Preeclampsia and Its Complications Exacerbate Development of Postpartum Depression: A Retrospective Cohort Study

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Abstract

Objective: We aimed to determine the incidence rate of PPD in PE patients and comprehensively evaluate the association between PPD and PE, including its severity and complications. Design: A retrospective cohort study. Setting: Two cities in China (Chongqing & Xining). Population: 425 pregnant women. Methods: Totally 425 participants including 130 PE mothers were enrolled in this study. Each woman was asked to complete a questionnaire within 6 weeks after delivery, integrating Edinburgh Postnatal Depression Scale (EPDS), Leakage Index Questionnaire, and a pain-scale questionnaire. Main Outcome Measures: The positive screening of postpartum depression between PE and normal pregnant population. Results: The positive rate for PPD in PE group was significantly higher than the control group (30.77% vs. 14.58%). Based on the results of the regression model, women diagnosed with severe PE and FGR were more inclined to develop PPD than normal ones. Postpartum pain tend to exacerbate the odds of PPD among PE patients. Conclusions: PE was an independent risk factor for PPD. Its severity and complications exacerbate the development of PPD. Families and society should pay more attentions on PE patients after delivery to against the development of PPD.

Introduction

Postpartum depression (PPD) is a major depressive episode that begins within 3-6 months after delivery[1]. PPD affects a significant number of mothers, children, and families, as the global prevalence of PPD reportedly ranges from 3% in Singapore to 38% in China[2,3]. Mothers with PPD often exhibit sadness, loss of interest and joy, feelings of helplessness, difficulty concentrating and remembering, and sleep disturbances. PPD may negatively impact maternal health, parenting, and subsequently the development of children. It may result in abusive parenting, maternal suicide, and infanticide[4,5]. Besides, it can lead to negative sequelae for the offspring, including delayed cognitive development, behavioral problems, and even suicidal ideation[6-8]. Therefore, identifying the risk factors of PPD is important for earlier detection and prevention of negative consequences of PPD.

This disorder may be caused by multiple risk factors, include the history of depression, cesarean delivery, preterm delivery, poor marital relationship, and low social income[9,10]. These factors have been fully elucidated to be associated with PPD, but few studies have evaluated the effects of pregnant complications on PPD, such as preeclampsia (PE).

As reported, the hypertensive disorder in pregnancy (HDP) is a risk factor for depression, and the prevalence is about 20%-30%[11,12]. PE is one HDP characterized as hypertension developing after 20 weeks of gestation with the coexistence of [?]1 of a new onset of (1) proteinuria, (2) maternal organ dysfunction, or (3) uteroplacental dysfunction[13]. PE is one of the leading causes of maternal/fetal mortality and morbidity worldwide and is responsible for around 60,000 deaths[14]. PE directly threatens mothers and causes various adverse fetal outcomes, leading to small-for-gestational-age babies, premature delivery, and infant death[15].

Our previous study demonstrated that PE patients had nearly 3-fold increased odds for PPD compared to normal women, and patients with severe PE had a more than 4-fold higher risk of screening positive for PPD[16]. However, whether the severity of PE and fetal outcomes would contribute to PPD has not been investigated.

Herein, we aimed to compare the incidence rate of PPD in PE and normal women by employing the EPDS, and to comprehensively evaluate the association between PPD and PE, especially its severity and complications. In addition, it has been previously reported the pelvic floor symptoms, urinary incontinence and pain would affect postpartum moods[17,18], so we also employed the Leakage Index Questionnaire and the Pain Scale.

Methods

Study design and participants

In this two-center retrospective cohort study, patients who delivered between January 1, 2018 and August 30, 2019 were enrolled from the First Affiliated Hospital of Chongqing Medical University and Qinghai Red Cross Hospital. All patients were asked to independently complete the questionnaires within about 6 weeks after delivery. With informed consent, the answers of the patients can be used here.

