, which was based on the Joanna Briggs Institute Data Extraction Form for Prevalence and Incidence Studies.[18] Additional items relevant to the current study were also added. The first and last authors (DEE and GF) examine each discrepancy in data extraction to reach consensus.

Ethics

Ethical approval was not required, as this study is a meta-analysis of publicly available data.

Statistics

For each outcome, we analysed comparative data on pregnancy, delivery, neonatal, and child outcomes.[19] Using the inverse-variance weighting method, a random effects model was used to calculate the odds ratio (OR) of each outcome and its 95% confidence interval (95% CI).[20,21] Number of included studies is indicated by symbol: k. When available, we used the numbers of events and the sample sizes instead of the OR.[22] If we found the odds ratio with its confidence interval without the raw values, we used the functionality of R's "metafor" package to be able to group this information with that from studies reporting raw values. Heterogeneity between studies was quantified with the I^2 statistic.[23] Q and I^2 were calculated to assess heterogeneity across all studies and within subgroups, with $I^2 \geq 50\%$ indicating significant heterogeneity.[24] Publication bias was assessed graphically with a funnel plot and statistically with Egger's test when at least ten studies were included in the meta-analysis.[25] Sensitivity analyses were performed using the "leave-one-out" method for each outcome.[26] Subgroup analyses for two binary variables (year of last inclusion and

country and matched or not studies) were used to evaluate factors that moderated the individual study estimates of the OR of each outcome. These subgroup analyses were performed if it was possible to have four studies in each subgroup.[19] All analyses and graphs were carried out using R software,[27] with the metafor and forest plot packages, respectively.[28,29]

Role of the funding source

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

Results

A total of 14 studies from six high-income countries (47,954 deliveries of women with bipolar disorder and 11,896,577 deliveries of women without bipolar disorder) were included (Flow-diagram Fig. 1).[2–5,30–39] The following cohort and countries were included (in order of year of first patient included): Australia (1980–1992, 2007–2011, 2007–2017), Sweden (2005–2009), Canada (Quebec: 1989–2013, Ontario: 2002–2010), Taiwan (2001–2003), US (nationwide U.S. cohort: 2002–2008, Nationwide and National Inpatient Sample (HCUP-NIS): 2008–2014, California: 2005–2008), Hong-Kong (2003–2018). No study has been carried out in low- or middle-income countries. All included studies were of unmatched population based retrospective cohorts. The characteristics of included studies are presented in Table 1. All the reported results below are available in the forest plot Fig. 2. All adjustment factors considered in each study are available in Supplementary Table S1/column 5. Each definition of each outcome, based on the included studies, is reported in Supplementary Table S2. The excluded studies and the reasons for their exclusion are presented in Supplementary Table S3.

Pregnancy outcomes

Compared to pregnant women without bipolar disorder, pregnant women with bipolar disorders had increased risk of antepartum haemorrhage (OR 2.02, 95% CI [1.30–3.13]; I^2 = 66.5%; k = 3), gestational diabetes (OR 1.46 [1.06–2.03]; I^2 = 86.6%; k = 5), pre-eclampsia or eclampsia abruption (OR 1.20 [1.05–1.36]; I^2 = 66.6%; k = 3), and gestational hypertension (OR 1.19 [1.02–1.40]; I^2 = 40.6%; k = 4). Pregnant women with bipolar disorders had no statistically significant increased risk for threatened preterm labour or placenta abruption (p > 0.05; k = 3 for each). There was not enough data to perform meta-analysis for thromboembolism, urinary infection, anaemia, chorioamnionitis, premature rupture of membrane, placental complication, oligohydramnios, polyhydramnios, and general infection during pregnancy.

Delivery outcomes

Compared to pregnant women without bipolar disorder, pregnant women with bipolar disorders had an increased risk of caesarean section (OR 1.35 [1.26–1.45]; I^2 = 55.7%; k = 6), and postpartum haemorrhage (OR 1.39 [1.20–1.62]; I^2 = 0.0%; k = 4). There was not enough data to perform meta-analysis for labour induction, instrumental delivery, foetal distress, breech presentation, and maternal death.

