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REVIEW ARTICLE

Preeclampsia as a risk factor for postpartum depression and psychosis: a systematic review and meta-analysis

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Abstract

Postpartum depression (PPD) and postpartum psychosis (PPP) are serious mental conditions that are usually not diagnosed early enough, leading to delayed treatment. Several studies confirmed an association between preeclampsia (PE) and psychiatric disorders during pregnancy. We conducted a systematic review of the literature aiming to investigate whether women with a history of PE are more likely to develop PPD or PPP, and whether PE is a risk factor for depression outside the perinatal period (PROSPERO protocol number CRD42018114188). We also conducted a meta-analysis to quantitatively assess the severity of depressive symptoms between women with and without a history of PE. A literature search with no year and no language restriction was conducted. The search yielded 950 articles, with 698 remaining after duplicate removal, and 13 being suitable for the systematic review. Eight of the 13 studies found an association between preeclampsia and depression. All studies assessed the impact of PE on depression, and only two studies assessed the impact of PE on PPP. Eight of the studies were included in the meta-analysis, which yielded a higher severity of depressive symptoms postpartum in women with PE. However, these results must be interpreted with caution considering the high heterogeneity of the included studies. Our meta-analysis also showed that women with a history of PE showed higher severity of depressive symptoms outside of the puerperal period. In conclusion, this systematic review and meta-analysis suggest that that PE is not only a risk factor for development of depression, but it is also associated with higher severity of depressive symptoms.

Keywords Preeclampsia · Depression · Postpartum psychosis · Pregnancy · Systematic review

Introduction

Preeclampsia is a complication of pregnancy occurring after 20 weeks of gestation and characterised by new-onset hypertension with coexisting one or more of the following: proteinuria, renal/hepatic involvement, neurological or haematological complications, or restriction of foetal growth (Tranquilli et al. 2014). Preeclampsia affects about 4.6% of all pregnancies worldwide (Abalos et al. 2013) and is considered a severe form of immune-related disorder of pregnancy due to its vascular pathology and hyperinflammation (Bergink et al. 2015).

A number of obstetric complications are known to increase the risk of perinatal mental health problems, such as postpartum depression (Koutra et al. 2018) and postpartum psychosis (Ballon et al. 2008; Mittal et al. 2008; Kotlicka-Antczak et al. 2017). For instance, gestational diabetes, which has a worldwide prevalence of 5.8–12.9% (Zhu and Zhang 2016), increases in 1.32 times the risk of postpartum depressive symptoms (Arafa and Dong 2019). Similarly, preterm birth, which affects 5–18% of pregnancies (Blencowe et al. 2012), is also known to increase in 1.6 times the risk of postpartum depression (de Paula Eduardo et al. 2019).

Postpartum depression is one of the most disabling disorders affecting from 7 to 15% of women worldwide (Gaynes et al. 2005; WHO - World Health Organization 2009), is a leading cause of maternal mortality and morbidity (Mathers and Loncar 2006), and has a significant negative impact on mother-infant bonding (Grace et al.

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2003; Howard et al. 2014). Notably, postpartum depression has been associated with developmental issues in the offspring (Cornish et al. 2005; Koutra et al. 2013). Several studies investigating the biological link between depression and the perinatal period have focused on hormonal sensitivity (Bloch et al. 2003), neurotransmitter dysregulation (Hirschfeld 2000; Bolte et al. 2001), inflammation (Harmon et al. 2016), hypothalamic-pituitary-adrenal (HPA) axis dysfunction (Kammerer et al. 2006), and oxidative stress and cell-mediated immunity (Leonard and Maes 2012; Bergink et al. 2013; Osborne and Monk 2013). More recently, studies have suggested an association between preeclampsia and postpartum depression (Chen et al. 2019; Mbarak et al. 2019). Blom et al. (2010) reported a significant association between preeclampsia and postpartum depression in a healthy population of Western females with high levels of education. Similarly, Strapasson et al. (2018) reported a positive correlation between depressive symptoms and hypertensive disorders of pregnancy and signs of eclampsia mainly in a more heterogeneous group of older, multiparous females who were 12 h postpartum.

Postpartum depression and postpartum psychosis are serious mental conditions that are often diagnosed late, leading to delayed effective treatment. Considering the potential deleterious consequences that both the mothers and their babies could suffer, the identification of clinical predictors of postpartum depression and postpartum psychosis has the potential to raise awareness of those individuals at higher risk, improving early detection and treatment, thereby reducing the associated negative health outcomes.

In the present study, we conducted a systematic review of the literature aiming at answering the following research questions: (1) Are women with a history of preeclampsia more likely to develop postpartum depression or postpartum psychosis compared with women without a history of preeclampsia? (2) Are women with a history of preeclampsia more likely to develop depression outside of the perinatal period compared with women without a history of preeclampsia? (3) Do women with a history of preeclampsia display higher severity of depressive symptoms compared with women without a history of preeclampsia?

Methods

The systematic review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under registration number CRD42018114188 (Cardoso et al. 2018). The Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines were followed for the present review.