Inclusion and Exclusion Criteria

The inclusion criteria were: 1. diagnose of PE by elevated blood pressure (Systolic pressure[?]140mmHg or diastolic pressure[?]90, and with proteinuria) after 20 weeks of gestational age according to the ACOG guidelines (2019); 2. diagnose with PE accompanied with fetal growth restriction (FGR); 3. Maternal age ranging from 18 to 45 years; 4. Gestational age [?]28 weeks. Moreover, severe PE was diagnosed as 1) systolic pressure[?]160 mmHg or diastolic pressure[?]110 mmHg, measured at least every 4 hours; 2) platelet count[?]100*10^9/L; 3) abnormal liver function (elevated liver enzymes twice the upper limit) without other diseases; 4) renal dysfunction (Scr[?]97.24 μmol/L) in the absence of other diseases; 5) pneumonedema; 6) new-onset headache without other diseases; 7) blurred vision[19]. FGR was defined as an infant birthweight below the 10^{th}percentile of the average of infants at the same gestational age. Patients without any complications during the perinatal period were eligible for enrolment in the normal group.

The exclusion criteria were as follows: 1. presence of other complications, such as gestational diabetes mellitus, chronic hypertension, intrahepatic cholestasis of pregnancy, and hyperthyroidism; 2. Preterm (gestational age less than 36^{+6} weeks) not caused by PE; 3. Pre-existing mental diseases, history of depression, or family depression; 4. Stillbirth or giving birth to a malformed fetus (including any minor anomalies).

Measurements

All details of maternal and neonatal conditions during pregnancy and delivery were obtained from the hospital information systems. After applying the inclusion and exclusion criteria, we invited mothers for a clinical visit within 6 weeks after delivery and encouraged them to participate in our questionnaires, including EPDS, Leakage Index Questionnaire, and Pain Scale (Numerical rating scales).

EPDS is the most commonly-used PPD scale worldwide and is one of the most authoritative self-evaluation scales to screen for PPD.[20] Each of its 10 items is divided into 4 grades and scored from 0 to 3. The total score ranges from 0 to 30, with higher scores signifying more serious PPD[21]. Compared to other questionnaires, it has a satisfactory diagnostic efficiency and is more concise to subjects.[22] The sensitivity of EPDS has been proven to range from 0.67 to 1.00, and the specificity is consistently 0.87 or higher when the cut-off value is 13.[23] Therefore, a score of EPDS [?]13 was determined to be positive for PPD screening in our study.

The Leakage Index Questionnaire (involving 3 items with multiple choices) and Pain Scale were used to evaluate the recovery of muscles in the pelvic floor and the degree of postpartum pain in mothers respectively. The scores of the former range from 0 to 6 and from 0 to 10 in the latter. The higher scores on the Leakage Index Questionnaire predict poorer recovery of pelvic floor muscles. Moreover, educational background,

annual family income, and milk feeding methods were also investigated in our questionnaire (details are shown in Figure S1).

Statistical Analysis

This study was designed to detect a 5% absolute difference between groups with 90% power and a 5% type I error rate. We assume that the incidence of PPD was about 30% in the PE group and 15% in the control group. Therefore, a sample size of 380 (88 in the PE group and 292 in the control group) was needed. The MedSci Sample Size Tools (MSST, version 5.7.15, copyright 2020 MedSci.cn) were applied for calculating. We recruited 130 PE patients and 295 healthy women.

Variables in accordance with normal distribution were compared via an independent t-test and presented as mean ± standard deviation. Otherwise, variables were described as mean ± quartile and examined by the Kruskal–Wallis test. Differences in the classified variables were evaluated by the Chi-squared test. $P < 0.05$ was considered as significant. A Multivariate logistic regression model was used to evaluate adjusted odds ratios. Confounding factors including age, BMI, gestational days, baby weight, delivery model, Leakage Index Score, milk-feeding ways, and Pain Scale, which were previously reported to be connected with PPD or unmatched between PE and normal groups. All statistical analyses were conducted on SPSS 23.0 (SPSS Inc, Chicago, USA).

