ORIGINAL RESEARCH

Reduced Intellectual Ability in Offspring Born from Preeclamptic Mothers: A Prospective Cohort Study

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Background: Severe preeclampsia may affect placental development, and high homocysteine (Hcy) levels are linked to intellectual disability. However, the correlation between perinatal Hcy levels and intellectual ability remains unknown in severe preeclampsia-affected offspring.

Objective: We aimed to investigate the intellectual ability in offspring born from preeclamptic mothers and examine the role of prenatal Hcy in the prediction of intellectual disability in preschool-aged offspring.

Methods: The IQ scores were compared between 101 children born to mothers with severe preeclampsia and 202 offsprings born to normotensive mothers. Maternal Hcy levels within 7 days prior to delivery and postnatal cord blood Hcy were measured. The associations of Hcy with IQ scores were evaluated, and the optimal cut-off values for predicting intellectual disability in the offspring were estimated.

Results: The children born to mothers with severe preeclampsia had a greater postnatal cord blood Hcy than those born from normotensive mothers ($P < 0.001$), and the mothers with severe preeclampsia presented a higher prenatal Hcy ($P < 0.001$). The children born to mothers with severe preeclampsia had significantly lower IQ scores than those born from normotensive mothers, and a higher Hcy was associated with a lower IQ in preeclampsia-affected offspring. The prevalence of intellectual disability was 2.86 times higher in severe preeclampsia-affected offspring than in children born from normotensive mothers, and the prevalence of low IQ was greater in children born to mothers with severe preeclampsia than in those from normotensive mothers. ROC curve analysis showed that both maternal and cord blood Hcy were predictors of intellectual disability, and the optimal cut-off for predicting intellectual disability was 17.7 and 9.75 μmol/L for maternal and cord blood Hcy.

Conclusion: Perinatal exposure to severe preeclampsia has an adverse effect on postnatal intellectual development, and high maternal and cord blood Hcy may contribute to this association.

Keywords: preeclampsia, homocysteine, intellectual ability, ROC curve analysis

Introduction

Preeclampsia, a condition characterized by high blood pressure in pregnant women, is estimated to affect 7.5% of the pregnancies worldwide.[1–4] This disorder has been found to adversely affect fetal brain development due to hypoxia,[5,6] and severe preeclampsia-affected offspring may present poorer neurodevelopmental functions, relative to those born from normotensive mothers, such as reduced cognitive performance[7,8] and verbal ability.[9–14] However, the effect of severe preeclampsia on the development of intelligence in the offspring has not been fully demonstrated until now.

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Previous studies have shown that severe preeclampsia is associated with endothelial dysfunction[15] and may affect placental development,[16] which results in reduced blood flow to the fetus and a relatively hypoxic state.[17] Homocysteine (Hcy) is an endogenous sulphydryl-containing amino acid produced by transmethylation of the essential sulfur-containing amino acid, methionine.[18] High Hcy levels have been reported to cause endothelial dysfunction,[19,20] a known risk factor for intellectual disability and hypoxic damage.[21,22] These pathophysiological changes may affect neurodevelopmental functions as early as the fetal stage.[23,24] To the best of our knowledge, however, the correlation between perinatal Hcy levels and intellectual ability remains unknown in severe preeclampsia-affected offspring. This prospective cohort study was therefore designed to investigate the intellectual ability in offspring born from preeclamptic mothers and examine the role of prenatal Hcy in the prediction of intellectual disability in preschool-aged offspring.

Methods
Study Subjects
A single-center prospective cohort study was designed with aims to compare the intellectual ability in children born to singleton pregnant women with and without severe preeclampsia delivered in the Department of Gynecology and Obstetrics, Fuzhou First Hospital (Fuzhou, China), during the period between January 2010 and December 2015. Severe preeclampsia was diagnosed based on at least one of the following criteria:[25] systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥110 mmHg on two occasions separated by at least 6 h after 20 weeks of gestation; proteinuria ≥5 g in 24 h or ≥3 g on a dipstick; oliguria (≤500 mL in 24 h); cerebral or visual disturbances; epigastric pain; thrombocytopenia; elevated serum liver enzymes; pulmonary oedema or cyanosis; uteroplacental dysfunction; and fetal growth restriction or eclampsia. Those who met the following criteria were excluded from the study: missing data, alcohol/drug/smoking abuse in one of the parents during or before pregnancy, mild preeclampsia or gestational hypertension, chronic hypertension (hypertension requiring treatment with antihypertensive agents before the relevant pregnancy), pre-gestational diabetes, renal diseases, systemic lupus erythematosus, multiple pregnancies, neonatal and fetal death, or major fetal congenital malformations.