Search strategy

A literature search with no year and no language restriction was conducted using the following databases: PubMed, PsycINFO, Scopus, and Embase. Searches were conducted to capture all articles published up to August 29, 2018, the date when the final search was conducted. We searched for a combination of the following search items (preeclamp* OR pre-eclamp* OR pregnancy induced hypertension OR hypertensive disorders of pregnancy OR hypertensive disorders in pregnancy) AND (depression OR major depressive disorder OR postpartum depression OR psychosis OR psychotic). The search yielded 950 articles (PubMed = 461, PsycINFO = 69, Scopus = 38, Embase = 382).

To determine whether an article was relevant to our study, we used the following inclusion criteria: the study should (1) present original data, (2) consider depression (unipolar or bipolar) and/or postpartum psychosis, and (3) include both women with a history of preeclampsia and a comparison group of women who had not experienced preeclampsia. The exclusion criteria were (1) reviews and meta-analyses, (2) case reports, (3) clinical trials testing treatment for preeclampsia or eclampsia, and (4) studies where depression or psychosis were considered as a risk factor and not as an outcome.

The studies were selected by two blinded reviewers (LC and TC) who determined if studies met inclusion criteria. Manuscripts were assessed independently by the two raters and divergences were resolved by consensus. Firstly, the raters screened articles by title, then by abstract, and finally by full-text. Duplicates, review articles, and articles not fulfilling the search criteria were removed. The details of the search strategy are depicted in Fig. 1.

Data extraction

Three researchers (LC, TC, and ME) were involved in the data extraction process. We extracted the following data: authorship, year of publication, aim of the study, study design, demographic characteristics, inclusion and exclusion criteria, clinical assessments, medical and obstetrical history, psychiatric history, main results, and potential confounder factors.

Quality assessment

The quality of the studies was assessed by three researchers (LC, TC, and ME). Each manuscript included was independently assessed by two blind researchers using the Newcastle-Ottawa Quality Assessment Scale (Wells et al. 2003). Disagreements were resolved by consensus between the three researchers.

