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Labor Epidural Anesthesia and Postpartum Depression Risk: Prospective Observation Study and Mendelian Randomization Analysis

Wei Zheng, Ping Gan, Xianwen Wan, Xiuhong Wang, Jie Gong, Jia Min

Department of Anesthesiology, The First Affiliated Hospital, Jiangxi Medical College, Nanchang University, Nanchang, People's Republic of China

Correspondence: Jia Min, Department of Anesthesiology, The First Affiliated Hospital, Jiangxi Medical College, Nanchang University, No. 17 Yongwai Main St., Nanchang, People's Republic of China, Email ndyfy02136@ncu.edu.cn

Background: Postpartum depression is a common mental disorder in mothers. Although the association between pain and depression is generally accepted, it remains uncertain whether labor epidural analgesia can effectively reduce the risk of postpartum depression. The objective of this study was to investigate the association between labor epidural analgesia and postpartum depression.

Methods: A total of 146 parturients with a single-term cephalic pregnancy who were preparing for vaginal delivery were recruited for this observational prospective study. The parturients were divided into a labor epidural analgesia group and a control group (routine care) by preference, with 73 in each group. Sociodemographic characteristics and peripartum data of the parturients were collected. Postpartum depression was defined as a score of ≥ 13 on the Edinburgh Postnatal Depression Scale (EPDS) at 6-weeks postpartum. Multivariable logistic analysis was applied to explore the risk factors for postpartum depression, and Mendelian randomization analyses were used to provide supporting evidence for the association between labor epidural analgesia and postpartum depression at the genetic level. Single-nucleotide polymorphisms associated with epidural or spinal anesthesia and postpartum depression were identified from publicly available genetic dataset of the United Kingdom biobank and FinnGen database.

Results: There was no statistically significant difference in the incidence of postpartum depression at 6-weeks postpartum between the epidural and non-epidural groups [12 (16.4%) vs 7 (9.6%), $P = 0.219$]. The multivariable logistic model suggested that prepartum EPDS scores, satisfaction with income and marital status, pain level before anesthesia, and comorbidity during pregnancy were independent predictors of postpartum depression incidence. Mendelian randomization analyses indicated that neither labor epidural (OR = 0.90, 95% CI: 0.78–1.05; $P = 0.18$) nor spinal anesthesia (OR = 1.10, 95% CI: 0.96–1.27; $P = 0.17$) potentially reduced the risk of postpartum depression.

Conclusion: These findings imply that administration of labor epidural analgesia during delivery has no influence on the incidence of postpartum depression.

Registration Number: The study protocol was registered in Chinese Clinical Trial Registry (ChiCTR2300078957).

Keywords: postpartum depression, labor epidural analgesia, neuraxial anesthesia, prospective observation study, Mendelian randomization

Introduction

Postpartum depression (PPD) is a common mental illness that occurs after delivery among mothers, with manifestations as insomnia, fatigue, mood lability, irritability, social disorders, and even suicidal ideation being reported.[1] Mothers suffering from PPD often experience awful mother–infant bonding and family ties,[2,3] and PPD may affect cognitive, psychological, and physical development of the offspring.[4,5] The prevalence of PPD ranges from 3% to 35% worldwide and 21.4% in China, which varies by levels of regional development, study design, culture backgrounds, evaluative instruments and diagnostic criteria.[6,7] A recent meta-analysis indicated that the worldwide pooled prevalence of PPD was 17% among women without a prior history of mental illness.[4] The symptom onset usually appears within 4–6 weeks following delivery, while the time-period window can be extended up to one year in clinical research.[8–10] Most

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individuals are afflicted with PPD for several weeks and spontaneously remit. However, symptoms of depression in some patients can last months or years without treatment.[3]

PPD is a multifactorial condition, whose biological aspects include genetic predisposition, hormonal fluctuation, metabolic issues, inflammation and psychosocial factors.[8,11] There are also numerous risk factors for PPD which have been recognized, including a history of depression, prenatal anxiety, impaired marital interactions, negative life events, and a lack of social and financial support.[1,9,12] Furthermore, delivery complications such as severe labor pain may also influence the risk for PPD.[13,14] Drug-induced labor analgesia, involving oral analgesics, inhaled, intravenous or neuraxial anesthesia, can effectively reduce or eliminate maternal pain in childbirth. Among these methods, labor epidural analgesia (LEA) with local anesthetics has been commonly used because of its excellent analgesic effect and few adverse reactions, which can also offer dose adjustment according to maternal demand.[15,16] Currently, the association between pain and depression has been generally accepted, but whether relief of pain with LEA is associated with a decreased risk of PPD remains unclear. A multicenter prospective cohort study conducted by Deng et al found that neuraxial analgesia during delivery was associated with a low incidence of 6-week PPD.[17] Meanwhile, a recent meta-analysis reported that the risk of PPD was reduced in parturients who underwent LEA as well.[18] Nevertheless, another three meta-analyses published in this issue challenged this protective effect of LEA or neuraxial labor analgesia, which showed that labor analgesia did not decrease PPD risk compared to the control group.[6,19,20] What is intriguing is that most previous studies were observational trials with inevitable confounding factors, which weakens the strength of the evidence.