A total of 172 mothers/children pairs that met the inclusion and exclusion criteria were recruited, and 101 pairs that agreed to participate in a follow-up until the children's age of 4 years

were included in the study (Figure 1). For each pair, we enrolled two controls matched by gestational age (within 1 week), birth weight (within 100 g), and current age of children (within 6 months). For control subjects, singleton pregnant women with normal blood pressure (systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg) during pregnancy were included, and those complicated by internal or surgical diseases, gestational diabetes, thyroid diseases or mental disorders were excluded from this study. Both preeclampsia patients and normotensive controls were recruited in this study via telephone follow-up by two well-trained senior obstetricians during the period between January 2014 and December 2019. Medical records were carefully reviewed and parental interviews were performed by two well-trained senior obstetricians to capture parental demographics, perinatal data, birth outcomes, and postnatal factors. In this study, the parental education level was categorized as (middle school or below), middle (high school), and high (college or above).

Measurement of Prenatal and Postnatal Hcy
Maternal Hcy levels within 7 days prior to delivery and postnatal cord blood Hcy levels were measured using enzyme-linked immunosorbent assay (ELISA) with a commercial kit (Senbeijia Biotechnology Co., Ltd.; Nanjing, China).

Assessment of Intellectual Ability in the Offspring
The Chinese Wechsler Young Children Scale of Intelligence (C-WYCSI) was employed to assess the intellectual ability in the pre-school children at the ages of 4 years.[26] The C-WYCSI is designed for assessment of intelligence in children at ages of 4 to 6 years and consists of five verbal subtests (arithmetic, information, comprehension, sorting, and vocabulary) and five performance subtests (picture completion, animal pegs, block design, object assembly, and mazes).[26] All subtests use a scaled scoring system, which is standardized using a mean of 10 and a standard deviation of 3 to transform the raw score. In addition, the verbal intelligence quotient (VIQ) and performance intelligence quotient (PIQ) scores were calculated with their sum representing the full intelligence quotient (FIQ) score. All intelligence tests were performed by two well-trained psychologists that were blinded to the study.

Ethics Consideration
This study was approved by the Ethics Review Committee of Fuzhou First Hospital (date of approval: December 5,

12273 women who underwent deliveries between Jan 2010 to Dec 2015

2013 women excluded
- 878 incorrect maternal information
- 1001 in correct paternal information
- 134 incorrect fetal or neonatal information

10260 women

3162 women excluded
- either of the couple alcohol/drug/smoking abuse during or before pregnancy

7098 women

1821 women excluded
- 1437 mild preeclampsia or gestational hypertension
- 78 chronic hypertension
- 17 pre-gestational diabetes
- 5 renal diseases
- 3 systemic lupus erythematosus
- 263 multiple pregnancy
- 18 fetal major congenital malformations

5277 women

172 severe preeclampsia

5105 normotensive

- 31 refused to participate
- 13 Fetal death
- 7 neonatal death
- 3 moved to other cities
- 10 loss to follow-up
- 7 non Hcy examination