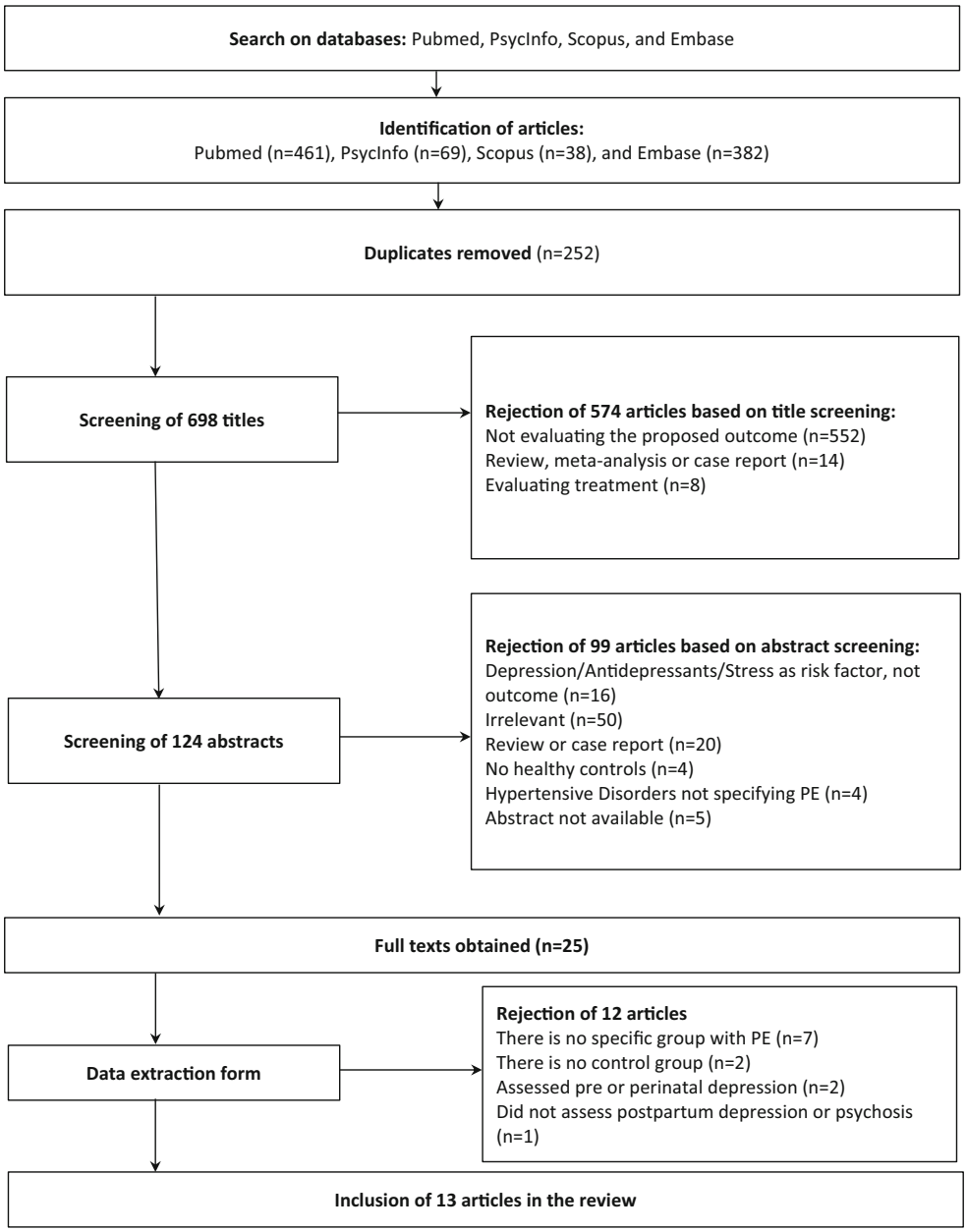

Fig. 1 PRISMA flow diagram

Statistical analysis

A random effects meta-analysis was performed using the RevMan 5.3. Firstly, we intended to analyse the studies that investigated preeclampsia as a risk factor for depression, as assessed with clinical interviews (Bergink et al. 2015; Youn et al. 2017). However, we found that this result was largely driven by one study (Youn et al. 2017), since its significantly larger sample explained 92.6% of the meta-analytic result. In another analysis, we included the studies that assessed the severity of depressive symptoms between women with or without a history of preeclampsia. For this aim, the reported means, sample sizes, and standard deviation were used to compute the standard mean difference. We chose this method because the studies used different clinical questionnaires to assess the severity of depressive symptoms. When two different clinical questionnaires were used to measure severity of depressive symptoms in the same study, we took the data from the most commonly used questionnaire for the meta-analysis. When medians and interquartile range were provided instead of means, we calculated the means and standard deviations using a pre-formatted Microsoft Excel® file (Wan et al. 2014). Significance was set as $p < 0.05$. Cochrane's Q test was performed to assess for statistical heterogeneity and the Higgins I2 statistic was used to determine the extent of variation between sample estimates with values ranging from 0 to 100%. If the information was not reported in the paper, we contacted the authors requesting the mean and standard

deviation obtained from clinical questionnaires in order to include the paper in the meta-analysis.

Results

The literature search yielded 950 articles. Once duplicates were removed, 698 papers remained. We excluded 574 studies based on the title, and 99 based on the abstract and a further 12 articles based on full-text screening, for a final number of 13 studies to be included in the systematic review. We hand-searched the references of the included studies and found no additional studies to include. Figure 1 displays the selection process for the included papers.

Characteristics of included studies

Table 1 shows an overview of the included studies. Among the 13 studies, publication dates ranged from 2005 to 2017. Seven studies were conducted in The Netherlands, two in Denmark, one in the USA, one in Colombia, one in South Korea, and one in Turkey. Total sample size ranged from 20 (Brussé et al. 2008) to 1,269,130 (Youn et al. 2017), and age ranged from 15 to 59 years. All studies assessed the impact of preeclampsia on depression, and two studies also assessed the impact of preeclampsia on postpartum psychosis. Ten studies had a longitudinal cohort design and three studies were cross-sectional. For the cohort studies, the time of follow-up assessments ranged from 6 weeks to 40 years after pregnancy. Regarding the assessment of depression, the majority of the studies used self-report scales ($n = 10$), while three studies used structured clinical interviews based on the International Classification of Diseases, 10th Revision (ICD-10) (WHO—World Health Organization 2004) or the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) (First et al. 1996) (Table 1).

Quality assessments of the included studies

Each study included in this review was examined and critically appraised using the Newcastle-Ottawa Scale for cohort studies (Wells et al. 2003) or the adapted version for cross-sectional studies (Wells et al. 2011). Results are shown in Table 2. The maximum score on the scale for cohort studies is 9, and the scores of our included studies ranged from 2 to 9, with a mean score of 5.3. The maximum score on the scale for cross-sectional studies is 10, and the scores of our included studies ranged from 2 to 10, with a mean score of 6.

Of the 13 included studies, four were classified as poor quality: three cohort studies and one cross-sectional study (Table 2). Two main factors contributed to poor quality of the three cohort studies: lack of exclusion of mental illness and depression at the start of the study (selection bias), and poor assessment of outcome (outcome bias). For the cross-sectional studies, only one study (Vinaccia et al. 2006) scored 2 out of 10 for its selection and outcome biases.

Preeclampsia and postpartum depression: evidence from cross-sectional studies

Out of the 13 included studies, eight of them found an association between preeclampsia and postpartum depression or depression outside the perinatal period (Table 1). Three out of the 8 were cross-sectional studies assessing postpartum depression, and their results were as follows: (1) higher severity of depressive symptoms in women with a history of preeclampsia compared with women without a history of preeclampsia (Vinaccia et al. 2006), (2) higher prevalence of postpartum depression in women who had preeclampsia compared with women without preeclampsia (OR 1.12; 95% CI 1.03–1.22) (Youn et al. 2017), and (3) severe preeclampsia was associated with poor psychological outcomes, including depression (Cetin et al. 2017). The total sample size of these studies ranged from 120 to 1,269,130.