Given the high incidence of PPD and the resultant great challenge to major public health, there is an urgent need to investigate this controversial issue further. Although randomized controlled trials have fewer methodological and inherent limitations, parturients' rights to painless childbirth should be considered. Therefore, we still undertook this study aimed to determine whether LEA is associated with PPD and explore the predictive factors of PPD from sociodemographic, psychosocial, and obstetric variables reported in the literature through an observational prospective cohort study.

Mendelian randomization (MR) is an epidemiological study design that employs selective genetic instrumental variables as proxies for actual exposures to assess the causality between exposures and outcomes with minimal bias, which is achieved by random allocation of alleles during embryo formation.[21] In this study, a two-sample MR analysis based on large-scale genome-wide association study (GWAS) data was combined with a prospective cohort study to further identify the link between LEA and PPD.

Methods

Observation Study Design

This prospective cohort study was conducted at the First Affiliated Hospital of Jiangxi Medical College, Nanchang University, between December 2023 and April 2024. The study protocol approved by the hospital ethics committee [No.2023(320)] was registered in the Chinese Clinical Trial Registry (ChiCTR2300078957), and the research process was consistent with principles expressed in the Declaration of Helsinki. After obtaining written informed consent, 146 parturients aged 20–35 years, at 37–42 gestation weeks, and singleton pregnancies with cephalic presentation preparing for spontaneous onset of childbirth were recruited for the study. The parturients stratified into labor epidural analgesia group and control group with no analgesia (receiving routine care, including psychological support, instruction in the correct breathing and delivery position) at a 1:1 allocation based on their willingness (73 parturients each group). The exclusion criteria were as follows: refusal by a parturient, previous abnormalities of the reproductive tract and diseases of the uterus, prepartum treatment with sedative and analgesic medication, history of psychiatric diseases or prepartum depression (Edinburgh postnatal depression scale $\geq$ 13), and referral for cesarean section.

Conduct Labor Epidural

Upon admission to the hospital, each parturient was informed of the benefits and risks associated with LEA and was permitted to decide whether to receive treatment or not, provided that they did not have any contraindications for epidural

analgesia, such as coagulopathy disorders, infection or deformity at the puncture site, or allergy to local anesthetics. For participators who requested analgesia, when cervical dilatation reached 2–3 cm, epidural catheterization was performed in the intervertebral space of L2–3 or L3–4 in the lateral position, while other women received no intervention during delivery. After an initial dose of 5 mL 1.5% lidocaine was administered, if no adverse effects were observed, a bolus dose of 10 mL mixture of 0.1% ropivacaine and 0.5 μg/mL dexmedetomidine was administered through the epidural catheter. Thereafter, parturients received a continuous background infusion (6 mL/h) of the above mixture using a patient-controlled epidural analgesia (PCEA) pump connected to the catheter, which was programmed to offer a demand bolus dose of 6 mL with a 15-minute lockout interval. The PCEA pump was stopped at full cervical dilation for a while, and the epidural catheter was removed 1 hour after the end of labor.

Data Collection

The demographic baseline and intrapartum data of the parturients, including age, body mass index (BMI), gestational weeks, primipara or multipara, use of LEA, history of surgery, comorbidity during pregnancy, duration, and estimated blood loss of labor, were obtained by searching the patients' electronic medical records. Neonatal data, including sex and Apgar scores at 1 and 5 minutes after birth, were also acquired. Moreover, the baseline numerical rating scale (NRS) scores and Edinburgh Postnatal Depression Scale (EPDS) scores were assessed upon admission to the delivery room. The NRS is an 11-point scale, with 0 indicating no pain and 10 indicating the worst pain. NRS pain scores were also recorded at full cervical dilation in all the participants. Additionally, for parturients who received LEA, NRS scores were recorded 30 minutes after treatment.

The EPDS is the most widely used questionnaire to assess perinatal depression assessment.[22] The Chinese version of the self-report questionnaire contained 10 items in which parturients were asked about their experiences during the previous 7 days. Each item was scored on a scale of 0 to 3, with a total score ranging from 0 to 30. A score of 13 on the EPDS was considered as the threshold for detecting perinatal depression in this study.[22,23] Follow-up was completed using web-based questionnaires to assess EPDS scores at 6 weeks postpartum. Meanwhile, other covariates identified as potential factors affecting PPD were collected via questionnaires, including educational background, health insurance, financial and marital satisfaction, prenatal education, and unscheduled pregnancies.[1,9,12]

Statistical Analysis

The primary outcome of this observational study was the incidence of PPD at 6 weeks postpartum. The sample size was calculated by two independent proportions of power analysis of PASS 11.0 software according to the previous study in which the reported PPD prevalence change was approximately 20% with LEA.[24] Considering a 10% dropout rate and allocation ratio of 1:1, the final number of participants enrolled should be 146 to meet $\alpha = 0.05$ and power = 0.80.