Results

Clinical characteristics between normal and PE mothers

A total of 130 PE patients met the inclusion and exclusion criteria. We randomly selected 295 normal women who met the inclusion criteria during the same period. In the PE group, 74 patients were diagnosed with mild PE, the others with severe PE. Clinical characteristics were compared between the normal and PE groups in Table S1. The layer distribution of pre-pregnancy body mass index (BMI) was significantly different, and PE mothers had a higher BMI than the normal ones (P=0.005). PE patients suffered a much higher rate of caesarean section (93.08% *vs.* 33.22%) and less gestational age (260 *vs.* 277 days) (both P¡0.001). As a result, the birthweight of the fetuses in the PE group was inferior to the normal one (2960 *vs.* 3255 g, P¡0.001). In terms of feeding, infant formula was more frequently used in PE group, no wonder the exclusive breastfeeding rate was lower (33.08% *vs.* 57.63%,P¡0.001). However, other clinical characteristics were not significantly different between groups, such as BMI increase, gravidity, parity, percentage of primipara, sex of the fetus, educational background, annual family income, and scores of the Leakage Index Questionnaire and Pain Scale.

Clinical characteristics between PPD and non-PPD groups

All participants were asked to finish EPDS, and the scores were compared between the normal and PE groups. No differences for clinical characteristics were found between PPD and non-PPD mothers in the normal group (Table S2). However, in PE group, mothers who had babies with FGR and low neonatal weight tended to develop PPD (P=0.024 and$P$=0.007; Table 1). Postpartum pain was another high-risk factor for PPD in PE group (P=0.012). Unlike PE group, the scores of pain scale showed no difference between PPD and non-PPD women in the normal group (P=0.209).

Severe PE and FGR womenwere inclined to develop higher EPDS scores

We tried to explore the associations between PPD and PE. The average EPDS score in the normal group was significantly lower than the mild PE subgroup (7.09±4.41 vs. 8.62±4.35, P=0.008; Table S3 and Figure 1). In the severe PE subgroup, the average EPDS score was even worse (10.58±5.41), indicating most of the severe PE patients developed PPD. Furthermore, 38 PE mothers were complicated with FGR and got the highest EPDS scores among the subgroups (11.61±5.29, P¡0.001).

Rather than caesarean section, PE showed direct tendency on PPD development

There was a higher caesarean section rate among PE patients than normal women (93.08% *vs.*33.22%). To

determine the effect of caesarean section on PPD development, we compared the EPDS scores and PPD incidence between C-section and vaginal delivery in the normal group. There was not any difference in the EPDS score (6.74+-4.42 *vs.* 7.27+-4.41, P=0.337) and PPD incidence (13.27% *vs.*15.32%, P=0.728) between the two delivery modes (Table S4). Interestingly, when compared the normal and PE groups suffered from cesarean section, it was found that both the EPDS (9.54+-4.80 *vs.* 6.74+-4.42,P¡0.001) score and PPD incidence (32.23% *vs.*13.27%,P=0.001) were much higher among PE group than the normal group (Table S5). It could be inferred that it was not cesarean section but PE directly increased the risk of PPD.

Much higher screening of PPD in PE mothers than the normal ones

We compared the rate of positive screening of PPD in each subgroup (Table 2). Totally 83 people were screened positive for PPD, while the remaining 342 were negative. The incidence of PPD was 14.58% in the normal group, whereas the rate was much higher among PE mothers. About 30.77% of women in the PE group met the diagnostic criterion for PPD. Furthermore, the incidences of PPD dramatically increased with the severity of PE and its complications. For instance, the incidences of PPD in the mild PE and severe PE subgroups were 27.03% and 36.96% respectively, which were significantly higher than the normal mothers (14.58%, P=0.014 & P=0.002). We also tried to explore the associations between PE complications and PPD development. In the PE+ FGR subgroup, the incidence of PPD was the highest among all the subgroups (44.74%). Thirty new-borns were extremely weak and had to be sent to the neonatal intensive care unit (NICU). Obviously, when the babies were sent to NICU, their mothers tended to develop PPD. PPD incidence among these mothers increased dramatically (36.66%), which was extremely high. Preterm, one of the common complications in PE, occurred in almost half of PE mothers (61 of 130). PPD occurrence was 32.79% in the PE + preterm subgroup.