Preeclampsia and postpartum depression: evidence from longitudinal studies

From the six cohort studies included assessing PE as a risk factor for postpartum depression, three cohort studies found that preeclampsia is a risk factor for depression. Blom et al. (2010) showed that preeclampsia increased the risk of depression by 2.58 times 2 months after childbirth. Bergink et al. (2015) showed that the highest risk of developing psychiatric disorders were observed at 0–3 months postpartum in women with preeclampsia, and preeclampsia increased the risk for unipolar depression by 2.85 times. Notably, this was the only study that controlled for obstetric complications, such as gestational diabetes and birth complications. Finally, Meltzer-Brody et al. (2017) reported that preeclampsia increased the risk of depression in the first year postpartum by 1.45 times. The total sample size of these studies ranged from 1155 to 400,717.

Despite the positive evidence for preeclampsia as a risk factor for depression in the abovementioned studies, another three cohort studies did not find this association. In the study of Brussé et al. (2008), although women with preeclampsia reported higher severity of depressive symptoms compared with controls in a follow-up of 3–7 months postpartum, the difference did not reach statistical significance. Baecke et al. (2009) did not find any difference regarding the levels of depression or fatigue among the four groups assessed (preterm

Table 1 Characteristics of the studies included

First author (year) country	Aim	Study design	Time of assessment	Population	Age	Parity	Instruments	Association?	Relevant findings
Meltzer-Brody et al. (2017) Denmark	To evaluate if pregnancy and obstetrical predictors have similar effects on different types of postpartum psychiatric disorders	Population-based cohort study	From date of delivery until first time psychiatric episode 1–12 months after birth	PE + depression 81 (8.24%) NPE + depression 902 (91.76%) PE + psychosis 8 (4.54%) NPE + psychosis 164 (95.25%)	Depression 38.35% 25–< 30 years old Psychosis 29.07% 25–< 30 years old	Restricted to first time live birth	Data derived from the DPCR and the NPR diagnosis were according to ICD-10	Yes	PPD was associated to PE (IRR 1.45, 95% CI 1.14–1.84). However, postpartum psychosis was not associated with PE
Fields et al. (2017) USA	To examine whether women with a history of PE were at increased risk of cognitive decline 35–40 years after the affected pregnancy	Cohort study	35–40 years after the affected pregnancy	Women with a history of PE, 40 Women with a history of NTP, 40	Median age at study consent Case 59.2 Control 59.6 Median age at 1st live birth Case: 24.5 Control 24.0	Median parity Case 3.0 Control 3.0	BDI-II PMS	No	There were no statistically significant differences regarding the severity of depressive symptoms between women with histories of PE compared with women with histories of NTP
Youn et al. (2017) South Korea	To identify the obstetric risk factors ofdepression during the postpartum period	Cross-sectional study	First year after delivery	Total 1269130 PPD 17483 Non-PPD 1251647	Mean age PPD 30.57 Non-PPD 30.86	Data was extracted for the 1st pregnancy only	They extracted data from a database that used ICD-10 code, F32, 33 to identify the presence of depression	Yes	PE was associated with PPD OR = 1.12 (95% CI 1.03–1.22), even after adjusting for age, obstetric complications, and previous history of depression
Cetin et al. (2017) Turkey	To investigate the psychopathological symptoms, psycho-emotional state, dream, anxiety, and insomnia in postpartum women with healthy, mild, and severe PE and the relation of those factors to the severity of PE	Cross-sectional study	Just after delivery before being discharged from the hospital	Healthy postpartum women 45 Mild PE 41 Severe PE 44	Mean age: Controls 30.1 Mild PE 30.4 Severe PE 28.4	Multipara were excluded	HADS	Yes	Both severe and mild PE showed higher severity of depressive symptoms compared with healthy controls
Mommersteeg et al. (2016) The Netherlands	To examine long-term psychosocial distress in women with a history of	Cohort study	On average 14.1 years after the index pregnancy	Women with a history of PE 265	Mean age PE 43.62 Controls 43.35	PE 80% primipara Controls 71% primipara	PHQ-9	Yes	Women with a history of PE reported more subsequent depressive symptoms and more fatigue compared

Table 1 (continued)