Continuous variables are expressed as mean values ± standard deviations or medians (interquartile ranges), and the results were compared using the *t*-test or Mann–Whitney *U*-test, depending on whether the data were normally distributed. Categorical variables are expressed as the total number (percent frequency), and the results were compared using Pearson's χ^2 test or Fisher's exact test. A univariable logistic regression analysis was used to screen for potential risk factors related to PPD. Factors with a *P*-value less than 0.10 were defined as candidate variables and were further analyzed in a multivariable logistic model with forward stepwise selection. Statistical analysis was carried out using the SPSS software (version 23.0; IBM Corp., NY, USA), and two sided level of statistical significance was set at $P < 0.05$.

Mendelian Randomization (MR) Design

As a widely used epidemiological method without much impact of confounders, two-sample MR analysis was performed to infer causal associations between LEA and PPD in this study. Valid instrumental variables (IVs), such as single-nucleotide polymorphisms (SNPs), should satisfy three essential assumptions as follows: that they must be strongly associated with the exposure (the relevance assumption); that they have no relationship with confounders (the independence assumption); and that they only affect the outcome through the exposure (the exclusion restriction assumption).[21] As the MR analysis was based on a publicly accessible database, ethical approval was not required.

Data Availability and IVs Selection

To minimize potential bias resulting from population heterogeneity, all patients in MR analysis were European. GWAS summary data of LEA were obtained from the United Kingdom Biobank (UKB) with 1,740 cases and 2,230 controls, which are publicly accessible online through the IEU OpenGWAS project (https://gwas.mrcieu.ac.uk/, GWAS ID: ukb-d-41219_2). SNPs closely related to spinal anesthesia during delivery were also derived from the UKB (GWAS ID: ukb-d-41219_3). The UKB is a large population-based prospective cohort study involving nearly half a million participants recruited across 22 centers in the UK from 2006 to 2010.[25] Summary-level GWAS statistics for PPD were extracted from the FinnGen database, which includes 13,657 cases and 236,178 controls (https://www.finngen.fi/fi, version: DF8, public release: December 1, 2022). PPD was diagnosed in patients with a delivery history of F32, F33, or F53.0 in the 10th edition of the International Classification of Diseases (ICD-10) code. The FinnGen project is a large-scale genomics initiative that utilizes Finnish individual samples to comprehensively investigate disease mechanisms and predispositions by correlating genetic variations with health data.[26]

For each cohort, we extracted SNPs as IVs with $P < 5 \times 10^{-8}$, which is widely considered as the criterion for a significant association with the phenotype. If few SNPs fulfilled the criteria, a liberal selection threshold ($P < 1\times10^{-5}$) was chosen.[27] To eliminate linkage disequilibrium (LD) bias, the R^2 threshold and maximum distance were set to 0.001 and 1000 kilobases apart respectively.[27] The F-statistic was calculated to estimate the strength of each SNP, and SNPs with an F-statistic of <10 were recognized as weak IVs that might bring in bias.[21]

MR Analysis

The random-effects inverse variance weighted (IVW) method was applied as the foremost way to evaluate MR estimates of the impact of neuraxial anesthesia on PPD, while the MR-Egger and weighted median (WM) methods were also used as additional analyses to assess the robustness of the results.[10] The strength of causal associations was shown as odds ratios (OR) and 95% confidence intervals (CI). Subsequently, the Cochran's Q value was calculated to estimate the heterogeneity between individual genetic variations. Then, the MR-Egger intercept and MR pleiotropy residual sum and outlier (MR-PRESSO) methods were used to examine the existence of horizontal pleiotropy, which means that unknown confounders were introduced in.[28] Furthermore, leave-one-out sensitivity analysis was conducted to demonstrate the stability of the MR results by exploring the impact of a single SNP on causal association. All MR analyses were performed using the R software (version 4.0.3) with the R package "TwoSampleMR." All two-sided statistical significance levels were set at $P < 0.05$.

Results

Characteristics of Parturients in Observational Study

There were 146 parturients (73 per group) enrolled in total, with the flow chart presented in Supplementary Figure S1. The baseline characteristics of the prospective observational study participants, according to LEA utilization category, are presented in Table 1. The demographic and clinical characteristics of the LEA and control groups were largely comparable, whereas women with LEA had a longer duration of labor and lower NRS scores at full cervical dilation. As shown in Table 1, the overall incidence of PPD at 6 weeks postpartum was 13%, and the differences in PPD occurrence between the two groups were not significant [7 (9.6%) vs 12 (16.4%), $P = 0.219$].