- 4903 women not included

101 severe preeclampsia

Matching 1:2 for gestational age, birth weight and age of children

202 normotensive

101 children of 101 mothers included analysis

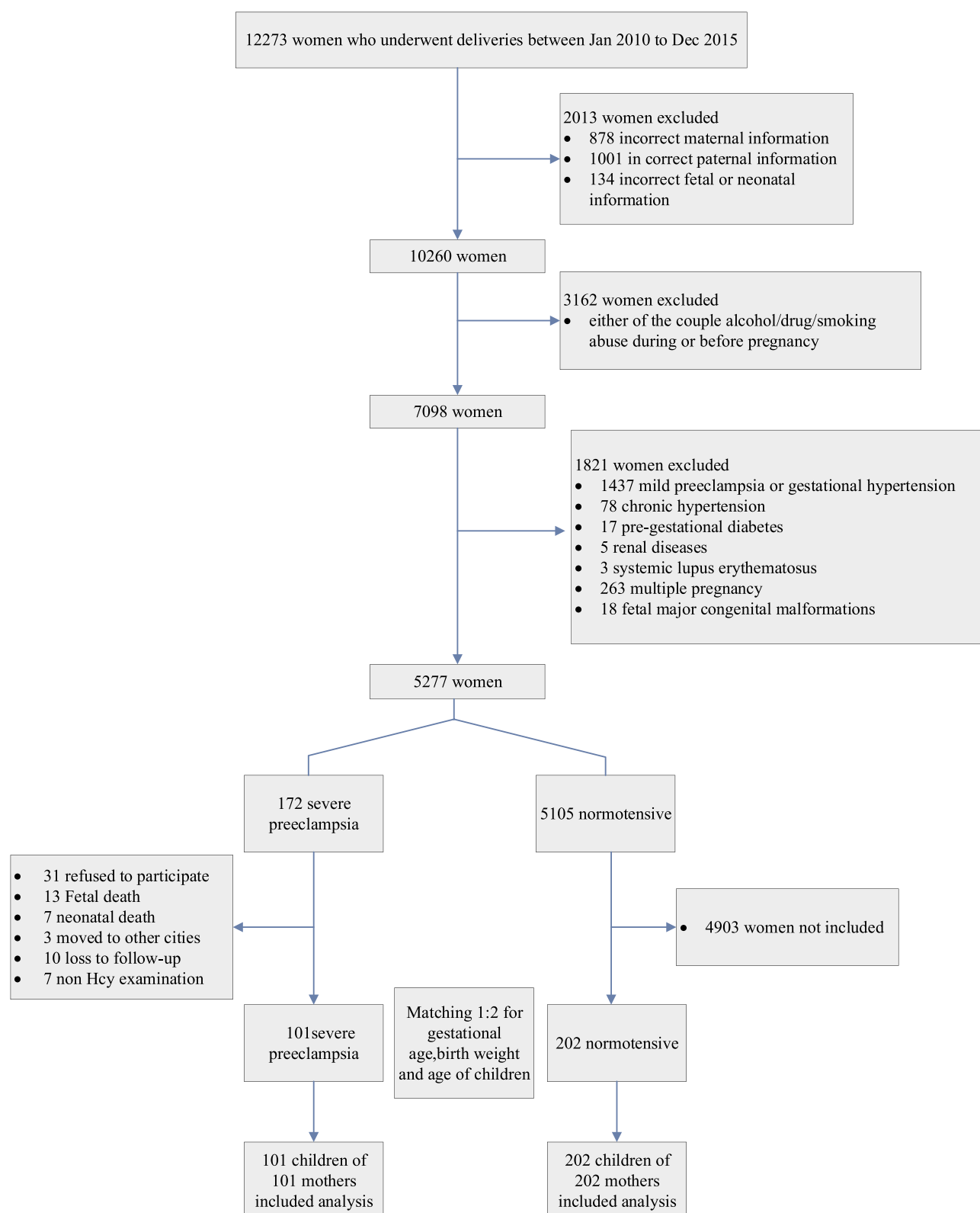202 children of 202 mothers included analysis

Figure 1 Flow chart of study subjects selection.

2017; approval no.: FZSY-201,700,854). All procedures were performed following the Declaration of Helsinki, as well as international and national laws, guidelines and regulations. Signed informed consent was obtained from all subjects with a detailed description of the purpose of the study.

Statistical Analysis

We analyzed the data distribution using the Kolmogorov–Smirnov and Shapiro–Wilk tests. All measurement data were expressed as mean ± standard deviation (SD) or median (interquartile range) as appropriate and were compared using the Student's *t*-test or Mann–Whitney *U*-test, while all categorical data were described as a number (percentage) and were compared using chi-square test or Fisher's exact test. The mean differences in FIQ, VIQ, and PIQ scores were calculated using a univariate general linear regression model after adjusting for confounding factors, and the associations of Hcy levels with IQ scores were examined using the Pearson correlation analysis and logistic regression analysis. The optimal cut-off values for predicting intellectual disability in the offspring were estimated with a receiver operating

characteristic (ROC) curve analysis. All statistical analyses were conducted using the statistical software SPSS version 19.0 (SPSS, Inc.; Chicago, IL, USA), and a *P* value of <0.05 was indicative of statistical significance.