First author (year) country	Aim	Study design	Time of assessment	Population	Age	Parity	Instruments	Association?	Relevant findings
	early-onset PE compared with women without a history of PE			Women with UP 268					with controls. The differences remained after adjustment for age, BMI, educational level, partner, employment, and physical activity
Bergink et al. (2015) Denmark	To investigate if =PE is a risk factor for first-onset postpartum psychiatric episodes	Epidemiological populated-based cohort study	First year postpartum divided into (0–3 months) compared with (4–12 months) postpartum	Total of 400,717 women PE 17149 Non-PE 383568	Assessment occurred between 1 January 1995 and 31 December 2011. They considered only women born in Denmark from 1 January 1960 to 31 December 1995	Primipara with singleton births	According to ICD-10: code O14 for PE, codes F32, F33, F34, F38, and F39 for defining unipolar depression	Yes	The highest risks for developing psychiatric disorders were observed 0–3 months postpartum in women with PE unipolar depression (IRR 2.85, 95% CI 1.84–4.42)
Postma et al. (2014) The Netherlands	To determine if subjective reports of cognitive difficulty in women who suffered PE and eclampsia could be interpreted as reflecting objective cognitive dysfunction	Cohort study	7 years after pregnancy	Women with former eclampsia 46 Women with former PE 51 Women with NTP 48	Mean age Eclampsia 39 PE 39 Controls 40	Primipara at index pregnancy Eclamptic 87% PE 67% Controls 44%	HADS	Yes	Significant differences were found for the HADS total score, anxiety, and depression subscales. Women with eclampsia and PE had similar scores, but significantly worse compared with controls
Gaugler-Senden et al. (2012) The Netherlands	To evaluate the impact of severe, early-onset PE on long-term maternal psychosocial outcome after preterm birth	Historical cohort study with outcome measurements at different follow-up lengths	4–15 years after pregnancy	Cases: women with severe early-onset PE before 32 weeks gestation 104 Controls: women with PT without PE 78	Median Cases 30 Controls 30	Cases 83% primiparaContro-ls 80% primipara	ZDS	No	There was no difference in the severity of depressive symptoms between women with or without PE
Stramrood et al. (2011) The Netherlands	To assess the prevalence and the risk factors for PTSD in women with	Prospective cohort study	Pregnancy, 6 weeks and	Women with PE 57	Mean age PE 29.4 PPROM 30.7	PE 80% primipara PPROM 49% primipara	BDI-II	No	There was no difference between groups regarding the prevalence of

Table 1 (continued)

First author (year) country	Aim	Study design	Time of assessment	Population	Age	Parity	Instruments	Association?	Relevant findings
	PE or PPROM compared with UP		15 months postpartum	Women with PPROM 53 Women with UP 65	Controls 31.9	Controls 74% primipara			depression at neither of the 3 time points
Blom et al. (2010) The Netherlands	To examine whether specific pregnancy and delivery complications are risk factors for PPD	Prospective cohort study	2 months after delivery	Women with PE 71 Women without PE 4870	Mean age of total study population 31.0	Total study population 57.9% primipara	EPDS	Yes	PE was significantly associated with an increased risk of PPD (OR 2.58, 95% CI 1.30–5.14) even after adjusting for generalpsychopathological symptoms, family functioning, maternal ethnicity and age, education level mother, and family income
Baecke et al. (2009) The Netherlands	To study both the frequency and severity ofcognitive complaints, mood disturbances and severe fatigue in the study population, and to assess cognitive functioning in women with PE compared with that of UPR	Historical cohort study with outcomes measured at different follow-up lengths	6–18 months postpartum	PEE 47 TPE 18 PBI 32 UPR 72	PPE 31.2 TPE 30.9 PBI 32.4 UPR 34.0	Primipara	BDI-PC	No	No difference in levels of depression, anxiety, and fatigue were found between the 4 studied groups
Brussé et al. (2008) The Netherlands	To compare cognitive functions 3–7 months after delivery in women with former sever PE and women after an UP	Historical cohort study with outcome measurements at different follow-up lengths	3–7 months postpartum	Former severe PE 10 NTP 10	Mean age Cases 34.4 Controls 33.8	Median parity Cases 1.4 Controls 1.6	CES-D	No	Although women with PE had somewhat higher severity of depressive symptoms, the differences did not reach statistically significance ($p = 0.67$)
Vinaccia et al. (2006) Colombia	To determine the disease behaviour in women who presented with PE and its relation with depression	Cross-sectional study	> 20 weeks pregnant	Pregnant women with PE 60 Pregnant women without PE 60	Cases 41.7% had 15–20 years old Controls 38.3% had 15–20 years old	Cases 36.7% primipara Controls 33.3% primipara	CES-D	Yes	Pregnant women with PE had higher severity of depressive symptoms

BDI-II, Beck Depression Inventory, second edition; *BDI-PC*, Beck Depression Inventory for Primary Care; *BMI*, body mass index; *CI*, confidence interval; *CES-D*, Center for Epidemiological Studies Depression Scale; *DPCR*, Danish Psychiatric Central Register; *EPDS*, Edinburgh Postnatal Depression Scale; *HADS*, Hospital Anxiety and Depression Scale; *ICD-10*, International Classification of Diseases 10th Revision; *IRR*, incidence rate ratio; *NPT*, non-preeclamptic; *NPR*, National Patient Register; *NTP*, normotensive pregnancy; *OR*, odds ratio; *PE*, preeclampsia; *PHQ-9*, Patient Health Questionnaire-9; *PPD*, postpartum depression; *PPE*, preterm PE; *PMS*, Profile of Mood State; *PPROM*, preterm premature rupture of membranes; *PT*, preterm birth; *PTSD*, post-traumatic stress disorder; *TPE*, term formerly preeclamptic women; *UP*, uneventful pregnancy; *UPR*, women with an uneventful pregnancy and term delivery in their history; *ZDS*, Zung Depression Scale