Predictive Factors Associated with PPD

To explore the predictive factors associated with PPD at 6 weeks postpartum, a univariable logistic analysis was conducted on twenty-one variables and eight variables were identified as potential factors ($P < 0.10$): prepartum EPDS scores, gestational weeks, primiparity, comorbidity during pregnancy, satisfaction with income and marriage, NRS pain scores before LEA, and at full cervical dilation. As expected, univariable results suggested that LEA was not associated with PPD. All candidate factors were analyzed using a multivariable logistic regression model. The results confirmed that prepartum EPDS scores, satisfaction with income and marriage, NRS pain scores before LEA, and comorbidities during pregnancy were independent predictors of PPD (Table 2).

Table 1 Distribution of Parturients by Demographic and Perinatal Characteristics

Variables	All Parturients (n =146)	No LEA (n =73)	LEA (n =73)	*P Value*
Age, years	27.6±3.2	28.0±3.4	27.2±3.0	0.132
BMI, kg/m^2	26.4±2.7	26.7±2.8	26.2±2.6	0.298
Gestation, weeks	38.7 (38.4–39.4)	38.6 (38.3–39.4)	39.1 (38.4–39.5)	0.458
Primiparity	74 (50.7%)	33 (45.2%)	41 (56.2%)	0.185
Comorbidity during pregnancy	30 (20.5%)	16 (21.9%)	14 (19.2%)	0.682
Previous surgeries	21 (14.4%)	7 (9.6%)	14 (19.2%)	0.099
Education > 12 years	132 (90.4%)	63 (86.3%)	69 (94.5%)	0.092
Social health insurance	141 (96.6%)	71 (97.3%)	70 (95.9%)	1.000
Satisfaction with family income	102 (69.9%)	49 (67.1%)	53 (72.6%)	0.471
Satisfaction with marriage	124 (84.9%)	60 (82.2%)	64 (87.7%)	0.355
Unplanned pregnancy	59 (40.4%)	31 (42.5%)	28 (38.4%)	0.613
Prenatal education	90 (61.6%)	41 (56.2%)	49 (67.1%)	0.173
Duration of labor, min	378 (245–510)	350 (230–430)	425 (263–533)	0.004
Blood loss during delivery, mL	200 (180–240)	200 (190–230)	210 (160–250)	0.781
NRS pain scores				
Before LEA	7 (7–8)	7 (6–8)	7 (7–8)	0.101
30 mins after LEA			2 (2–3)	
At full cervical dilation	7 (5–9)	9 (9–10)	5 (4–6)	<0.001
Neonatal sex, male	76 (52.1%)	37 (50.7%)	39 (53.4%)	0.740
Apgar score after birth				
1-min	10 (10–10)	10 (10–10)		0.546
5-min	10 (10–10)	10 (10–10)		0.322
EPDS scores				
Prepartum	6 (5–9)	6 (5–9)	6 (5–9)	0.207
6 weeks postpartum	8 (7–10)	9 (7–12)	8 (7–9)	0.137
Postpartum depression (EPDS≥13)	19 (13%)	12 (16.4%)	7 (9.6%)	0.219

Notes: Statistics are presented as mean value ± standard deviation, median (interquartile range) or total number (proportion).
Abbreviations: BMI, body mass index; NRS, numerical rating scale; LEA, labor epidural analgesia; EPDS, Edinburgh postnatal depression scale.

Two-Sample MR Analysis

When we selected SNPs with $P < 5 \times 10^{-8}$, only one SNP fulfilled the inclusion criteria of IVs for LEA, and no SNP was found for labor spinal anesthesia (LSA). Therefore, a liberal threshold *P*-value was adopted. Fifteen independent variants qualified for IVs for LEA (GWAS significance, $P < 1 \times 10^{-5}$, $R^2 < 0.001$, and distance greater than 1000 kb), while two of them (rs76499851 and rs184695056) were unavailable in the GWAS summary statistics of PPD (Supplementary Table S1).

Table 2 Univariable and Multivariable Logistic Analysis of PPD at 6 weeks Postpartum

Variables	Univariable		Multivariable	
	OR (95% CI)	***Pval* <0.10**	**OR (95% CI)**	***Pval***
Gestation, weeks	0.61 (0.35–1.08)	0.091		
Primiparity	0.32 (0.11–0.94)	0.038		
Comorbidity during pregnancy	10.38 (3.61–29.88)	<0.001	14.83 (2.92–75.36)	0.001
Satisfaction with family income	3.92 (1.45–10.58)	0.007	13.47 (2.41–75.20)	0.003
Satisfaction with marriage	7.89 (2.71–22.96)	< 0.001	32.67 (4.93–216.40)	< 0.001
NRS Before LEA	1.61 (1.04–2.49)	0.032	2.31 (1.14–4.68)	0.020
NRS At full cervical dilation	1.31 (1.03–1.66)	0.030		
Prepartum EPDS scores	1.56 (1.25–1.95)	< 0.001	1.67 (1.21–2.30)	0.002

Abbreviations: BMI, body mass index; NRS, numerical rating scale; LEA, labor epidural analgesia; EPDS, Edinburgh postnatal depression scale.