Newborn outcomes

Compared to newborns of women without bipolar disorder, newborns of women with bipolar disorders had increased risk of very preterm birth (OR 1.84 [1.32–2.57]; I^2 = 74.0%; k = 4), low birth weight (OR 1.54 [1.19–1.99]; I^2 = 70.1%; k = 6), preterm birth (OR 1.49 [1.29–1.72]; I^2 = 86.5%; k = 11), small for gestational age (OR 1.28 [1.14–1.45]; I^2 = 56.5%; k = 4), congenital malformations (OR 1.29 [1.09–1.53]; I^2 = 42.4%; k = 4), and infant death (OR 1.77 [1.01–3.13]; I^2 = 41.4%; k = 3). Newborns of women with bipolar disorders had no statistically significant increased risk for large for gestational age or stillbirth (all, p > 0.05; k = 3). There was not enough data to perform meta-analysis for asphyxia, Apgar score at 5 min < 7, intensive care, and high birth weight.

Funnel plots and Egger's test were performed only for preterm delivery measured in more than ten studies. Visual analysis of the funnel plot and Egger's test (p > 0.05) found no publication bias. Study quality is presented in Table 2 and detailed in Supplementary Table S1. Ten out of fourteen studies were deemed to be of good quality according to AHRQ criteria regarding the Newcastle–Ottawa scale. Sensitivity analyses using the leave-one-out method was made concerning the following variables: caesarean section, gestational diabetes, gestational hypertension, low birth weight, obesity, preeclampsia or eclampsia, preterm birth, small for gestational age, and stillbirth. During the 'leave-one-out' procedure, the results were maintained after removing each of the included studies except for placenta abruption (excluding Dejong et al., 2018 or Mei-Dan et al., 2015), for diabetes gestational (excluding Chan et al., 2024, Dejong et al., 2018, or Frayne et al., 2019), for gestational hypertension (excluding Nguyen et al., 2014), for postpartum haemorrhage (excluding Dejong et al., 2018), very prematurity (excluding Männistö et al., 2016), low birth weight (excluding Nguyen et al., 2014), infant death (excluding Jablensky et al., 2005 or Nguyen et al., 2014). According to the AMSTAR 2 tool, these results correspond to moderate-quality evidence (Supplementary Table S4 in Supplementary Material). All forest plot and funnel plot produced are presented in Supplementary Material. Subgroup analyses could not be performed due to a lack of data.