Results
Cohort Characteristics

A total of 12,273 women underwent deliveries in the Department of Gynecology and Obstetrics, Fuzhou First Hospital during the period between January 2010 and December 2015, and finally, 101 severe preeclampsia-affected offspring and 202 children born from normotensive mothers were enrolled in this study according to the inclusion and exclusion criteria (Figure 1). Tables 1 and 2 present the study subjects' characteristics. The children born to mothers

Table 1 Children and Perinatal Baseline Characteristics

Characteristic	Severe Preeclampsia-Affected Offspring (n = 101)	Offspring Born from Normotensive Mothers (n = 202)	P value
Age (year)	4.16 ± 0.17	4.16 ± 0.31	0.81
Male (N, %)	44 (43.56)	108 (53.46)	0.066
BMI (kg/m^2)	16.32 ± 1.26	16.62 ± 1.48	0.083
Hcy level (μmol/L)	5.55 ± 1.78	5.18 ± 1.24	0.292
Gestational complications			
GDM (N, %)	29 (28.71)	37 (18.32)	0.039
Pregnancy with thyroid dysfunction (N, %)	5 (4.95)	12 (5.94)	0.724
ICP (N, %)	0 (0)	1 (0.50)	0.999
Placenta previa (N, %)	3 (2.97)	5 (2.48)	0.802
Placental abruption (N, %)	2 (1.98)	1 (0.5)	0.259
PROM (N, %)	9 (8.91)	32 (15.84)	0.138
NEUC (coils, cm)	0 (0, 1)	0 (0, 1)	0.058
GBS (N, %)	3 (2.97)	7 (3.47)	0.819
Post-delivery cord blood Hcy (μmol/L)	11.6 ± 3.28	6.45 ± 2.75	<0.001
Delivery data			
Labor time (h)	6.36 ± 4.36	6.77 ± 4.67	0.462
Birth weight (g)	2824.93 ± 775.90	2867.79 ± 777.04	0.651
Gestational age at delivery (weeks)	37.37 ± 2.51	37.48 ± 2.55	0.725
Cesarean section (N, %)	65 (65.36)	108 (53.46)	0.071
Apgar score < 7 at 5 min (N, %)	8 (7.92)	7 (3.47)	0.053
Respiratory distress syndrome (N, %)	3 (2.97)	1 (0.49)	0.259
Assisted ventilation	11 (10.89)	11 (5.45)	0.085
Admission to NICU	33 (32.67)	46 (22.77)	0.064
Turbid amniotic fluid, (N, %)	17 (16.83)	19 (9.41)	0.683
Breastfeeding (month)	10 (5.5, 12)	10 (6, 13)	0.772

Notes: Data are described as mean ± standard deviation, number (percent) or median (interquartile range). *P* values are calculated by independent Student's *t*-test, Mann–Whitney *U*-test, chi-square test or Fisher's exact test.
Abbreviations: PE, preeclampsia; BMI, body mass index; Hcy, homocysteine; GDM, gestational diabetes; ICP, Intrahepatic cholestasis of pregnancy; PROM, premature rupture of fetal membranes; NEUC, umbilical cord around the neck; GBS, group B streptococcal.

Table 2 Parental Baseline Demographic and Clinical Characteristics

Characteristic	Mothers with Severe PE (n = 101)	Normotensive Mothers (n = 202)	P value
Maternal factors			
Maternal age (year)	29.58 ± 4.74	28.80 ± 4.85	0.181
Gravidity	2 (2, 4)	2 (1, 3)	0.477
Parity	2 (1, 3)	2 (1, 2)	0.316
BMI at delivery (kg/m^2)	23.61 ± 1.85	24.35 ± 2.05	0.711
Pre-delivery maternal Hcy (μmol/L)	17.42 ± 6.67	6.53 ± 1.79	<0.001
Maternal education level			
Low (N, %)	21 (20.79)	68 (33.66)	0.064
Middle (N, %)	45 (44.55)	62 (30.69)	
High (N, %)	35 (34.65)	72 (35.64)	
Hemoglobin (g/L)	96.66 ± 9.75	96.1 ± 9.59	0.635
Cholesterol (mmol/L)	4.35 (3.97, 5.21)	2.3 (1.86, 4.52)	<0.001
HDL-C (μmmol/L)	1.43 (1.22, 1.93)	1.87 (0.9, 2.56)	0.908
LDL-C (mmol/L)	2.14 (1.79, 3.03)	1.9 (1.23, 3.46)	0.3
Paternal age (year)	30.63 ± 4.7	30.25 ± 5.2	0.534
Paternal education level			
Low (N, %)	18 (17.82)	34 (16.83)	0.976
Middle (N, %)	62 (61.39)	126 (62.38)	
High (N, %)	21 (20.79)	42 (20.79)	