Independent risk factors for PPD

Then multiple logistic regression was performed to evaluate the independent risk factors for PPD. With PPD as the dependent variable, PE, severe PE, FGR, NICU admission were regarded as independent variables individually, while age, BMI, gestational days, baby weight, delivery model, Leakage Index Score, milk-feeding ways and Pain Scale analysed as confounding factors. Women with mild PE demonstrated 2-fold higher odds of PPD (AOR=2.117, 95% CI: 1.001-4.479; Table 3). Furthermore, severe PE, FGR, and NICU admission all increased nearly 3-fold risk for PPD positive screening. These findings indicate that the severity and complications of PE will increase the risk of PPD (as shown on Figure S2). Besides PE, postpartum pain was another independent risk factor for PPD (AOR=1.509, 95%CI: 1.078-2.114). The effect of breastfeeding on PPD has not been clearly indicated before, but in our study, exclusive breastfeeding seemed not to positively affect the mood of the mothers (AOR=0.752, 95%CI: 0.445-1.270). Pelvic floor muscle recovery has always been a concern among new mothers and can dramatically influence their moods. After evaluating pelvic floor function, we found the dysfunction of pelvic floor muscles had no negative effect on PPD (AOR=1.137, 95%CI: 0.952-1.358). Moreover, we observed there were no correlations between the caesarean section and PPD (AOR=1.177, 95%CI: 0.620-2.232).

Discussion

Among the general population, hypertension has already been proved to be an independent risk factor for depressive disorder.[24]Hypertension increased 1.12-fold of developing depression among 6,237 old Chinese adults.[25]For pregnant women, few studies were exploring the connection between PE and PPD. To our knowledge, this is the first retrospective cohort study to clarify the associations of the severity and complications of PE with PPD in Chinese population. The number of cases (425) in our trial is the largest among the existing relevant studies.

As reported, PPD occurred in 20.5% PE patients in Tanzanian and in about 21% PE mothers in Greek.[1,26]In our study, the percentage of a positive screening for PPD in PE group was even higher (30.77%). Besides PE, its complications could also increase the risk of PPD. Similar to our findings, Hoedjes M. et al. discovered that the prevalence of PPD was 23% in mild PE patients and 44% in severe PE.[27]These studies suggest PE affects PPD strongly.

For PE mothers, besides unfavourable experience of hypertension, other conditions such as additional costs, concerns of the new-borns with complications also increase mothers' psychological burden.[28,29]The outcomes of infants play an important role in PPD development among severe PE patients. [27]This conclusion was confirmed in our study, especially for growth-restricted babies. A study reported the prevalence of PPD among FGR family was 48.2%, which was similar to our result (44.74%).[28] 38% of mothers experienced significant depressive symptoms when their babies were sent to NICU.[30]These studies mentioned that baby conditions and financial problems maybe two of the most risk factors of PPD. In our clinical trial, mothers were asked 'what most upsets you?' The majority of mothers told us that they were bothered most by the poor outcomes of their babies and NICU admission. In our study, 30 neonates were admitted to NICU. Notably, the incidence of PPD among these mothers was very high (36.6%). Many randomized controlled trials have implicated that insufficient contact with babies will increase the odds of PPD.[31-33] Therefore, clinical healthcare workers should provide psychological supplies to mothers with NICU babies. The financial problem was the second problem: seven of them received lower annual income (less than 80 k RMB per year), they felt huge burden on children hospital expenses.

Whether the cesarean section will increase the risk of PPD is still controversial. In China, some healthy pregnant women would like to choose cesarean section due to social-psychological factors. In this research, mothers with PE preferred to have a cesarean section to avoid possible adverse outcomes. This can explain why the rate of operative delivery in China among PE patients is so high.

First of all, to figure out the effect of cesarean section for PPD, we compared delivery models among normal women. Patel et al. demonstrated that operative delivery would not increase the incidence of PPD in 14,633 women.[34] A meta-analysis in 2017 also reported that elective cesarean section would not significantly exacerbate the odds of PPD (AOR: 1.15, 95%CI: 0.92-1.43).[35] In our study, there was not any difference in the EPDS score and PPD incidence between the two delivery models among normal pregnant populations.

However, in PE group, we found that both EPDS score and PPD incidence were much higher in mothers suffered from operation. It could be inferred that PE directly increased the risk of PPD rather than cesarean section. Then we applied subgroup analysis to find the reason. In PE+ FGR subgroup, the incidence of PPD was the highest among all the subgroups. Obviously, mothers tended to showing anxiety when babies were sent to NICU. Another common complication is preterm. Almost half of PE mothers occurred preterm. As expected, mothers in the PE+preterm group experienced higher psychological distress than others. Weigl et al. pointed new mothers of preterm infants exhibited higher scores of depression, anxiety and stress than parents of term infants. Preterm mothers showed lower levels of estradiol, progesterone, and prolactin, as well as a heightened post-awakening cortisol response compared to term mothers[36]. These results are consistent with our finding.