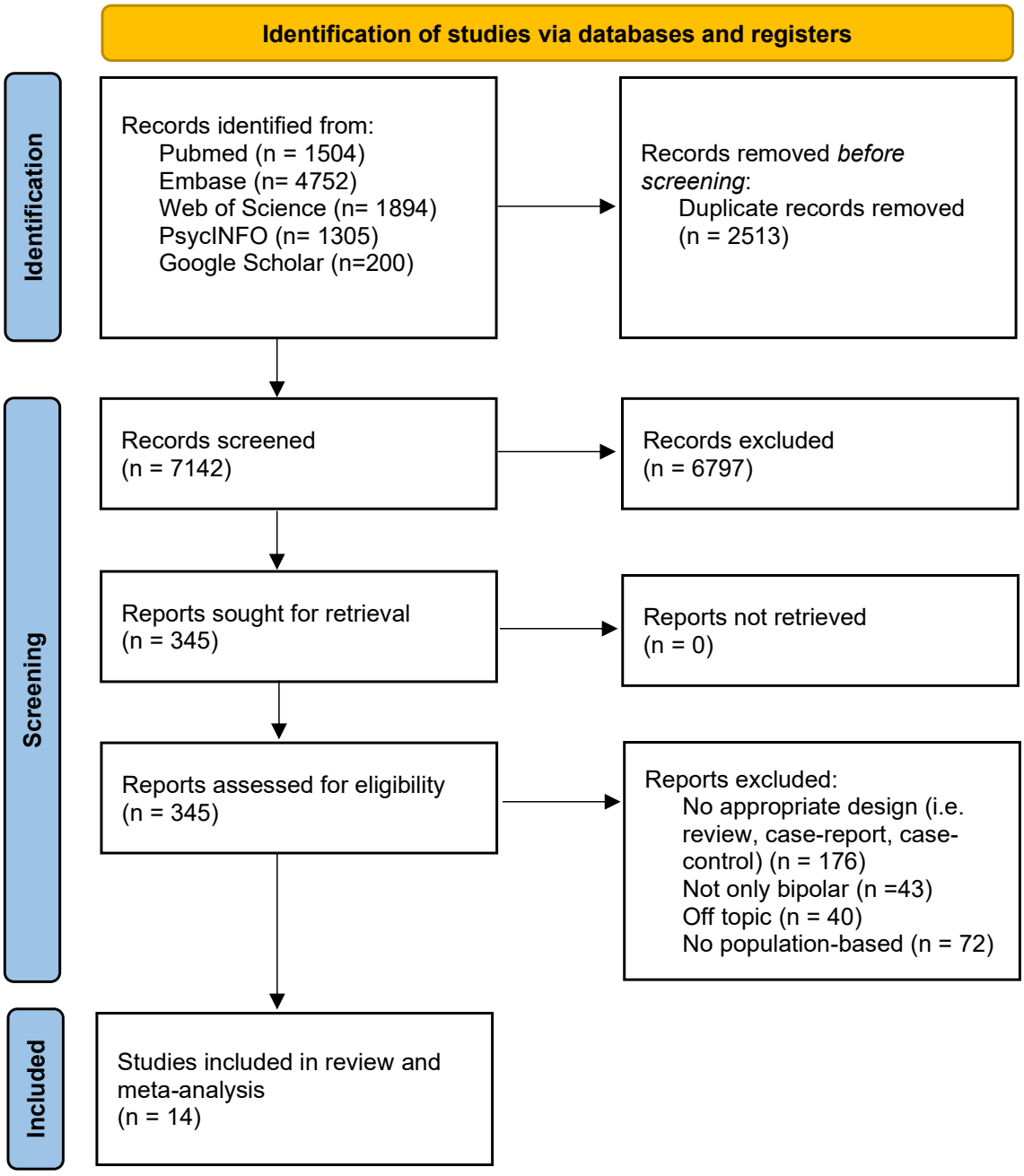

Fig. 1: PRISMA 2020 flow diagram outlining the identification, screening, and inclusion process for studies in the systematic review and meta-analysis. The diagram demonstrates the systematic identification of 14 eligible studies from 7142 initially screened records.

Discussion

Pregnant women with bipolar disorder may face an increased risk of complications during pregnancy and childbirth, and their children may also be at a higher risk of neonatal complications. In this meta-analysis, despite wide confidence intervals to be taken with caution, we observed an increased risk in gestational diabetes in women suffering from bipolar disorder compared with women without bipolar disorder. They also appeared to have a higher risk of gestational hypertension. Both of which can exacerbate other pregnancy-related complications,[40–42] including antepartum haemorrhage, and the development of pre-eclampsia, or eclampsia.[43]

