

Association of Pregnancy-Induced Hypertension and Preeclampsia with Early Infant Neurodevelopment: Findings from PERSIAN Isfahan Birth Cohort Study

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Abstract

Background

Maternal hypertensive disorders of pregnancy, including pregnancy-induced hypertension (PIH) and preeclampsia, may influence fetal brain development through placental dysfunction, inflammation, oxidative stress, and prematurity-related pathways. Evidence from non-Western birth cohorts remains limited, particularly for domain-specific neurodevelopment during infancy.

Methods

We analyzed 3,108 mother-child pairs from the PERSIAN Birth Cohort with available maternal hypertensive-disorder data and 12-month neurodevelopmental assessment. Infant neurodevelopment was evaluated using the Ages and Stages Questionnaire (ASQ) across five domains: communication, gross motor, fine motor, problem solving, and personal-social development. Mean ASQ scores were compared by PIH and preeclampsia exposure status. Linear regression models were fitted for each ASQ domain and adjusted for maternal age, maternal body mass index, socioeconomic status (SES), and gestational age at delivery. Results are presented as beta coefficients (β), standard errors (SE), and two-sided p values.

Results

Infants exposed to PIH had lower adjusted gross motor ($\beta = -2.44$, SE = 1.17, $p = 0.037$), fine motor ($\beta = -1.89$, SE = 0.77, $p = 0.013$), and problem-solving scores ($\beta = -1.72$, SE = 0.84, $p = 0.039$) than unexposed infants. Similar patterns were observed for preeclampsia, with lower adjusted gross motor ($\beta = -3.07$, SE = 1.31, $p = 0.019$), fine motor ($\beta = -2.36$, SE = 0.85, $p = 0.006$), and problem-solving scores ($\beta = -2.20$, SE = 0.93, $p = 0.018$). Communication and personal-social scores were not significantly associated with either exposure.

Conclusion

In this PERSIAN Birth Cohort sub-study, PIH and preeclampsia were associated with modest but consistent reductions in motor and problem-solving ASQ scores at 12 months. These findings support targeted developmental surveillance for infants exposed to hypertensive disorders in utero, while emphasizing the need for longer follow-up in future studies.

Introduction

Early childhood neurodevelopment is a central determinant of later cognitive, behavioral, educational, and social functioning. During the first years of life, rapid brain growth, myelination, synaptogenesis, and experience-dependent neural plasticity make children particularly vulnerable to adverse prenatal and perinatal exposures [1, 2]. Developmental delay may involve communication, gross motor, fine motor, problem-solving, and personal-social domains, and impairment in one domain may influence the maturation of others [3]. Because early delays can be subtle and potentially modifiable, standardized screening tools such as the Ages and Stages Questionnaire (ASQ) are widely used to identify infants who may benefit from closer monitoring or early intervention [2].

Hypertensive disorders of pregnancy (HDP), including gestational hypertension, PIH, chronic hypertension, and preeclampsia, are among the most important pregnancy complications and are associated with preterm birth, fetal growth restriction, placental dysfunction, and neonatal morbidity [4, 5]. Preeclampsia is a particularly severe HDP

phenotype because it combines maternal hypertension with proteinuria or other systemic manifestations and reflects a broader maternal-placental vascular disorder. These pathways are biological contributors to altered fetal brain development because impaired placental perfusion, fetal hypoxia, systemic inflammation, oxidative stress, and endothelial dysfunction may disrupt neurogenesis, synaptogenesis, myelination, and cerebral vascular development [6–10].