Notes: Data are expressed as mean ± standard deviation, number (percent) or median (interquartile range). P values are calculated by independent Student's t-test, Mann–Whitney U-test, chi-square test or Fisher's exact test.
Abbreviations: PE, preeclampsia; BMI, body mass index; Hcy, homocysteine; HDL, high-density lipoprotein cholesterol; LDL, Low-density lipoprotein cholesterol.

with severe preeclampsia had a greater postnatal cord blood Hcy concentration than those born from normotensive mothers ($P < 0.001$), and the mothers with severe preeclampsia presented a higher prenatal maternal Hcy level ($P < 0.001$) and maternal serum cholesterol ($P < 0.001$), and were more likely to be affected by gestational diabetes mellitus ($P = 0.039$). No between-group differences were observed in terms of other perinatal and parental characteristics ($P > 0.05$). Therefore, these variables were excluded as potential confounders to maintain a steadier model.

A Lower IQ Score is Measured in Severe Preeclampsia-Affected Offspring

Compared to the control group (unadjusted), children exposed to severe preeclampsia exhibited lower VIQ (11.39, 95% CI: 8.68–14.09), PIQ (10.32, 95% CI: 8.06–12.59), and FIQ scores (5.83, 95% CI: 3.44–8.21), and adjustment for maternal cholesterol and gestational diabetes mellitus in the general linear regression model did not attenuate this association. However, the differences were insignificant after adjusting for postnatal cord blood Hcy in model 3 (FIQ = 1.22, 95% CI: –4.21–1.77) and

maternal Hcy in model 4 (FIQ = 2.62, 95% CI: –0.98 to 6.21) (Table 3).

A Higher Hcy Level is Associated with a Lower IQ Score

To further investigate the effect of high Hcy levels on intellectual disability in children born from mothers with severe preeclampsia, the case and control groups were further divided into the high- and low-Hcy subgroups according to the 75th percentile of the maternal serum Hcy level at delivery, and the mean maternal Hcy concentrations were 14.21 μmol/L in the low-Hcy case subgroup, 27.32 μmol/L in the high-Hcy case subgroup, 5.90 μmol/L in the low-Hcy control subgroup and 8.84 μmol/L in the high-Hcy control subgroup, respectively. In addition, a higher FIQ score was measured in the low-Hcy control subgroup than in both the high- and low-Hcy case subgroups, and a lower FIQ score was found in the high-Hcy case subgroup than in the low-Hcy case and control subgroups. In addition, there was no significant association between the high- and low-Hcy control subgroups (Figure 2A), and similar results were observed for subgroups based on the postnatal cord blood Hcy (Figure 2B).

Table 3 Evaluation of Intellectual Ability in Children

IQ	Severe PE-Affected Offspring (n = 101)	Children Born from Normotensive Mothers (n = 202)	P	Mean Difference in Intellectual Ability (95% CI)				
				Unadjusted	Adjusted Model 1	Adjusted Model 2	Adjusted Model 3	Adjusted Model 4
Verbal IQ score	96.73 ± 11.84	108.12 ± 11.01	< 0.001	−11.39 (−14.09 to −8.68)	−10.62 (−13.43 to −7.81)	−11.20 (−13.93 to −8.47)	−0.32 (−3.24 to 2.6)	−0.89 (−4.934 to 3.12)
Performance IQ score	102.83 ± 9.69	113.15 ± 9.32	< 0.001	−10.32 (−12.59 to −8.06)	−10.39 (−12.75 to −8.03)	−10.42 (−12.7 to −8.13)	−6.42 (−9.28 to −3.56)	−0.73 (−4.05 to 2.59)
Full IQ score	100.15 ± 10.64	105.98 ± 9.58	< 0.001	−5.83 (−8.21 to −3.44)	−6.02 (−8.51 to −3.54)	−5.46 (−7.84 to −3.07)	−1.22 (−4.21 to 1.77)	2.62 (−0.98 to 6.21)