First author, years of publication	Aim of study	Study design	Register	Diagnostic tool	Period	Sample	Pharmaceutic treatment	Length of follow-up	Country
Ayoub et al., 2017	To determine if a history of mental illness in women as associated with the risk of having an infant with a central nervous system defect, one of the most common congenital anomalies in newborns.	Retrospective cohort study	Maintenance and Use of Data for the Study of Hospital Clientele dataset	ICD-9 and ICD-10	1989–2013	654,882 women, 2432 BD and 652,450 controls	No information regarding medical treatment	Pregnancy and birth	Quebec, Canada
Baer et al., 2016	Women with mental illness would be at increased risk of preterm birth and that risk would differ by gestation at delivery and mental illness classifications.	Retrospective cohort study	California Office of Statewide Health Planning and Development	ICD-9	2007–2011	25,796 women, 1004 BD and 24,792 controls	No information regarding medical treatment	Pregnancy, birth and post-partum (1 year)	California, USA
Bodén et al., 2012	To investigate the risks of adverse pregnancy and birth outcomes for treated and untreated bipolar disorder during pregnancy	Retrospective cohort study	three Swedish nationwide registers maintained by the National Board of Health and Welfare	ICD-10	2005–2009	332,137 deliveries, 874 BD and 331263 controls	Treated BD with mood stabilizer	Pregnancy and birth	Sweden
Chan et al., 2024	to comprehensively examine the associations of bipolar disorder and mood stabilizers (i.e., lithium, anticonvulsants and antipsychotics) with the risk of adverse pregnancy, delivery and neonatal outcomes,	Retrospective cohort study	Clinical Data Analysis and Reporting System	ICD-10	2003–2018	458,741 women; 302 BD and 458,439 controls	Treated and non-treated women	Pregnancy and birth	Hong-Kong
Dejong et al., 2018	To determine the differences in pregnancy outcomes observed in women diagnosed with bipolar disorder in comparison to unaffected women	Retrospective cohort study	md	md	md	1,853,219 women	No information regarding medical treatment	Pregnancy and birth	California, USA
Frayne et al., 2019	To describe 10 years of antenatal care and outcomes for women with a severe mental illness (SMI)	Retrospective cohort study	Childbirth and Mental Illness (CAMI) antenatal clinic	ICD-10	2007–2017	33,636 deliveries, 178 BD and 33,458 controls	No information regarding medical treatment	Pregnancy and birth	Western Australia
Heun-Johnson et al., 2019	To estimate the association between serious mental illness and a broad range of adverse gestational, obstetric and fetal outcomes on maternal records in a national database of U.S. hospital discharges	Retrospective cohort study	Healthcare Cost and Utilization Project–Nationwide and National Inpatient Sample (HCUP-NIS)	ICD-9	2008–2014	5510557 women, 34,818 BD and 5,475,739 controls	No information regarding medical treatment	Pregnancy and birth	USA
Hoffman et al., 2019	To determine if women with BD and their children have higher charges and health service utilization	Retrospective cohort study	Denver Health and Hospital Authority institutional data warehouse	ICD-9	2011–2012	3977 deliveries, 77 BD and 3900 controls	No information regarding medical treatment	Pregnancy and post-partum (2 years)	Colorado, USA
Jablensky et al., 2005	To determine the frequency, nature, and severity of obstetric complications experienced by women with affective disorders and women without a diagnosed psychiatric disorder	Retrospective cohort study	Mental Health Information System and Maternal and Child Health Research Database	ICD-9	1980–1992	4430 deliveries, 1301 BD and 3129 controls	No information regarding medical treatment	Pregnancy, birth and post-partum (1 year)	Western Australia
Lee et al., 2010	To investigate pregnancy outcomes among women with bipolar disorder, compared with women with no history of mental illness, using nationwide population-based data	Retrospective cohort study	National Health Insurance Research Dataset and birth certificate registry published by theMinistry of the Interior in Taiwan	ICD-9	2001–2003	528,398 deliveries, 337 BD and 528,061 controls	No information regarding medical treatment	Pregnancy and birth	Taiwan
Männistö et al., 2016	To study the effect of maternal psychiatric disorders and odds of preterm birth	Retrospective cohort study	Consortium on Safe Labor	ICD-9	2002–2008	207,832 deliveries, 836 BD and 206,996 controls	No information regarding medical treatment	Pregnancy and birth	USA

(Table 1 continues on next page)