Thirteen SNPs were identified as final IVs in the MR analysis. However, as listed in Supplementary Table S1, all the IVs included in the analysis had F-statistics less than 10, which indicates that the strength of the SNPs was weak and potential bias may exist.

As revealed by the results of the IVW method, no causal effect of LEA on PPD was observed (OR = 0.902, 95% CI = 0.776–1.049; P = 0.180). The results of the other two MR analysis methods were consistent (Table 3). The forest and scatter plots of the results are presented in Figure 1 and Supplementary Figure S2, respectively. Cochran's Q test suggested no significant heterogeneity in SNP effects (IVW method, Q = 3.007, P = 0.995), and no evidence of horizontal pleiotropy bias was detected according to MR-PRESSO global tests (P = 0.996) and MR-Egger regression intercept tests (P = 0.277) (Table 3). Furthermore, leave-one-out analyses indicated that no extreme values influenced causal inference (Figure 2), and funnel plots confirmed that the estimates were unbiased (Supplementary Figure S3).

Additionally, 23 SNPs were used to explore the causal effect of LSA on PPD (Supplementary Table S2). The MR analysis did not provide evidence of an association between LSA and PPD (OR = 1.103, 95% CI = 0.959–1.270; P = 0.170). Detailed results are shown in Table 3 and Supplementary Figures S4 and S5. No significant heterogeneity or pleiotropy was observed (Table 3). Leave-one-out analyses and funnel plots indicated that MR estimates were robust (Supplementary Figures S6 and S7).

Table 3 MR Results of Neuraxial Anesthesia on Risk of Postpartum Depression

Exposures	OR (95% CI)	*Pval*	Numbers of SNPs	Cochrane Q	Heterogeneity *pval*	Pleiotroy *pavl*
Epidural anesthesia			13			0.277
MR Egger	0.75 (0.53–1.07)	0.136		1.697	0.999	
Weighted median	0.86 (0.71–1.05)	0.143				
Inverse variance weighted	0.90 (0.78–1.05)	0.180		3.007	0.995	
Spinal anesthesia			23			0.227
MR Egger	1.32 (0.96–1.82)	0.100		14.041	0.868	
Weighted median	1.05 (0.85–1.28)	0.669				
Inverse variance weighted	1.10 (0.96–1.27)	0.170		15.591	0.836	

Abbreviation: MR, Mendelian Randomization.