Table 2 Risk of bias for cohort and cross-sectional studies as assessed by the Newcastle-Ottawa Scale. The greater the total score, the higher the quality of the study

Cohort studies

Author (year)	Representativeness of exposed cohort (selection bias)	Selection of non-exposed cohort (selection bias)	Ascertainment of exposure (selection bias)	Demonstration that outcome was not present at start of study (selection bias)	Comparability of cohorts (comparability bias)	Assessment of outcome (outcome bias)	Adequate follow-up (outcome bias)	Adequacy of follow-up of cohorts (outcome bias)	Total score
Meltzer-Brody et al. 2017	1	1	1	1	1	1	1	1	8/9
Mommersteeg et al. 2016	1	1	1	–	1	–	1	1	6/9
Fields et al. 2017	1	1	1	–	–	–	1	–	4/9
Bergink et al. 2015	1	1	1	1	2	1	1	1	9/9
Postma et al. 2014	–	–	1	–	–	–	1	–	2/9
Gaugler-Senden et al. 2012	1	1	1	–	1	–	1	–	5/9
Stramrood et al. 2011	1	1	1	–	1	1	1	1	7/9
Blom et al. 2010	1	1	1	–	1	–	–	1	5/9
Baecke et al. 2009	1	1	1	–	1	–	1	–	5/9
Brussé et al. 2008	–	–	1	–	–	–	1	–	2/9

Cross-sectional studies

Author (year)	Representativeness of the sample (selection bias)	Sample size (selection bias)	Non-respondents (selection bias)	Ascertainment of exposure (selection bias)	Comparability (comparability bias)	Assessment of outcome (outcome bias)	Statistical test (outcome bias)	–	Total score
Vinaccia et al. 2006	–	–	–	–	1	2	–	–	2/10
Cetin et al. 2017	1	–	–	2	1	1	1	–	6/10
Youn et al. 2017	1	1	1	2	2	2	1	–	10/10

preeclampsia, term preeclampsia, preterm birth, and controls) in a follow-up of 6–18 months postpartum. Finally, Stramrood et al. (2011) did not find any significant difference between the 3 studied groups (preeclampsia, preterm premature rupture of membranes, and controls) regarding the prevalence of depression at neither of the 3 time points (pregnancy, 6 weeks postpartum, and 15 months postpartum). One possible reason for these discrepancies may be the relatively low power of the latter three studies, since the total sample size of these studies ranged from 20 to 175.

Preeclampsia and depression outside the perinatal period: evidence from longitudinal studies

Four cohort studies assessed preeclampsia as a risk factor for depression outside of the perinatal period, and two of them found a positive association. For instance, Mommersteeg et al. (2016) stated that women with a history of preeclampsia reported more subsequent depressive symptoms and more fatigue compared with controls in a follow-up of up to 14 years. In addition, Postma et al. (2014) found a higher severity of depressive symptoms in women who had preeclampsia, 7 years after the delivery. However, two studies did not find association between preeclampsia and depression outside of the perinatal period. Fields et al. (2017) found no differences in severity of depressive symptoms between women with history of preeclampsia compared with women with normotensive pregnancy 35–40 years after the affected pregnancy. Also, Gaugler-Senden et al. (2012) did not find differences regarding the severity of depressive symptoms in women with preeclampsia compared with controls in a follow-up of 4–15 years after pregnancy.

Preeclampsia and postpartum psychosis

Only two studies assessed the association between preeclampsia and postpartum psychosis. Cetin et al. (2017), in a cross-sectional study including 130 women, showed that severe preeclampsia was associated with psychotic features. On the other hand, Meltzer-Brody et al. (2017) found no association between preeclampsia and postpartum psychosis in a population-based cohort study with 1 year of follow-up, including 1155 women. However, it is important to mention that the number of women with preeclampsia and psychosis in this study was very small ($n = 8$).

Meta-analysis

Association between preeclampsia and severity of depressive symptoms in the postpartum period: In studies that assessed the severity of postpartum depressive symptoms in the postpartum period between women with or without preeclampsia(Vinaccia et al. 2006; Brussé et al. 2008; Baecke et al. 2009; Gaugler-Senden et al. 2012; Cetin et al. 2017), we found that the standard mean difference between groups was 1.04 (CI 95% 0.22, 1.86; $p = 0.01$), indicating higher severity of depressive symptoms in women with a history of preeclampsia. However, these results must be interpreted with caution considering the high heterogeneity of the studies included ($I^2 = 96\%$) (Fig. 2).