Notes: Data are described as mean ± standard deviation, or mean difference (95% confidence interval). Model 1, adjustment for cholesterol; Model 2, adjustment for gestational diabetes mellitus; Model 3, adjustment for cord blood Hcy; Model 4, adjustment for maternal Hcy level at delivery.

Higher Prevalence of Intellectual Disability in Severe Preeclampsia-Affected Offspring

We investigated the prevalence of intellectual disability (IQ < 80) in both groups, and the prevalence of intellectual disability was 2.86 times higher in the severe preeclampsia-affected offspring than in children born from normotensive mothers, and the prevalence of low VIQ, PIQ and FIQ were all greater in children born to mothers with severe preeclampsia than in those from normotensive mothers (Table 4).

Prenatal Hcy Contributes to Intellectual Disability in Severe Preeclampsia-Affected Offspring

Linear correlation analysis revealed negative associations of maternal ($r = -0.404$, $P < 0.001$) and cord blood Hcy ($r = -0.367$, $P < 0.001$) with FIQ score in a pooled group (n = 303). Then, the case group was further divided into the intellectual disability (n = 20) and non-intellectual disability (n = 81) subgroups based on the IQ scores (a score of <80 in one or more of the IQ tests was defined as intellectual disability), and a higher rate of gestational diabetes mellitus, a higher proportion of caesarean section, higher levels of maternal and cord blood Hcy, a lower gestational age at delivery, and lower birth weight were found in the intellectual disability subgroup than in the non-intellectual disability subgroup ($P < 0.05$). These factors were therefore included in the logistic regression analysis. After adjusting for potential confounders, multivariate logistic regression analysis showed that the maternal and cord blood Hcy were independent risk factors for intellectual disability with an adjusted relative risk of 0.82 (95% CI: 0.67−0.99) and 0.68 (95% CI: 0.54–0.86), respectively (Table 5). ROC curve analysis showed that both maternal (area under the curve = 0.87, 95% CI: 0.79−0.94) and cord blood Hcy (area under the curve = 0.91, 95% CI: 0.85−0.95) were predictors of intellectual disability (Figure 3), and the optimal cut-off for predicting intellectual disability was 17.7 and 9.75 µmol/L for maternal and cord blood Hcy, which exhibited a satisfactory sensitivity (Table 6).

Discussion

In this study, we found a significantly higher prevalence rate of intelligence ability in severe preeclampsia-affected
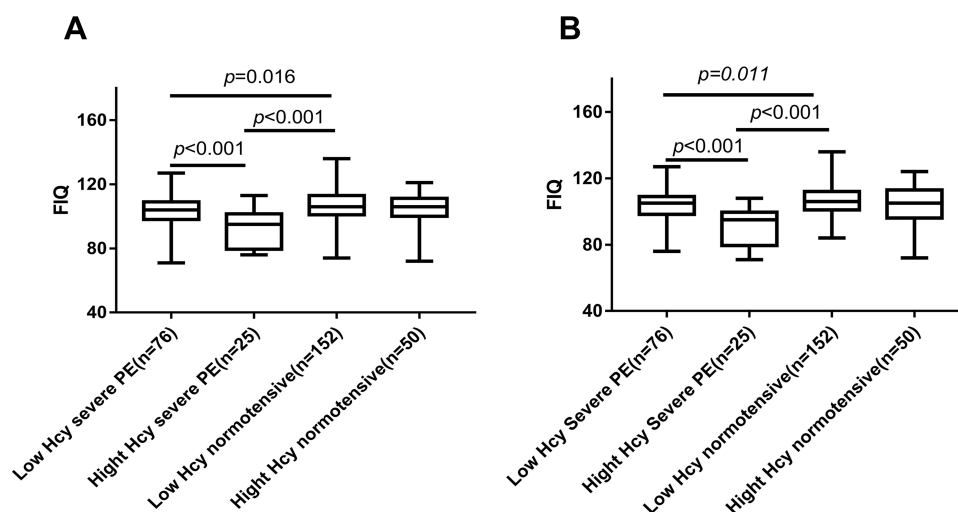
Figure 2 Association of Hcy levels with intelligence quotient scores. (**A**) Higher maternal serum Hcy levels are associated with lower intelligence quotients. The boxes extend from the 25th to 75th percentiles, and the whiskers indicate the 5th and 95th percentiles. The lines in the middle of the boxes are plotted at the median value. (**B**) Higher cord blood Hcy levels are associated with lower intelligence quotient scores. The boxes extend from the 25th to 75th percentiles, and the whiskers indicate the 5th and 95th percentiles. The lines in the middle of the boxes are plotted at the median value.
Abbreviations: PE, preeclampsia; FIQ, full intelligence quotient.