Epidemiological evidence suggests that children exposed to HDP may have higher risks of neurodevelopmental disorders and developmental delay. Still, findings vary by HDP subtype, gestational age, birthweight, age at assessment, outcome definition, and confounder adjustment. A recent comprehensive systematic review and meta-analysis of 121 studies and more than 29 million offspring found that HDP was associated with higher unadjusted risks of several neurodevelopmental outcomes; however, associations were attenuated when studies adjusted for gestational age at birth or birthweight, highlighting the difficulty of separating direct intrauterine effects from prematurity and fetal-growth pathways [11]. Prospective and population-based studies have similarly reported heterogeneous results: some found lower ASQ or Bayley scores after preeclampsia or maternal hypertension [12–16], whereas others observed no independent association after accounting for perinatal and sociodemographic factors [17–19].

Despite this growing literature, several gaps remain. First, many studies focus on later diagnoses such as autism spectrum disorder, attention-deficit/hyperactivity disorder, or intellectual disability, whereas fewer evaluate domain-specific developmental scores in infancy, when early surveillance can be initiated. Second, evidence from Middle Eastern and other non-Western populations remains limited, even though maternal health profiles, socioeconomic context, nutrition, health-care access, and postnatal environments may modify developmental trajectories. Third, the relative vulnerability of ASQ domains after PIH and preeclampsia remains incompletely characterized. Therefore, this study aimed to examine the association of PIH and preeclampsia with ASQ neurodevelopmental scores at 12 months of age among mother-child pairs in a sub-study of the PERSIAN Birth Cohort.

Methods

Study design and participants

This study used data from the Isfahan site of the PERSIAN Birth Cohort [20]. The analytic sample included 3,108 mother-child pairs with available maternal hypertensive disorder information and 12-month ASQ neurodevelopmental assessment.

Exposure definitions

PIH was defined as new-onset systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg after 20 weeks of gestation in the absence of proteinuria or biochemical/hematologic abnormalities. Preeclampsia was defined as new-onset systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg after 20 weeks of gestation with proteinuria, consistent with standard diagnostic criteria [4]. Maternal hypertensive status was extracted from pregnancy and delivery records.

Outcome assessment

Infant neurodevelopment at 12 months was assessed using the Ages and Stages Questionnaire (ASQ), a parent-completed developmental screening instrument covering communication, gross motor, fine motor, problem-solving, and personal-social domains. Each domain includes six items scored as “yes” (10 points), “sometimes” (5 points), or “not yet” (0 points), yielding domain scores from 0 to 60. The Persian version of the ASQ has been culturally adapted, validated,

and standardized for Iranian children and has shown acceptable psychometric properties. In the national Iranian validation study, internal consistency was satisfactory, with Cronbach's alpha ranging from 0.76 to 0.86, and inter-rater reliability was 0.93. The adapted ASQ literature used in Iran has also reported sensitivity and specificity of approximately 88.0% and 82.5%, respectively, supporting its use as a developmental screening tool in this population [21–23]. Questionnaires were administered or checked by trained interviewers using the cohort protocol. Scores below the relevant cut-off were used descriptively to identify children with possible developmental concerns; continuous ASQ domain scores were used as the primary outcomes in regression models. Participants with missing exposure, outcome, or covariate data were excluded from the corresponding analyses.

Covariates

Maternal and infant characteristics included maternal age, pre-pregnancy body mass index (BMI), socioeconomic status, parity, gestational diabetes, pregnancy-induced hypertension, gestational age at delivery, birthweight, folic-acid supplementation, feeding method at discharge, and other available perinatal variables. The primary adjusted models included maternal age, BMI, socioeconomic status, and gestational age at delivery.

Ethical consideration

This cohort was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of Isfahan University of Medical Sciences [IR.ARI.MUI.REC.1401.282]. Written informed consent was obtained from participating mothers or legal guardians as required by the PERSIAN Birth Cohort protocol.

Statistical analysis

Maternal and infant characteristics were summarized as means with standard deviations for continuous variables and frequencies with percentages for categorical variables. Independent samples *t*-tests were employed to compare mean neurodevelopmental scores across the five domains of the Ages and Stages Questionnaire (ASQ) between infants exposed and unexposed to PIH and preeclampsia.