First author, years of publication	Aim of study	Study design	Register	Diagnostic tool	Period	Sample	Pharmaceutic treatment	Length of follow-up	Country
(Continued from previous page)									
Mei-Dan et al., 2015	To evaluate the risk of adverse perinatal outcomes among pregnant women previously hospitalized for BD	Retrospective cohort study	health administrative data housed at the Institute for Clinical and Evaluative Sciences	ICD-9 and ICD-10	2002–2010	434,217 deliveries, 1859 BD and 432,358 controls	No information regarding medical treatment	Pregnancy, birth and post-partum (1 year)	Ontario, Canada
Nguyen et al., 2012	To evaluate the obstetric and neonatal outcomes of pregnant women with severe mental illness (SMI)	Retrospective cohort study	Western Australian Midwives' Notification System.	ICD-10	2007–2011	29,861 deliveries, 56 BD and 29,805 controls	Psychotropic treatment	Pregnancy and birth	Western Australia
Nguyen et al., 2014	To examine the possible association between women withbipolar disorder and adverse pregnancy outcomes	Retrospective cohort study	md	md	2005–2008	3880 BD	No information regarding medical treatment	Pregnancy, birth and post-partum (1 year)	California, USA

BD: Bipolar Disorder; ICD: International Classification of Diseases.

Table 1: **Characteristics of the included studies.**

Additionally, an increased risk of caesarean section and postpartum haemorrhage is found during childbirth. This significant number of caesarean sections raises questions regarding the non-elective caesareans and their indications. For example, in several articles, gestational diabetes mellitus can be considered a risk factor for non-elective caesarean section.[44,45] Gestational diabetes appears to be associated with poor contractility