Postpartum pain, urinary incontinence, and feeding methods were also evaluated in the regression model. Postpartum pain was an independent risk factor for PPD, increasing the odds by 1.5-fold. A few trials showed that untreated pain is associated with a risk of PPD.[37,38]The usage of painkillers can help decrease the incidence of PPD in some cases.[39,40]Our study implied postpartum pain as another risk factor of PPD in the PE group. This was probably because PE mothers suffered more postpartum pain from the operation. Therefore, it is reasonable to use painkillers for PE mothers during the postnatal period.

Hullfish Kl. et al has demonstrated a correlation between urinary incontinence and PPD[41], but Doering AD. et al showed no such connection[42]. In our study, there was no significant result about urinary incontinence in PPD development. Nonetheless, more authoritative urinary incontinence scales need to be tested in the future. Non-breast-feeding was regarded as a risk factor for PPD in many cases.[43,44]But in our study, exclusive breastfeeding did not help decrease the incidence of PPD.

Although the connection between PE and PPD is still unclear, some mechanisms, such as clinical symptoms, inflammation, and genetic changes, have been used as hypotheses for the reason between PE and PPD. The pathogenesis for PE, a placenta disease, can be explained by the "two-stage theory".[45]At the first stage, vascular remodeling disorders of uterine spiral arterioles caused by multiple factors result in "superficial

placental implantation" and ultimately cause insufficient placental perfusion and impairment of placental function. In the second stage, the ischemic placenta will experience oxidative stress and release inflammatory factors, such as IL-6, leading to systemic endothelial dysfunction. Therefore, PE patients often have excessive inflammatory factors in blood circulation.[46-49]For example, abnormally elevated C-reactive protein (CRP) and tumour necrosis factor (TNF)-α are detected in the serum of PE mothers, resulting in vascular remodelling dysfunction of the placenta.[50]Consistently, like PE, inflammatory biomarkers also take part in PPD development.[51] Studies confirm that increased IL-6 and TNF-α levels during the perinatal period can intensify the risk of PPD.[52-54] Based on these studies, we speculate that inflammatory cytokines are released by the dysfunctional placenta in PE mothers, finally leading to the development of PPD.[50,55,56]Our further research will pay more attention to these inflammatory cytokines.

We must admit that there are some limitations in our study. As a retrospective study, it suffered from bias and case limitations. Firstly, patients were recruited from 2 hospitals and the local bias may be relatively reduced, but there is still a need for a study involving multiple centres. Secondly, it was hard to control operation rate in PE group, although this delivery mode was not found to be a risk factor in our regression model. In future, we would like to initiate larger randomized controlled trials and more in-depth mechanistic studies.

Conclusions

PE can be an independent risk factor for PPD. Moreover, its severity and complications exacerbate the development of PPD. Severe PE, FGR, and NICU admission all increased nearly 3-fold risk for PPD positive screening. Patients with PE should be offered suitable interventions, such as pain management, more Cognitive-behavioral therapies (CBT) and interpersonal psychotherapies (IPT) to prevent the development of PPD.

Disclosure of interests

None declared. Completed disclosure of interest forms are available to view online as supporting information.

Contribution to authorship

HBQ and NS contributed to the study design. YY, LC and JNX collected data. YY and QJD analyzed data and wrote this manuscript. XL and CT provided some advice on data analysis and helped editing this manuscript. HBQ and NS revised the manuscript and are corresponding authors of this study. All authors made substantial contributions to the paper and read and approved the final manuscript.

Details of ethics approval

The study was approved by the ethics committee of the First Affiliated Hospital of Chongqing Medical University on 1 December 2019 (NO.20198101). An electronic informed consent was obtained before completing the questionnaire.

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Data sharing

The data used and analyzed during the current study are available from the corresponding author on reasonable request.