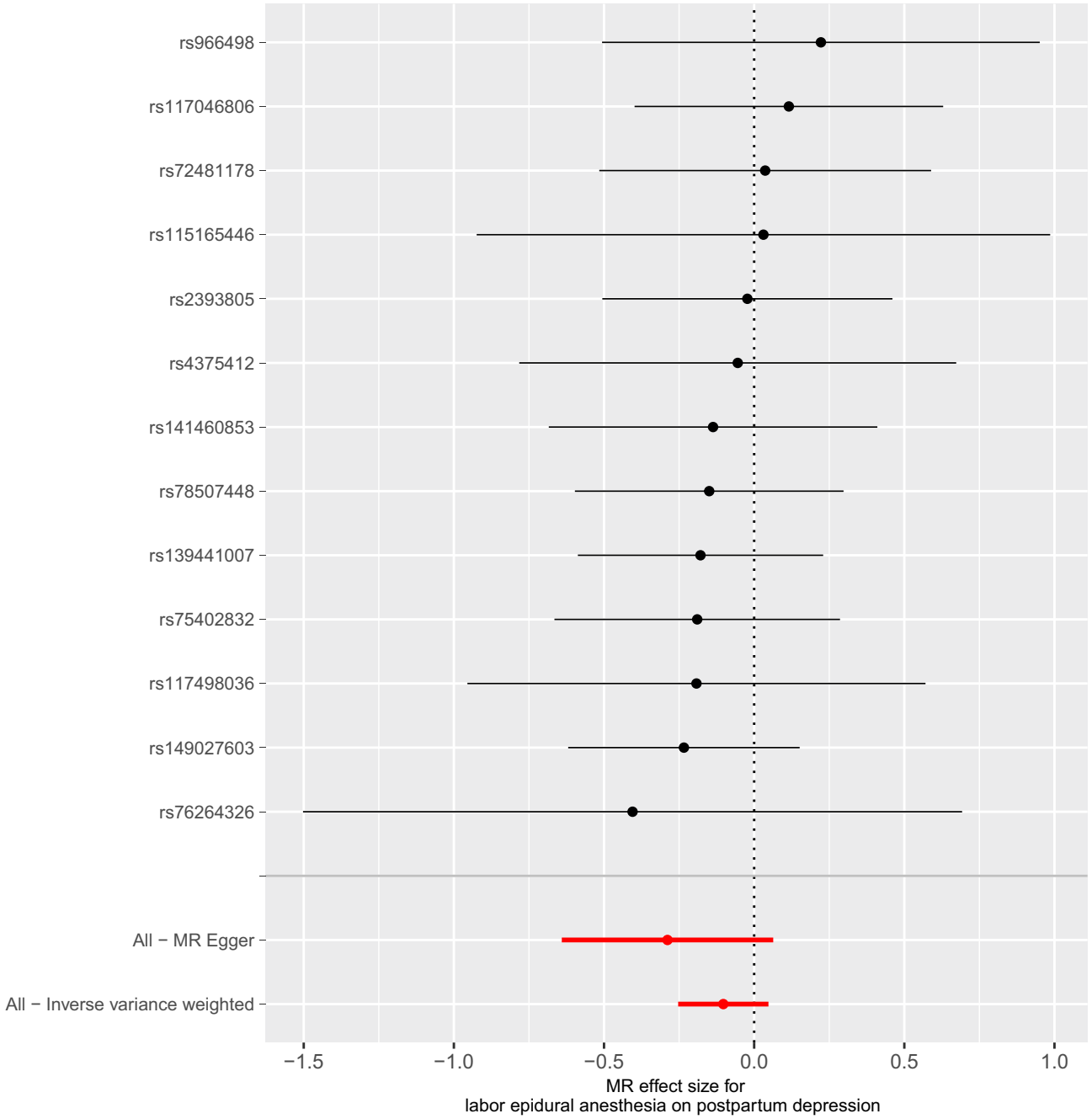

Figure 1 The forest plot for the association between labor epidural anesthesia and postpartum depression.

Discussion

In this prospective cohort study and two-sample MR analysis, we explored the relationship between LEA and PPD in parturients. According to the results, LEA did not show a protective effect against PPD development at 6 weeks postpartum in women with single-term cephalic pregnancy preparing for vaginal delivery, and there was no causal association between neuraxial anesthesia during labor (LEA and LSA) and PPD.

Our results were consistent with the latest meta-analysis, which included 31 observational studies (12,064 women) and concluded a negative association between neuraxial anesthesia and postpartum mental illness.[20] Due to ethical concerns, randomized controlled trial (RCT) is usually conducted with utmost caution in parturients. Recently, the largest RCT to date, conducted by Tan et al, reported no significant differences in the incidence of PPD at 6–10 weeks between

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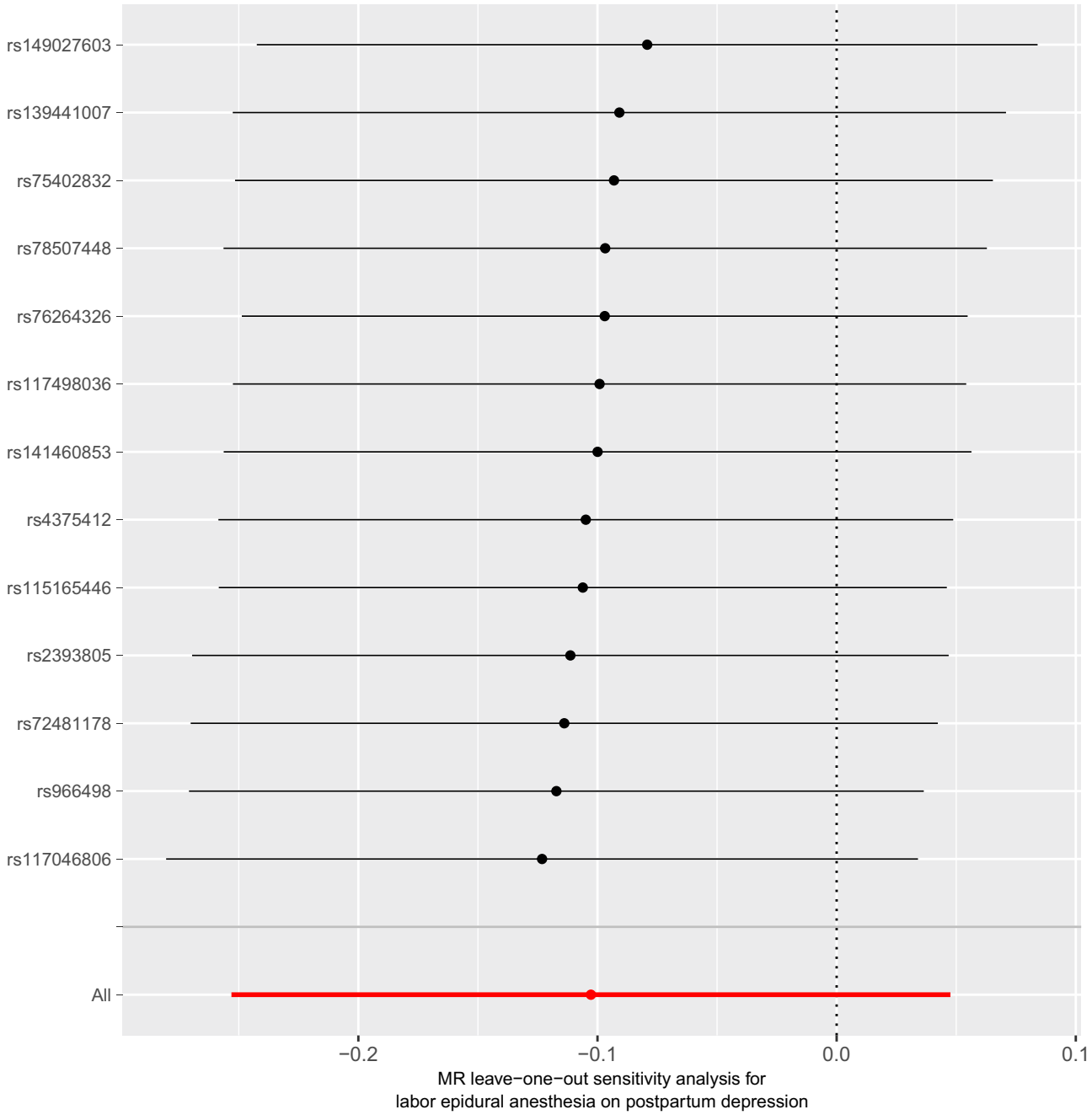