offspring than in children born from normotensive mothers at the ages of 4 years. To the best of our knowledge, this is the first study to report a strong association between increased maternal and cord blood Hcy levels and intellectual disability in children born to mothers with severe preeclampsia.

Preeclampsia is a pregnancy-specific complication influenced by a number of factors.[27,28] Among numerous pathological changes involved in preeclampsia, the most important

are endothelial dysfunction, local inflammation, and oxidative stress.[29–31] Previous studies have shown that increased Hcy levels augment cellular oxidative stress and cause generalized endothelial dysfunction,[32–34] and increased plasma oxidative stress has been reported in mothers with preeclampsia.[35] In addition, elevated Hcy levels appear to impair endothelium and lead to ischemic hypoxia through impaired nitric oxide-dependent vasodilation, endothelial toxicity and injury, oxidative stress, and systemic inflammation.[36–40] A recent study reported a significant association of serum Hcy concentration with the severity of the intellectual disability,[41] and increased plasma Hcy levels have also been identified as an independent risk factor for cognitive decline and atrophic changes in the brain.[42–44] It is therefore hypothesized that mothers with preeclampsia may present endothelial dysfunction induced by elevated Hcy levels, which results in hypoxic damages and leads to subsequent adverse effects on fetal neurodevelopment.

In this study, the offspring of normotensive mothers had greater intellectual performance scores than those born to mothers with severe preeclampsia at age of

Table 4 Prevalence of Intellectual Disability in the Offspring

IQ	Severe Preeclampsia-Affected Offspring (n = 101)	Offspring Born from Normotensive Mothers (n = 202)	P value
Verbal IQ	14 (13.86%)	8 (3.96%)	0.002
Performance IQ	6 (5.94%)	0 (0.00%)	0.001
Full IQ	9 (8.91%)	5 (2.48%)	0.015

Notes: Intellectual disability is defined as an IQ score of < 80. Data are shown as N (%). *P* values were calculated using the chi-square test or Fisher's exact test.

Table 5 Multivariate Logistic Regression Analysis of Risk Factors for Intellectual Disability in Severe Preeclampsia-Affected Offspring

Factor	RR (95% CI)	P	aRR (95% CI)	P
Pre-delivery maternal Hcy	0.89 (0.69–0.99)	0.044	0.82 (0.67–0.99)	0.043
Post-delivery cord blood Hcy	0.67 (0.52–0.84)	0.001	0.68 (0.54–0.86)	0.001