References

1. Jahangard L, Mikoteit T, Bahiraei S, et al. Prenatal and Postnatal Hair Steroid Levels Predict Post-Partum Depression 12 Weeks after Delivery. *Journal of clinical medicine*2019; **8** (9).

2. Hahn-Holbrook J, Cornwell-Hinrichs T, Anaya I. Economic and Health Predictors of National Postpartum Depression Prevalence: A Systematic Review, Meta-analysis, and Meta-Regression of 291 Studies from 56 Countries. *Front Psychiatry* 2017; **8** : 248.

3. Nakano M, Sourander A, Luntamo T, Chudal R, Skokauskas N, Kaneko H. Early risk factors for postpartum depression: A longitudinal Japanese population-based study. *J Affect Disord* 2020; **269** : 148-53.

4. Weng SC, Chang JC, Yeh MK, Wang SM, Chen YH. Factors influencing attempted and completed suicide in postnatal women: A population-based study in Taiwan. *Sci Rep*2016; **6** : 25770.

5. Krischer MK, Stone MH, Sevecke K, Steinmeyer EM. Motives for maternal filicide: results from a study with female forensic patients. *Int J Law Psychiatry* 2007;**30** (3): 191-200.

6. Brand SR, Brennan PA. Impact of antenatal and postpartum maternal mental illness: how are the children?*Clin Obstet Gynecol* 2009; **52** (3): 441-55.

7. Avan B, Richter LM, Ramchandani PG, Norris SA, Stein A. Maternal postnatal depression and children's growth and behaviour during the early years of life: exploring the interaction between physical and mental health. *Arch Dis Child* 2010;**95** (9): 690-5.

8. Hammerton G, Zammit S, Thapar A, Collishaw S. Explaining risk for suicidal ideation in adolescent offspring of mothers with depression. *Psychol Med* 2016;**46** (2): 265-75.

9. Azale T, Fekadu A, Hanlon C. Postpartum depressive symptoms in the context of high social adversity and reproductive health threats: a population-based study. *Int J Ment Health Syst* 2018; **12** : 42.

10. Baumgartner JN, Parcesepe A, Mekuria YG, et al. Correlates of postpartum common mental disorders: results from a population-based study in Amhara region, Ethiopia.*Arch Womens Ment Health* 2016; **19** (5): 937-42.

11. B M, C K, S K, BF S. Postpartum depression among women with pre-eclampsia and eclampsia in Tanzania; a call for integrative intervention. *BMC pregnancy and childbirth*2019; **19** (1): 270.

12. L C, X W, Q D, N S, H Q. Development of Postpartum Depression in Pregnant Women with Preeclampsia: A Retrospective Study. *BioMed research international* 2019; **2019** (undefined): 9601476.

13. Brown MA, Magee LA, Kenny LC, et al. Hypertensive Disorders of Pregnancy: ISSHP Classification, Diagnosis, and Management Recommendations for International Practice.*Hypertension* 2018; **72** (1): 24-43.

14. GJ B, CW R, JM R, A M. Pre-eclampsia: pathophysiology and clinical implications. *BMJ (Clinical research ed)* 2019; **366** (undefined): l2381.

15. EA P, R T, T B, SA K. Pre-eclampsia: pathogenesis, novel diagnostics and therapies.*Nature reviews Nephrology* 2019; **15** (5): 275-89.

16. Chen L, Wang X, Ding Q, Shan N, Qi H. Development of Postpartum Depression in Pregnant Women with Preeclampsia: A Retrospective Study. *Biomed Res Int* 2019;**2019** : 9601476.

17. CW S, JA D, JK H, MB B, DE F. Postpartum depression screening and pelvic floor symptoms among women referred to a specialty postpartum perineal clinic. *American journal of obstetrics and gynecology* 2018; **218** (3): 335.e1-.e6.

18. D S, M H-M, K I, S F, S T, M K. Acute postoperative pain is correlated with the early onset of postpartum depression after cesarean section: a retrospective cohort study. *Journal of anesthesia* 2020.

19. Z L, Y L, L C, P C, Y H. Prevalence of Depression in Patients With Hypertension: A Systematic Review and Meta-Analysis. *Medicine* 2015; **94** (31): e1317.