Figure 2 The leave-one-out analysis for the association between labor epidural anesthesia and postpartum depression.

an epidural group (n = 389) and non-epidural group (n = 384), which received other analgesic measures, including intramuscular pethidine, nitrous oxide, and intravenous remifentanil [adjusted risk difference (95% CI) = 1.6 (–3.0–-6.3%), $P = 0.49$].[29] However, just as we focus on the Chinese population, Deng et al and Liu et al indeed found neuraxial labor anesthesia was associated with a reduced risk of PPD at 6 weeks postpartum and 2 years after childbirth, respectively, in multicenter prospect cohort studies.[17,30]

Based on these previous studies, various reasons lead to these contradictory results, and we propose the following: First, the discrepancy in study designs and settings might explain the inconsistent conclusions. Currently, there is no consensus on the optimal period for PPD assessment. Although most studies assessed PPD at 6–8 weeks postpartum, the evaluation time points ranged from 3 days to 2 years in different studies.[6,24,30] Moreover, the cut-off value of EPDS

scores as a screening tool for PPD varies between studies. Our research adopted a value ≥ 13 as indicative of depression, in accordance with the studies by Johnstone et al and Munro et al,[31,32] whereas some studies used a value ≥ 10 as the criterion for minor depression.[17,24,30,33] As prepartum EPDS scores were identified as independent risk factors for PPD in our multivariable logistic regression model, patients with EPDS scores greater than 10 and less than 13 were included in our cohort, which obviously impacted the results. Even in our MR analysis, the definition of PPD was broad and lacked sufficient accuracy according to ICD-10 codes. Second, although we reported that NRS pain scores before LEA application independently influenced PPD incidence, it should be noted that the pathogenesis of depression is complex, and pain is only one of several contributing factors. In fact, both labor pain and prenatal and postpartum pain appear to be linked to PPD.[34] On one hand, inadequate pain control throughout the perinatal period resulting from the administration of neuraxial analgesia exclusively during labor may increase the risk of PPD. On the other hand, in some studies, women without LEA received other analgesic measures, such as local anesthesia, nitrous oxide, intravenous or intramuscular drug therapy, and even non-pharmacological measures,[17,29,33,35] which may reduce the risk of PPD. In our study, we only offered LEA for pain relief, with the PCEA pump being discontinued at full cervical dilation and resumed for a period of one hour at the end of the third stage of labor, which may have contributed to the negative differences in the occurrence of PPD between the two groups. Furthermore, the decision to accept LEA may be partly based on antenatal anxiety and fear of labor pain, which are associated with postpartum depressive symptoms. This may explain the higher incidence of PPD observed 6 months after childbirth in women who underwent anesthetic vaginal delivery than in those who did not, as reported by Suzumori et al in Japan.[36]