Notes: The model is adjusted for gestational diabetes, cesarean section, pre-delivery maternal serum Hcy, post-delivery cord blood Hcy, gestational age at delivery and birth weight.
Abbreviations: RR, relative risk; aRR, adjusted relative risk; CI, confidence interval.
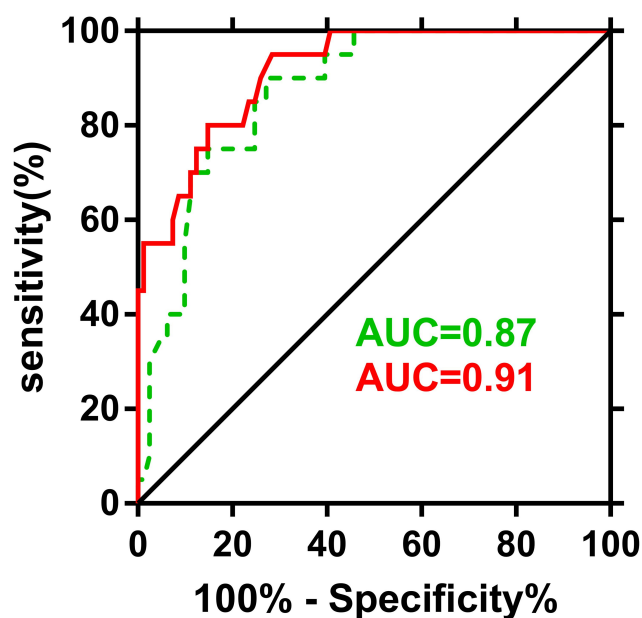
Figure 3 ROC curve analysis of maternal and cord blood Hcy levels for prediction of intellectual disability.

4 years, which was consistent with previous studies reporting the development of impaired IQ in severe preeclampsia-affected offspring as early as childhood.[10–14] Preeclampsia has been identified as an adverse risk factor for impaired cognitive development in children;[7] however, there is also evidence showing no association between preeclampsia impaired cognitive development among infants, 9–15-year-old children, and adults.[11,45,46] Unlike previous studies, the present study enrolled participants with severe preeclampsia without hypertension or mild preeclampsia, in line with the previously reported direct association between Hcy and severe preeclampsia but not hypertension or mild preeclampsia.[47] Another distinctive feature of our study is that we matched covariates such as birth weight, gestational age, and current age of children, which improved the between-group estimation of the association between severe preeclampsia and childhood IQ. This supports our findings that prenatal exposure to severe preeclampsia reduces intellectual ability in the offspring.

Notably, we observed no significant differences in the IQ scores after adjusting for maternal and cord blood Hcy levels in models 3 and 4, respectively, indicating that prenatal Hcy levels may affect intelligence ability. Then, the participants were further divided into the high- and low-Hcy subgroups according to the 75th percentile of the maternal serum Hcy level at delivery, and a reduced FIQ score was measured in the high-Hcy case subgroup, which had mean maternal and cord blood Hcy levels of 27.32 and 15.55 μmmol/L, respectively. In addition, linear correlation analysis demonstrated a negative effect of Hcy levels on offspring IQ. We divided the case group into two subgroups based on the IQ score, and logistic regression analysis identified maternal and cord blood Hcy levels as independent risk factors for predicting intellectual disability. These findings indicate a strong value of increased Hcy levels for predicting adverse neurological functions. ROC curve analysis revealed the optimal maternal and cord blood Hcy cut-off of 17.7 and 9.75 μmmol/L for intellectual disability, respectively. These data suggest that prenatal Hcy level may be a predisposing factor affecting intellectual development in severe preeclampsia-affected offspring. However, the maternal gestational Hcy levels, as well as other biomarkers including glutathione peroxidase, catalase, malondialdehyde, superoxide dismutase, and nitric oxide synthase, which may affect offspring IQ, were not measured. Further studies are required to investigate the impact of other potential factors on intellectual development in severe preeclampsia-affected offspring.

This study has several limitations. First, all participants were recruited from a single center. Second, we only evaluated the intelligence levels at a single time point (at 4 years of age) rather than at multiple time points.

In summary, the results of the present study demonstrate that perinatal exposure to severe preeclampsia has an adverse effect on postnatal intellectual development, and high maternal and cord blood Hcy levels may contribute to this association. Our data provide insights into the management of intellectual disability in children born from mothers with severe preeclampsia.

Table 6 ROC Curve Analysis of Maternal and Cord Blood Hcy for Prediction of Intellectual Disability

Hcy Level	AUC (95% CI)	Cutoff	Maximum Youden's Index	Sensitivity (%)	Specificity (%)	P value
Pre-delivery maternal Hcy (μmol/L)	0.87 (0.79–0.94)	17.7	0.628	90	72.8	< 0.001
Post-delivery cord blood Hcy (μmol/L)	0.91 (0.85–0.95)	9.75	0.321	100	32.1	< 0.001

Abbreviation: AUC, area under the curve.

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Disclosure

The authors declare no relevant financial, personal, political, intellectual or religious conflicts of interests for this work.

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