20. ACOG Committee Opinion No. 757: Screening for Perinatal Depression. *Obstetrics and gynecology*2018; **132** (5): e208-e12.

21. Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression. Development of the 10-item Edinburgh Postnatal Depression Scale. *Br J Psychiatry* 1987; **150** : 782-6.

22. WV B, BP Y. Concise review for physicians and other clinicians: postpartum depression. *Mayo Clinic proceedings* 2014; **89** (6): 835-44.

23. E OC, RC R, M H, HC G, BU B. Primary Care Screening for and Treatment of Depression in Pregnant and Postpartum Women: Evidence Report and Systematic Review for the US Preventive Services Task Force. *JAMA* 2016; **315** (4): 388-406.

24. J X, S C, HR B, W T, L L, Y C. The prevalence of depressive symptoms among older patients with hypertension in rural China. *International journal of geriatric psychiatry* 2017; **32** (12): 1411-7.

25. Y J, Y L, P H. Hypertension, socioeconomic status and depressive symptoms in Chinese middle-aged and older adults: Findings from the China health and retirement longitudinal study. *Journal of affective disorders* 2019; **252** : 237-44.

26. K K, M V, V G, et al. Pregnancy, perinatal and postpartum complications as determinants of postpartum depression: the Rhea mother-child cohort in Crete, Greece.*Epidemiology and psychiatric sciences* 2018; **27** (3): 244-55.

27. M H, D B, I V, et al. Postpartum depression after mild and severe preeclampsia. *Journal of women's health (2002)* 2011; **20** (10): 1535-42.

28. N H, C B, S E, A vdW, Y N, C B. Postpartum anxiety and adjustment disorders in parents of infants with very low birth weight: Cross-sectional results from a controlled multicentre cohort study. *Journal of affective disorders* 2016;**194** (undefined): 128-34.

29. L G, D H-D, CS C, et al. Risk factors for postpartum depressive symptoms in low-income women with very low-birth-weight infants. *Advances in neonatal care : official journal of the National Association of Neonatal Nurses* 2015;**15** (1): E3-8.

30. A A, E M, A L. Stress levels and depressive symptoms in NICU mothers in the early postpartum period.*The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians* 2014; **27** (17): 1738-43.

31. K M, E H-R, P T-V, I B, B R, A K. Delivery room skin-to-skin contact for preterm infants-A randomized clinical trial. *Acta paediatrica (Oslo, Norway : 1992)* 2020;**109** (3): 518-26.

32. NV S, AG G, KH C. The effect of skin-to-skin care on postpartum depression among mothers of preterm or low birthweight infants: A systematic review and meta-analysis.*Journal of affective disorders* 2019; **253** : 376-84.

33. KHM C, R B, AC R, C dW. Effectiveness of skin-to-skin contact versus care-as-usual in mothers and their full-term infants: study protocol for a parallel-group randomized controlled trial. *BMC pediatrics* 2017; **17** (1): 154.

34. Patel R, Murphy D, Peters T. Operative delivery and postnatal depression: a cohort study. *BMJ (Clinical research ed)* 2005; **330** (7496): 879.

35. Xu H, Ding Y, Ma Y, Xin X, Zhang D. Cesarean section and risk of postpartum depression: A meta-analysis.*Journal of psychosomatic research* 2017; **97** : 118-26.

36. Weigl T, Schneider N, Stein A, Felderhoff-Muser U, Schedlowski M, Engler H. Postpartal Affective and Endocrine Differences Between Parents of Preterm and Full-Term Infants.*Front Psychiatry* 2020; **11** : 251.

37. ACOG Committee Opinion No. 742 Summary: Postpartum Pain Management. *Obstetrics and gynecology*2018; **132** (1): 252-3.

38. JH M, SY W, HY Y, et al. Prophylactic use of ketamine reduces postpartum depression in Chinese women undergoing cesarean section. *Psychiatry research* 2019;**279** : 252-8.

39. HY Y, SY W, CX Q, et al. Dexmedetomidine Alleviates Postpartum Depressive Symptoms following Cesarean Section in Chinese Women: A Randomized Placebo-Controlled Study. *Pharmacotherapy* 2019; **39** (10): 994-1004.