To enhance maternal birthing experience and provide more benefits to parturients, the drug formulation in the PCEA pump was modified in our study. Currently, a combination of ropivacaine and an opioid, such as fentanyl or sufentanyl, is widely administered in LEA to provide analgesia. It is well known that opioids have adverse effects such as nausea, vomiting, pruritus, urinary retention, and respiratory depression. In addition, Jiang et al found that genetically predicted opioid use was causally linked to an increased risk of PPD in a MR analysis using a large-scale GWAS dataset.[10] A recent meta-analysis reported by Li et al found that epidural dexmedetomidine, a highly selective α_2 agonist, offered satisfactory pain relief during labor with no discernible adverse effects on parturients or fetuses.[15] Thus, dexmedetomidine, which has anxiolytic, sedative, and analgesic features, was administered instead of the opioids in the PCEA pump in this study. Analgesia induced by dexmedetomidine appears to be mediated by the activation of presynaptic and postsynaptic α_2-adrenoceptors, which subsequently results in a reduction in the release of glutamate and other pain signals.[37] Rather than we expect, the incidence of PPD did not appear to decline with this ameliorated medication regimen, as evidenced by the insignificant difference observed between the epidural and non-epidural groups. As discussed above, pain relief covering the entire perinatal period may play a more crucial role than the medication regimen in PPD.

Finally, the logistic regression analysis in the present study revealed that satisfaction with income and marriage, as well as comorbidity during pregnancy, independently influenced PPD incidence. Patients with a dissatisfied income or marriage usually have a difficult life and worry more about the future, indicating a lack of support from family and society. As demonstrated by Cho et al adequate social support at the emotional, practical, or financial level is associated with a reduced likelihood of PPD, and that women who lack social support are more likely to experience PPD.[38] The comorbidities observed in this study during pregnancy included gestational diabetes mellitus, pregnancy-induced hypertension, and hypothyroidism, which have the potential to exacerbate prenatal anxiety and affect postpartum emotions.

There are still several limitations in this study. First, a prospective observational study with unidentified confounders was conducted on a finite number of parturients, which was preceded by sample size calculation. This can inevitably lead to bias, and the lack of significance may be due to the small sample size. Since patients receiving epidural anesthesia were not randomized in this study, the results may differ in future large-scale multicenter RCTs. Meanwhile, the logistic analysis did not take all the risk factors into consideration, for instance, adverse life events and breastfeeding,[12,24] which might influence the results. Second, as the most extensively studied evaluation scale based on self-reported questionnaires, although the EPDS is generally used for screening PPD in previous studies, the time point and cutoff value for PPD screening have not been universally reached by consensus.[6,22] Therefore, definitive diagnosis should be confirmed

by a professional psychiatrist. Besides the EPDS, no other validated scale was employed for the assessment of prenatal depression in this study, which may have introduced inherent selective bias. Third, although Mendelian randomization analysis is less prone to introduce confounding bias, all selected SNPs used as IVs in this study exhibited F-statistics < 10, which falling below the conventional threshold (F > 10) for acceptable IVs strength. This indicates that the genetic IVs for LEA and LSA are relatively weak, explaining only a small proportion of the variance in the exposure. The limited IVs strength, attributable to the small sample size of the GWAS dataset for PPD, increases the risk of weak IVs bias. This bias, which typically inflates Type I error rates in statistical theory and attenuates causal effect estimates towards the null, may partly explain the observed lack of a significant causal relationship between neuraxial analgesia and PPD reduction.[39] However, we believe that our conclusions are reliable given the results of various sensitivity analyses in the stage mentioned above. Nevertheless, further MR analyses based on larger GWAS datasets are required for further confirmation.

Conclusions

In conclusion, our prospective observational study and two-sample MR analysis supported the absence of a significant association between LEA and PPD incidence. We also found that prepartum EPDS scores, satisfaction with income and marriage, pain level before anesthesia, and comorbidity during pregnancy were independent predictors of PPD at 6 weeks postpartum in parturients. Further research with a larger sample size and an optimized study design is warranted to evaluate the influence of LEA on PPD. For example, future studies could employ a multicenter, large-sample randomized controlled trial or utilize propensity score matching in observational studies to mitigate the impact of preoperative baseline imbalances. Additionally, future investigations should adopt validated methods to assess mental illness in parturients, and the diagnosis of PPD must be confirmed by psychiatrists.

Highlights

The findings of this prospective cohort study, complemented by a two-sample Mendelian randomization analysis, suggest that the administration of epidural analgesia to parturients exclusively during labor has no effect on the incidence of postpartum depression.

Abbreviations

PPD, postpartum depression; LEA, labor epidural analgesia; MR, Mendelian randomization; GWAS, genome-wide association study; PCEA,patient-controlled epidural analgesia; NRS, numerical rating scale; EPDS, Edinburgh Postnatal Depression Scale; IVs, instrumental variables; SNPs, single-nucleotide polymorphisms; UKB, United Kingdom Biobank; ICD-10, International Classification of Diseases; IVW, inverse variance weighted; OR, odds ratios; CI, confidence intervals; LSA, labor spinal anesthesia; RCT, randomized controlled trial.

Data Sharing Statement

The relevant data underlying this study's findings are available from the corresponding author (Jia Min) upon reasonable request.

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Disclosure

The authors declare no conflicts of interest in this work.

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