To assess the association between maternal hypertensive disorders and neurodevelopmental outcomes at 12 months, linear regression models were fitted separately for each ASQ domain. Both crude and adjusted models were constructed. Adjusted models included maternal age, pre-pregnancy body mass index (BMI), socioeconomic status, and gestational age at delivery as covariates. Results are reported as β coefficients with standard errors (SE) and corresponding *p*-values.

All statistical analyses were performed using SPSS version 29, and a two-tailed *p*-value of less than 0.05 was considered statistically significant.

Results

Most infants were of normal birthweight (91.2%) and were born at term (80.1%). Slightly more than half of mothers were classified as having low socioeconomic status (50.9%), and most were giving birth to their first child (59.8%). Gestational diabetes (7.5%) and PIH (2.3%) were relatively uncommon. At discharge, most infants were primarily breastfed (74.3%). Mean gestational age was 38.52 ± 1.85 weeks, mean birthweight was 3108.55 ± 464.55 g, mean maternal age was 29.90 ± 5.24 years, and mean maternal BMI was 25.56 ± 4.26 kg/m².

Table 1

Table 2 presents the mean neurodevelopmental scores at 12 months of age across five domains of the ASQ, stratified by maternal PIH and preeclampsia status.

Infants born to mothers with PIH demonstrated significantly lower mean scores in the gross motor (52.27 vs. 54.86; $p = 0.022$), fine motor (55.55 vs. 57.38; $p = 0.013$), and problem-solving domains (55.36 vs. 57.13; $p = 0.028$) compared to those born to mothers without PIH. No significant differences were found in the communication or personal-social domains.

Similarly, infants exposed to preeclampsia in utero had significantly lower scores in gross motor (51.40 vs. 54.86; $p = 0.007$), fine motor (55.00 vs. 57.38; $p = 0.004$), and problem-solving (54.77 vs. 57.13; $p = 0.009$) domains compared to their unexposed peers. Again, communication and personal-social scores did not differ significantly between groups.

Although absolute mean-score differences were modest, the proportion of children scoring below the screening cut-off was consistently higher in the PIH and preeclampsia groups across motor and problem-solving domains.

Table 2

Table 3 shows the results of linear regression models assessing the association between maternal PIH and infant neurodevelopmental scores across five ASQ domains at 12 months of age. The adjusted models account for maternal age, BMI, socioeconomic status, and gestational age at delivery.

Infants of mothers with PIH had significantly lower gross motor scores compared to those without PIH. The association remained significant after adjustment ($\beta = -2.44$, $SE = 1.17$, $p = 0.037$), indicating that PIH was associated with a 2.44-point reduction in gross motor scores, independent of other maternal and prenatal factors. There was a significant negative association between PIH and fine motor performance. After adjustment, infants exposed to PIH scored 1.89 points lower on average ($p = 0.013$), suggesting a consistent adverse effect. Exposure to PIH was also significantly associated with lower infants' problem-solving scores in crude and adjusted models ($\beta = -1.72$, $SE = 0.84$, $p = 0.039$). No significant associations were found between PIH and scores in the communication or personal-social domains in crude or adjusted models ($p > 0.1$ in all cases).

Table 3

Table 4 presents the results of linear regression analyses examining the association between maternal preeclampsia and neurodevelopmental outcomes at 12 months of age across the five domains of the ASQ. After adjusting for confounders, significant associations were observed in the gross motor, fine motor, and problem-solving domains.

Infants born to mothers with preeclampsia had significantly lower gross motor scores ($\beta = -3.07$, $SE = 1.31$, $p = 0.019$), indicating a reduction of over 3 points in adjusted mean scores compared to those not exposed. Similarly, fine motor development was adversely affected, with an adjusted mean difference of -2.36 ($SE = 0.85$, $p = 0.006$). A significant association was also found for problem-solving scores, with an adjusted estimate of -2.20 ($SE = 0.93$, $p = 0.018$), suggesting that exposure to preeclampsia may delay early cognitive processing abilities.