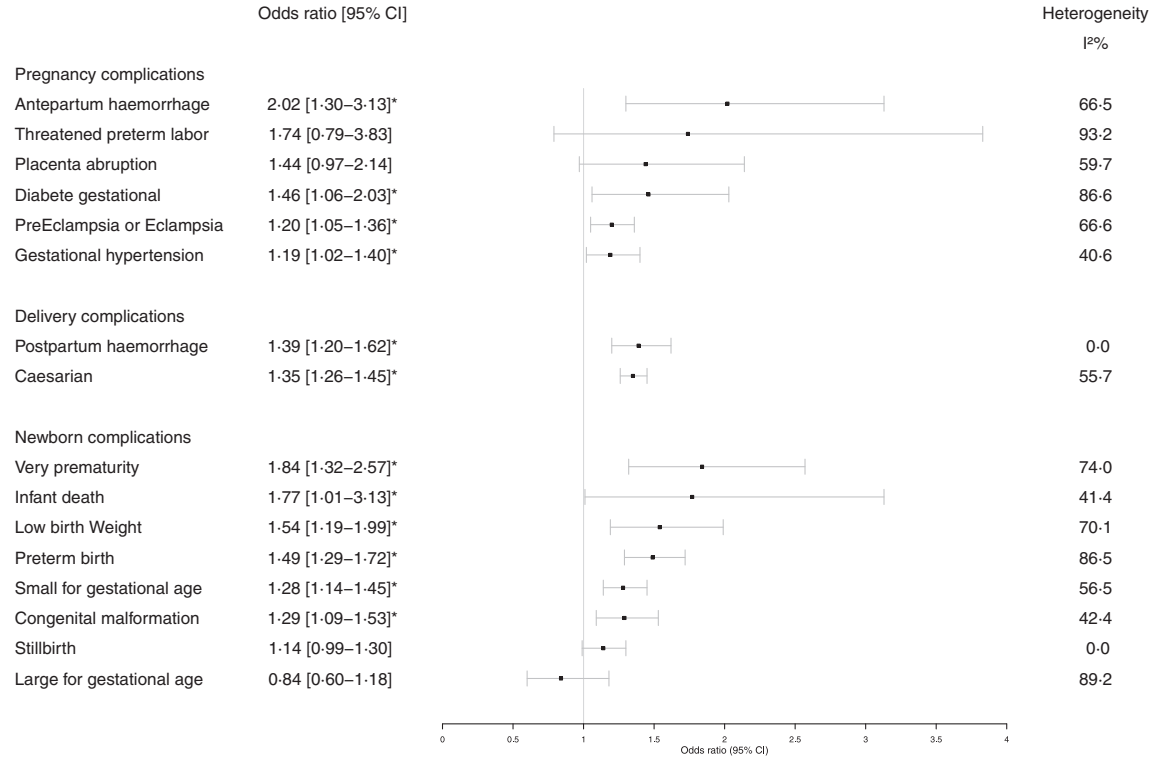

Fig. 2: Forest plot presenting odds ratios (ORs) and 95% confidence intervals (CIs) for associations between pregnancy, delivery, and newborn complications. Significant results are marked with an asterisk (*). Heterogeneity across studies is expressed as I^2 percentages for each outcome.

Authors, year	Selection				Comparability	Exposure			Quality
	1	2	3	4	5	6	7	8	
Ayoub et al., 2017	*	*	*	*	**	*	*	*	Good
Baer et al., 2016	*	*	*	*	**	*	*	*	Good
Bodén et al., 2012	*	*	*	*	**	*	*	*	Good
Chan et al., 2024	*	*	*	*	**	*	*	*	Good
Dejong et al., 2018	–	*	–	*	–	*	*	*	Poor
Frayne et al., 2019	*	–	*	*	–	*	*	*	Poor
Heun-Johnson et al., 2019	*	*	*	*	**	*	*	*	Good
Hoffman et al., 2019	*	*	*	*	*	*	*	*	Good
Jablensky et al., 2005	*	*	*	*	**	*	*	*	Good
Lee et al., 2010	*	*	*	*	**	*	*	*	Good
Männistö et al., 2016	*	*	*	*	**	*	*	*	Good
Mei-Dan et al., 2015	*	*	*	*	**	*	*	*	Good
Nguyen et al., 2012	*	–	*	*	–	*	*	*	Poor
Nguyen et al., 2014	*	*	–	*	*	*	*	*	Fair

Selection: 1/Representativeness of the exposed cohort; 2/Selection of the non-exposed cohort; 3/Ascertainment of exposure; 4/Demonstration that outcome of interest was not present at start of study; 5/Comparability of cohorts on the basis of the design or analysis; 6/Assessment of outcome; 7/Was follow-up long enough for outcomes to occur; 8/Adequacy of follow up of cohorts.

Table 2: **Assessment of study quality using the Newcastle–Ottawa Scale for cohort studies.**

during childbirth,[45] which can lead to non-elective caesarean sections and post-partum haemorrhage. In addition, the large number of post-partum haemorrhages raises the question of other potential factors leading to uterine atony.

These various complications, during pregnancy and childbirth, are likely to increase the risk of low birth weight, being small for gestational age, prematurity, very premature birth, and congenital anomalies in newborns observed in our results. In the case of prematurity, a meta-analysis involving more than 60,000 children found poor neurological development linked to this complication, which persists at various ages of follow-up, from childhood to adulthood.[46]

These challenges encountered during pregnancy and the neonatal period underscore the significance of integrated care approaches that prioritise the mother's psychiatric stability, pregnancy-related care, and neonatal well-being. This meta-analysis supports these guidelines by providing data on the risks associated with obstetric and neonatal complications, enabling better clinical decision-making and adaptation of care protocols. Screening for gestational diabetes currently uses urine strips during consultations.[47] Several clinical studies have proposed to evaluate the systematic use of the oral glucose tolerance test for women with psychiatric disorders, as it is often recommended over other tests.[48,49] For preeclampsia, self-monitoring of blood pressure could prevent unnecessary premature deliveries caused solely by proteinuria.[50]