40. S O-Z, R L, AB H, et al. The Relationship Between Women's Intention to Request a Labor Epidural Analgesia, Actually Delivering With Labor Epidural Analgesia, and Postpartum Depression at 6 Weeks: A Prospective Observational Study.*Anesthesia and analgesia* 2018; **126** (5): 1590-7.

41. KL H, DE F, SA S, J V, A C, WD S. Postpartum depression, urge urinary incontinence, and overactive bladder syndrome: is there an association? *International urogynecology journal and pelvic floor dysfunction* 2007; **18** (10): 1121-6.

42. AD D, AF H, CO H, JA B, CD L, JA S. Is There an Association Between Bothersome Urinary Symptoms and Postpartum Depression? *Female pelvic medicine & reconstructive surgery* 2019; **25** (4): 323-7.

43. T S, X G, C C, et al. A prospective study of maternal postnatal depressive symptoms with infant-feeding practices in a Chinese birth cohort. *BMC pregnancy and childbirth* 2019; **19** (1): 388.

44. EL S, J S, CM R, ES M. The Association between Positive Antenatal Depression Screening and Breastfeeding Initiation and Continuation. *American journal of perinatology* 2019; **undefined** (undefined): undefined.

45. S R, E L, JP G, SA K. Preeclampsia: Pathophysiology, Challenges, and Perspectives.*Circulation research* 2019; **124** (7): 1094-112.

46. BWJ M, CT R, S T, LA M, CJM dG, GJ H. Pre-eclampsia. *Lancet (London, England)* 2016;**387** (10022): 999-1011.

47. A E. Immunology of the maternal-fetal interface. *Annual review of immunology* 2013;**31** : 387-411.

48. S G, ST D. Molecular mechanisms of maternal vascular dysfunction in preeclampsia. *Trends in molecular medicine* 2015; **21** (2): 88-97.

49. T C, P C, L Y, R R. Pre-eclampsia part 1: current understanding of its pathophysiology. *Nature reviews Nephrology* 2014; **10** (8): 466-80.

50. E L-S, N G-L, DM O. An immunological insight into the origins of pre-eclampsia. *Human reproduction update* 2010; **16** (5): 510-24.

51. J G, T M, S M-B. Predictors of Postpartum Depression: A Comprehensive Review of the Last Decade of Evidence. *Clinical obstetrics and gynecology* 2018;**61** (3): 591-603.

52. M L, F G. [Inflammatory Biomarkers and Postpartum Depression: A Systematic Review of Literature]. *Canadian journal of psychiatry Revue canadienne de psychiatrie* 2019; **64** (7): 471-81.

53. H L, Y Z, Y G, Z Z. Elevated levels of Hs-CRP and IL-6 after delivery are associated with depression during the 6 months post partum. *Psychiatry research* 2016;**243** (undefined): 43-8.

54. ES M, D H, E P, WA G, KL W. The association of serum C-reactive protein with the occurrence and course of postpartum depression. *Archives of women's mental health* 2019;**22** (1): 129-32.

55. KK F, JD M, TF M, B M, DE C. Repeated measures of inflammation and oxidative stress biomarkers in preeclamptic and normotensive pregnancies. *American journal of obstetrics and gynecology* 2017; **216** (5): 527.e1-.e9.

56. AC H, DC C, LM A, et al. The role of inflammation in the pathology of preeclampsia. *Clinical science (London, England : 1979)* 2016; **130** (6): 409-19.

Figure legends

1. The average EPDS score in the normal group was significantly lower than the mild PE subgroup.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. The questionnaires were used in the study, including EPDS, Leakage Index Questionnaire and Pain Scale.

Figure S2. Odds ratio of PPD for each characteristic.

Table S1. Comparation of baseline characteristics between normal and PE women.

Table S2. Comparation of baseline characteristics between PPD and Non-PPD women in the normal group.

Table S3. Comparation of EPDS Scores in each subgroup.

Table S4. Comparation of characteristics between two different delivery modes in normal women.

Table S5. Comparation of baseline characteristics in normal and PE women suffered cesarean section.

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`Table BJOG.docx` available at https://authorea.com/users/354164/articles/477786-preeclampsia-and-its-complications-exacerbate-development-of-postpartum-depression-a-retrospective-cohort-study