In contrast, no statistically significant associations were found in the communication ($\beta = -1.41$, $SE = 1.11$, $p = 0.206$) or personal-social domains ($\beta = -0.69$, $SE = 1.22$, $p = 0.571$).

Table 4

Discussion

The present PERSIAN Birth Cohort analysis suggests that maternal PIH and preeclampsia are associated with modest but consistent reductions in selected infant neurodevelopmental scores at 12 months. This pattern was domain-specific. Exposed infants had lower gross motor, fine motor, and problem-solving scores, whereas communication and personal-social scores did not differ significantly after adjustment. The effect sizes were small in absolute ASQ-score units, but their consistency across two related hypertensive exposures and across motor/problem-solving domains indicates a signal that is clinically relevant for surveillance, particularly because developmental vulnerabilities may become clearer with longer follow-up.

These findings are broadly consistent with evidence linking HDP to adverse child neurodevelopment, while also emphasizing the complexity of this association. A recent systematic review and meta-analysis reported higher unadjusted risks of global developmental delay, fine motor delay, gross motor delay, intellectual disability, and lower mean intelligence among children exposed to HDP, but also noted attenuation after adjustment for gestational age and birthweight [11]. Similarly, prior cohort studies reported lower developmental scores after severe preeclampsia or maternal hypertension during infancy or early childhood [12–16]. The recent Japanese birth cohort study further supports the importance of domain-specific assessment, reporting that early-onset preeclampsia was most clearly associated with delayed problem-solving trajectories by age 4 years [24]. However, not all studies have observed independent associations after adjustment for perinatal and sociodemographic factors. The All Our Families prospective cohort did not find a significant increase in motor or cognitive delay at 36 months after accounting for confounders [18], and the P4 study did not identify clinically significant delays at 6 months or 2 years after considering prematurity, small-for-gestational-age status, and parental education [19]. These differences may reflect heterogeneity in HDP severity and subtype, timing of disease onset, gestational age distribution, fetal growth restriction, assessment tools, age at assessment, and adjustment strategies. They also underscore that gestational age and birthweight may act as mediators rather than simple confounders; therefore, adjusted estimates should be interpreted as associations independent of those measured perinatal pathways rather than as estimates of the total causal effect of HDP.

Several biological pathways could explain the observed vulnerability of motor and problem-solving domains. Preeclampsia and PIH are characterized by placental vascular dysfunction, endothelial activation, inflammatory signaling, oxidative stress, and impaired maternal-fetal perfusion [6, 8]. These processes may reduce oxygen and nutrient delivery to the developing fetal brain, alter cerebral hemodynamics and metabolism, affect white-matter microstructure and cortical development, and induce epigenetic or imprinting-related changes relevant to neurodevelopment [9, 25]. Motor and early problem-solving skills at 12 months may be especially sensitive to disruptions in sensorimotor integration, cerebellar-cortical networks, and early executive/visual-motor processing, although the ASQ is a screening instrument and cannot localize the underlying neurobiological substrate.

The added value of this study is its focus on 12-month domain-specific developmental scores in a Middle Eastern birth-cohort setting. Most available evidence comes from high-income Western or East Asian cohorts and often focuses on later neurodevelopmental diagnoses rather than early developmental screening results. By showing a consistent association in the PERSIAN Birth Cohort, this study supports the generalizability of the HDP-neurodevelopment signal across populations and highlights the feasibility of integrating developmental surveillance into follow-up pathways for pregnancies complicated by PIH or preeclampsia. From a clinical perspective, the findings do not imply that all exposed infants will develop persistent impairment, but these infants may need a structured screening, and timely referral.