The studies included in this work do not report the medications used during pregnancy. Nonetheless, two studies have compared groups treated and not treated with mood stabilisers in order to differentiate between the impact of bipolar disorder itself and the effects of medication treatment on pregnancy-related complications.[32,39] The only statistically significant result linked to treatment with mood stabilisers was gestational diabetes, found in the most recent study, which compared 168 treated women with bipolar disorder, 134 untreated women with bipolar disorder, and 458,439 controls, after accounting for other confounding factors.[39] Unfortunately, given the paucity of data, it is not possible to propose any guidelines for drug treatment during pregnancy in this study, apart from paying particular attention to gestational diabetes when continuing treatment with mood stabilisers. Identifying the minimum effective dose appears to be a prudent strategy based on current evidence. Notably, a dose-dependent relationship has been observed, in a observational study about 101 women with bipolar disorder, between blood lithium concentration and the risk of preterm birth.[51] Further research specifically addressing medication treatment during pregnancy in bipolar disorder is necessary. Beyond treatments, various clinical factors related to gestational diabetes should be investigated, such as dietary habits,[52] physical activity during pregnancy,[53] or sleep.[54]

Pregnant women with bipolar disorder should be informed of possible complications and monitored closely with gynaecologists to monitor risk for gestational diabetes and pregnancy-induced hypertension, thereby avoiding more serious complications later. The use of mood stabilisers may be associated with gestational diabetes. Therefore, special monitoring of diabetes with more sensitive tests, such as the oral glucose tolerance test, should be the subject of studies to reduce subsequent pregnancy and childbirth complications, as well as neurodevelopmental complications in the child.

In the current literature, research primarily focuses on high-income countries, neglecting low and middle-income settings. Future investigations should explore these regions for a comprehensive understanding. Women with mild bipolar disorder may not seek healthcare and thus may not be included in the studies. Additionally, the absence of information on psychotropic medication use during pregnancy presents a notable gap for analysis and consideration. A meta-analysis of clinical studies could provide complementary data to the present results. The limited number of studies per outcome and the inability to conduct subgroup analyses hinder the interpretation of the data, making it challenging to identify sources of heterogeneity. Using gestational diabetes as an example, the limited studies available do not permit us to propose clinical factors, such as treatments, dietary habits, or lifestyle habits, that could explain the observed heterogeneity. Consequently, a significant limitation of this study is the substantial heterogeneity that remains difficult to address due to the scarcity of available studies. Our strategy focused on selecting studies with a consistent design to methodologically mitigate this heterogeneity. Although the findings suggest that complications were more frequent among women with bipolar disorder compared to women without bipolar disorder, the reported odds ratios should be interpreted with great caution, given the impossibility of exploring the heterogeneity associated with these results. Further studies are needed to either confirm or refute these results.

The first large-scale meta-analysis suggest a significant association between bipolar disorder and heightened pregnancy complications. With nearly 50,000 cases of bipolar disorder analysed, this study provides a foundation for further investigation.

No psychiatric disorder is identified as a risk factor of pregnancy complications in international guidelines on pregnancy-related disorders.[55] While our results suggest an association between bipolar disorder and an increased risk of complications such as gestational diabetes, gestational hypertension, and preterm birth, these findings must be interpreted cautiously due to the high heterogeneity and wide confidence intervals observed. Further prospective, real-world, multicentre studies are essential to validate these results and provide robust evidence to inform international guidelines. Until then, any consideration of bipolar disorder as a potential risk factor should remain provisional and subject to additional confirmation.

Contributors

All authors have read and approved the final version of the manuscript. Three authors have verified the underlying data (DE-E, GF and LB). Conceptualization, Formal Analysis, Funding acquisition, Investigation, Methodology, Software, Validation, Visualization, Writing—original draft, Writing—review & editing: DE-E. Conceptualization, Investigation, Methodology, Validation, Writing—original draft, Writing—review & editing: LB, GF. Writing—review & editing: MR, DKY, LS.

Data sharing statement

All the data supporting the results of this study are available in the article, in its Supplementary information and on reasonable request.

Declaration of interests

No author reports any conflicts of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.103007.

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