Association between preeclampsia and severity of depressive symptoms outside the perinatal period: In studies that assessed the severity of depressive symptoms outside of the perinatal period between women with or without a history of preeclampsia (Gaugler-Senden et al. 2012; Postma et al. 2014; Mommersteeg et al. 2016; Fields et al. 2017), we found that the standard mean difference between groups was 0.18 (CI 95% 0.05, 0.31; $p = 0.007$), indicating higher severity of depressive symptoms in women with a history of preeclampsia (Fig. 3).

Discussion

This systematic review found that preeclampsia is a risk factor for the diagnosis of depression. In addition, the meta-analysis showed that women with preeclampsia experience a higher severity of depressive symptoms compared with women without preeclampsia. The increased severity of depressive symptoms was significant for women during the postpartum period, as well as later in women's life. Regarding the possibility of preeclampsia being a risk factor for postpartum psychosis, no definite conclusion can be made given the small number of studies and the inconsistency of their results. A previous systematic review (Delahaije et al. 2013) reported inconclusive evidence regarding the association between preeclampsia or HELLP (haemolysis, elevated liver enzymes, and low platelets) and depression. In our current systematic review, we were able to include a larger number of studies.

The association between preeclampsia and depression may be explained by psychological and neurobiological factors. For instance, preeclampsia is associated with obstetric complications and poor neonatal outcomes, such as placental abruption, stillbirth, foetal growth restrictions, and preterm delivery (Sibai et al. 2005), all of which have been associated with higher risk of depression. Psychologically, preeclampsia may lead to increased worrying, grief, acute stress, and PTSD-like symptoms, which, in turn, increases vulnerability to

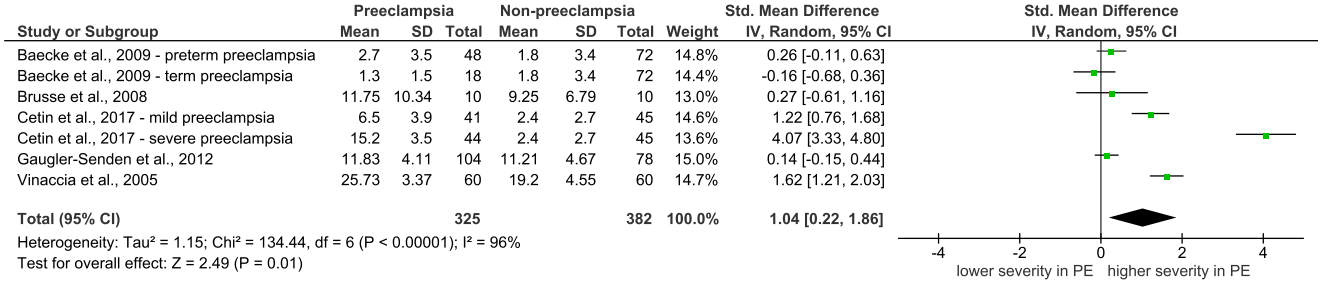

Fig. 2 Severity of depressive symptoms in the postpartum period

postpartum depression and anxiety (Hoedjes et al. 2011; Shlomi Polachek et al. 2016).

Even during normal pregnancies, women experience changes in their immunologic and inflammatory responses. Preeclampsia causes an intravascular inflammatory reaction following an exaggerated endothelial activation (Steegers et al. 2010), and it is suggested that an altered immune response could be involved in its pathogenesis. Several studies found increased pro-inflammatory cytokines in preeclamptic pregnancies, which includes the cytokines produced by macrophages, natural killer (NK) cells, and by Th1 cells (Ahn et al. 2011). Cell-mediated immunity and inflammation, together with nitrosative and oxidative stress, have also been correlated with the onset of depressive symptomatology in unipolar depression. Some of the factors involved are increased pro-inflammatory cytokines produced by activated macrophages (IL-1β, IL-6, TNF-α), and increased production of IFN-γ and IL-2 (Th1 cytokines). These cytokines have been shown to induce changes in 5-HT receptors and activate indoleamine 2,3-dioxygenase (IDO), which is an enzyme that activates the catabolism of tryptophan (a main monoamine precursor), with a corresponding decreased plasma level of tryptophan (Leonard and Maes 2012). Although there is a growing body of evidence correlating inflammatory biomarkers with perinatal mood symptoms, conclusions regarding postpartum depression are still limited due to the heterogeneity in the methods used to assess mood, and due to the significant variety of the biomarkers studied (Osborne and Monk 2013; Lambert and Gressier 2019).