Strengths and Limitations

This study has several strengths. It was conducted within a birth-cohort framework and included a relatively large sample of mother–child pairs with standardized neurodevelopmental assessment at 12 months. The use of domain-specific ASQ scores allowed us to examine whether the association between hypertensive disorders of pregnancy and early neurodevelopment differed across communication, motor, problem-solving, and personal-social domains, rather than

relying only on a global developmental outcome. In addition, the study contributes evidence from a Middle Eastern population, which remains underrepresented in the existing literature on hypertensive disorders of pregnancy and offspring neurodevelopment.

Several limitations should also be considered when interpreting the findings. Because of the observational design, the associations reported in this study should not be interpreted as causal. Although the models were adjusted for important maternal and perinatal factors, residual confounding may remain. Variables such as maternal education, parental neurodevelopmental history, home stimulation, infant sex, postnatal illness, small-for-gestational-age status, and other environmental or caregiving factors could influence ASQ scores but were not fully captured in the present analysis. In addition, detailed clinical information on the severity, timing of onset, treatment, and progression of PIH and preeclampsia was not available. These characteristics may be important because early-onset or severe hypertensive disorders may have different implications for fetal growth, placental function, and neurodevelopment compared with milder or late-onset disease. Another important consideration is that gestational age and birthweight may lie on the causal pathway between hypertensive disorders and child neurodevelopment. Therefore, adjustment for these factors may estimate associations independent of these perinatal pathways, rather than the total effect of maternal hypertensive disease. Finally, the ASQ is a validated developmental screening tool but not a diagnostic neurodevelopmental assessment, and the analysis was limited to outcomes at 12 months. Longer follow-up using more comprehensive developmental and cognitive assessments is needed to determine whether the observed early differences persist, resolve, or become more pronounced later in childhood.

Conclusion

In this sub-study of the PERSIAN Birth Cohort, exposure to PIH and preeclampsia was associated with lower gross motor, fine motor, and problem-solving ASQ scores at 12 months, while communication and personal-social scores were not significantly different. The magnitude of the observed differences was modest, but the domain-specific pattern supports developmental surveillance for infants born after hypertensive pregnancies. Future follow-up should evaluate whether these early differences persist, resolve, or evolve into later cognitive, motor, behavioral, or educational outcomes, and should clarify the mediating roles of prematurity and fetal growth.

Abbreviations

ASQ
Ages and Stages Questionnaire
BMI
Body Mass Index
HDP
Hypertensive Disorders of Pregnancy
PIH
Pregnancy-Induced Hypertension
SES
Socioeconomic Status

Declarations

Ethics approval and consent to participate

This cohort was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of Isfahan University of Medical Sciences [IR.ARI.MUI.REC.1401.282]. Written informed consent was

obtained from all participating mothers or legal guardians as required by the PERSIAN Birth Cohort protocol.

Consent for publication

Not applicable. This manuscript does not contain any person's data in any form (including individual details, images, or videos).

Competing interests

The authors declare that they have no conflicts of interest.

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Author Contribution

MY and MB conceived and designed the study, interpreted the data, and drafted the manuscript. OY and SSD contributed to data acquisition, data interpretation, and critical revision of the manuscript for important intellectual content. RK supervised the study, critically revised the manuscript, and provided overall scientific oversight. All authors read and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

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Data Availability

The datasets generated and analysed during the current study are available from the corresponding author on reasonable request.