Another potential mechanism that may be related with the association between preeclampsia and depression involves the intravascular inflammatory reaction and endothelial activation. Endothelial dysfunction can significantly increase blood-brain barrier permeability (Amburgey et al. 2010) which, in the context of hyperinflammation, can impact brain neurotransmitter function (Blom et al. 2010), neuroendocrine function, synaptic plasticity, and neural circuits implicated in mood regulation (Capuron and Miller 2011). Investigators have found increased blood-brain barrier permeability in animal models with preeclampsia (Johnson et al. 2014; Wallace et al. 2018); however, a recent study in humans found no evidence of blood-brain barrier impairment or neuroinflammation in preeclampsia, through measurements of albumin, complement proteins, and cytokines in cerebrospinal fluid of preeclamptic women (Burwick et al. 2019). Nevertheless, the later study had a small sample size, and larger studies are needed. Additional brain changes have been correlated with poor autonomic regulation in pregnant women with preeclampsia, such as increased brain water content, white matter lesions, and loss of cerebrovascular regulation (Logue et al. 2016). Furthermore, preeclampsia has been linked with brain atrophy and impaired cognition following decades (Mielke et al. 2016) and has recently been associated with 3- to 6-fold increased risk of vascular dementia (Basit et al. 2018).

Genetic changes such as polymorphism in the folate metabolism gene 5,10-methylenetetrahydrofolate reductase (MTHFR) were another attempt to explain the relationship between postpartum depression and preeclampsia where the abnormal expression of such gene may increase the susceptibility to postpartum depression in preeclamptic patients (Wu et al. 2015; Yan et al. 2017).

Time of assessment had a significant impact on the results of our systematic review. We found that most of the recent higher-quality studies, which reported an association between preeclampsia and depression, assessed women from childbirth throughout the first year postpartum (Bergink et al. 2015;

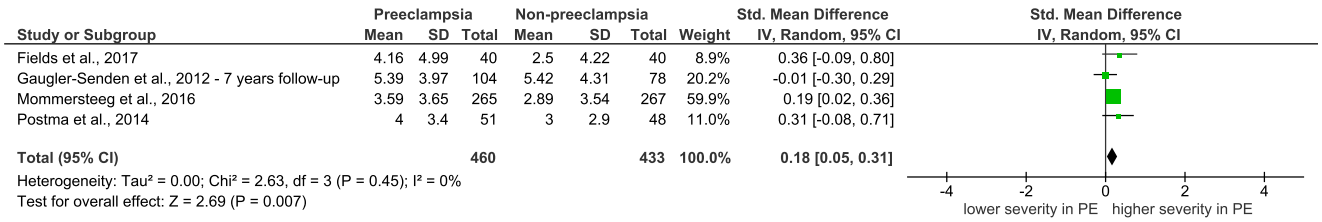

Fig. 3 Severity of depressive symptoms outside the perinatal period

Meltzer-Brody et al. 2017; Cetin et al. 2017; Youn et al. 2017). Two of four included studies were subject to recall bias as they asked participants to recall their mood status 4–15 years after delivery (Gaugler-Senden et al. 2012) and 7 years after pregnancy (Postma et al. 2014). This issue might have contributed to the heterogeneity of the results, which is also a limitation of our study. In addition, the previous systematic review of Delahaije et al. (2013) included studies with predominantly Caucasian women. It is worth noting that the association between preeclampsia and depression has been observed in countries with diverse ethnic backgrounds (The Netherlands, South Korea, Turkey, Colombia, and Denmark). Lack of control for potential confounders, such as history of pregestational depression, was another limitation of a previous systematic review (Delahaije et al. 2013). In the current systematic review, the studies that excluded individuals with previous history of psychiatric conditions found a positive association between preeclampsia and severity of depressive symptoms (Vinaccia et al. 2006), psychotic features (Cetin et al. 2017), and a diagnosis of depression (Bergink et al. 2015; Meltzer-Brody et al. 2017; Cetin et al. 2017; Youn et al. 2017). These results suggest that there is an association between preeclampsia and psychiatric disorders, even in individuals without a previous history of psychiatric disorders.

Conclusions and future recommendations

In this systematic review and meta-analysis, we found that preeclampsia is associated with a greater risk of depression diagnosis and higher severity of depressive symptoms. The association between preeclampsia and postpartum psychosis is inconclusive due to the paucity of studies and inconsistent results, an area which requires future attention. Our findings underscore the importance of raising awareness on the potential risk of depression following preeclampsia, which seems to be independent of previous history of psychiatric disorders. Thus, we suggest that women who develop preeclampsia should be educated about early signs and symptoms of postpartum depression. Additionally, they should be closely monitored by their healthcare professionals for depressive symptoms during the first year postpartum, especially during the first 3 months (Bergink et al. 2015), with validated screening tools such as the Edinburgh Postnatal Depression Scale (O'Connor et al. 2016). Perinatal women in mental distress ought to be assessed and receive timely treatment when necessary. Screening, early detection, and early intervention will positively impact the quality of life and mental health of the mother, infant, and the family in general.

Future research should, ideally, design studies with two parallel cohorts: women with and without a history of mental health problems. Furthermore, studies should control for associated risk factors, such as preterm labour and other obstetric complications. A better understanding of the possible biological and psychosocial mechanisms mediating the association between preeclampsia and depression is also encouraged. Moreover, it would be important to investigate if individuals with depression following preeclampsia respond equally to pharmacotherapy and psychotherapy compared with individuals without a history of preeclampsia.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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