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Tables

Table 1. Mother and Infant Characteristics

Characteristic	Category	n (%) or Mean $\pm$ SD
Low Birth Weight	Low birth weight	272 (8.8)
	Normal weight	2836 (91.2)
Preterm or Term	Preterm	548 (19.9)
	Term	2202 (80.1)
Socioeconomic Status	Low	1595 (50.9)
	Moderate	1228 (39.2)
	High	308 (9.8)
Parity	First child	1104 (59.8)
	Second or greater child	743 (40.2)
Gestational Diabetes	No	2708 (92.5)
	Yes	219 (7.5)
Pregnancy-Induced Hypertension	No	2859 (97.7)
	Yes	68 (2.3)
Inducting Labour	No	3047 (97.6)
	Yes	74 (2.4)
Maternal Folic Acid Supplementation	Taken prior to pregnancy	846 (27.0)
	Started once pregnancy	1353 (43.2)
	Not taken	935 (29.8)
Feeding Method at Discharge	Breastfeeding	2217 (74.3)
	Breastfeeding + Formula	638 (21.4)
	Formula	129 (4.3)
Gestational Age (week)		38.52 $\pm$ 1.85
Birth Weight (gr)		3108.55 $\pm$ 464.55
Maternal age (years)		29.90 $\pm$ 5.24
BMI (kg/m²)		25.56 $\pm$ 4.26

Table 2. Neurodevelopmental scores at 12 months by PIH and preeclampsia status during pregnancy

Developmental Domain	Total	PIH		p	Preeclampsia		p
		No	Yes		No	Yes	
Score							
Communication	54.93 ± 7.08	54.96 ± 7.08	53.82 ± 6.66	0.237	54.96 ± 7.09	53.49 ± 6.77	0.178
Communication <1SD		25 (1.1)	1 (2.3)		25 (1.2)	1 (1.8)	
Gross Motor	54.79 ± 8.30	54.86 ± 8.20	52.27 ± 11.30	0.022	54.86 ± 8.20	51.40 ± 11.92	0.007
Gross Motor<1SD		74 (3.4)	4 (9.3)		74 (3.4)	4 (7.3)	
Fine Motor	57.33 ± 5.42	57.38 ± 5.39	55.55 ± 6.21	0.013	57.38 ± 5.39	55.00 ± 6.55	0.004
Fine Motor<1SD		56 (2.6)	3 (7.0)		56 (2.6)	3 (5.5)	
Problem Solving	57.09 ± 5.90	57.13 ± 5.81	55.36 ± 8.60	0.028	57.13 ± 5.81	54.77 ± 9.38	0.009
Problem Solving<1SD		66 (3.0)	4 (9.3)		66 (3.0)	4 (7.3)	
Personal Social	55.27 ± 7.71	55.28 ± 7.73	54.82 ± 6.80	0.66	55.28 ± 7.73	54.53 ± 6.97	0.53
Personal Social<1SD		49 (2.3)	1 (2.3)		49 (2.3)	1 (1.8)	

Table 3. Association Between Pregnancy-Induced Hypertension (PIH) and Neurodevelopmental Scores at 12 Months

ASQ Domain	Crude model		Adjusted model	
	β (SE)	p-value	β (SE)	p-value
Communication	−1.14 (0.97)	0.237	−1.30 (1.00)	0.192
Gross Motor	−2.59 (1.13)	0.022	−2.44 (1.17)	0.037
Fine Motor	−1.84 (0.74)	0.013	−1.89 (0.77)	0.013
Problem Solving	−1.77 (0.81)	0.028	−1.72 (0.84)	0.039
Personal-Social	−0.46 (1.05)	0.66	−0.58 (1.09)	0.597

Adjusted for maternal age, BMI, socioeconomic status, and gestational age at delivery.

Table 4. Association Between Preeclampsia and Neurodevelopmental Scores at 12 Months

ASQ Domain	Crude model		Adjusted model	
	β (SE)	p-value	β (SE)	p-value
Communication	-1.47 (1.09)	0.178	-1.41 (1.11)	0.206
Gross Motor	-3.47 (1.28)	0.007	-3.07 (1.31)	0.019
Fine Motor	-2.38 (0.83)	0.004	-2.36 (0.85)	0.006
Problem Solving	-2.37 (0.91)	0.009	-2.20 (0.93)	0.018
Personal-Social	-0.75 (1.19)	0.53	-0.69 (1.22)	0.571

Adjusted for maternal age, BMI, socioeconomic status, and gestational age at delivery.

Supplementary Files

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