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Neurodevelopmental assessment of infants born to mothers with hypertensive disorder of pregnancy at six months of age

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Abstract

Infant neurodevelopment is a complex process which may be affected by different events during pregnancy, such as hypertensive disorders of pregnancy (HDP). We conducted a prospective cohort study to compare the prevalence of neurodevelopmental disorders in infants born to mothers with and without HDP at six months of age. Participants attended the Health Observatory of Instituto de Desarrollo e Investigaciones Pediátricas "Prof. Dr. Fernando E. Viteri" during 2018 and 2019. Infant neurodevelopment was assessed with the Bayley Scales of Infant and Toddler Development—Third Edition (Bayley-III). Data were analyzed using Chi-square, Student's *t*-test and Mann–Whitney test. Of the 132 participating infants, 68 and 64 were born to mothers with and without HDP, respectively. At six months, the prevalence of risk of neurodevelopmental delay was significantly higher in infants born to mothers with than without HDP (27.9% vs. 9.4%; $p = 0.008$) (odds ratio, 3.71; 95% confidence interval, 1.30; 12.28). In conclusion, infants born to mothers with HDP had three times increased risk of neurodevelopmental delay at six months of age.

Introduction

The first years of a child's life are essential for brain development because the nervous system grows and develops more rapidly than at any other stage of life, mostly as a result of neuroplasticity.[1]

Neurodevelopment is a dynamic, complex, and precise process involving the interaction of the child with the environment, which results in the maturation of the nervous system and the subsequent development of brain function and personality traits.[2,3]

Brain development starts at conception and continues for many years after birth. Between 8 and 16 weeks of gestation, around 200,000 neurons per minute are formed.[4] Differentiated cells migrate from the ventricular (central) zone of the brain to the developing cortex (neocortex) through radial glial cells, which guide the movement of migrating neurons.[4] The average brain weight in term infants is 400 g, approximately 900–1100 g at two years, and around 1400 g in the adult.[4-6] In this way, the first 1,000 d of life are a window of opportunities to implement interventions in development, metabolic, nutritional, and immunological areas that will affect the entire life course, including the future generations.[7]

Adverse maternal conditions during pregnancy may impact negatively on the health of the offspring. For instance, hypertensive disorders of pregnancy (HDP) have a 5%–16% incidence in pregnant women with or without risk factors.[8] These HDP include preexisting (chronic) hypertension, gestational hypertension, preeclampsia (PE), PE superimposed on chronic hypertension and eclampsia (E).[9] PE, which is defined as high blood pressure (BP) after the first 20 weeks of gestation associated with proteinuria, affects 2%–7% of pregnant women.[9,10] Other complications may also develop in high-risk pregnancies, including comorbidities (kidney disease, autoinmune disease, chronic hypertension), previous history of diabetes or gestational hypertension, current signs of hypertension, multiple pregnancy, and maternal obesity.[11,12]

HDP have been associated with intrauterine growth restriction (IUGR), prematurity and infant neurodevelopmental disorders.[12] Both IUGR and prematurity increase the risk of infant neurodevelopmental disorders, having different effects on language, cognitive, and motor skills. Furthermore, preterm infants with IUGR or evidence of fetal circulatory redistribution are the most severely affected.[13,14]

The identification of infant developmental disorders during the first years of life is generally performed using different assessment tools. Among them, the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III) are the most widely used tool worldwide.[15] This screening instrument has become a gold standard because it provides objective, valid, and reliable measures of the development of children from birth to 42 months of age. It also allows to design timely interventions to minimize the effects of neurodevelopmental delay.[15]

In Argentina, only a few studies have reported the functional assessment of neurodevelopment in apparently healthy infants and children.[16] Studies performed in developing countries have shown that 15% of pediatric consultations are about child development and behavior.[3] In those countries, the prevalence of developmental disorders is 16%–18%, which include intelectual disabilities, learning, and language impairments in 90% of cases. Such prevalence rate increases to 22% when behavioral disorders are considered.[3,16]

Keeping in mind that HDP are among the most frequent complications during pregnancy and the high prevalence of neurodevelopmental disorders in apparently healthy infants, we compared the prevalence of neurodevelopmental disorders in six-month old infants born to mothers with and without HDP.

Materials and methods

Study design and population

We conducted a prospective cohort study in two groups of infants born in the Maternity Ward of La Plata Hospital "General San Martín": 1) born to mothers with HDP and 2) born to mothers without HDP. Routine follow-up visits were performed at the Child Development Clinic of the Health Observatory of IDIP (Instituto de Desarrollo e Investigaciones Pediátricas "Prof. Dr. Fernando E. Viteri"), La Plata Children's Hospital, from June 2018 to December 2019.

Pregnant women with HDP were followed up in the Maternity and the Cardiometabolic Disease Unit of La Plata Hospital "General San Martín." After delivery, they were followed up in the Mother and Child Consultation Office of IDIP's Health Observatory. Both study cohorts included apparently healthy infants who were followed up by IDIP professionals up to six months of age.

Exclusion criteria were infants whose mothers missed antenatal appointments after 20 weeks of pregnancy and/or who did not record BP readings in their health cards, infants with genetic disorders or any other diagnosed disease, acute fetal distress, IUGR, less than 36 weeks of gestation, diabetes, gestational diabetes, neonatal hypoglycemia, or any other pathological perinatal record. The assessment of IUGR was performed through Doppler ultrasound at 20 and 24 weeks of gestation to identify abnormal blood flow patterns in the major fetal vessels.[17]

Sample size was estimated with 95% confidence interval (CI) and 0.80 power based on a previous report showing that the prevalence of infant developmental disorders was around 20%, regardless of the maternal background.[16] The expected prevalence in infants born to mothers with and without HDP was 30% and 10%, respectively. Thus, the required sample size was 124 mother–infant pairs ($n = 62$ each). After adjusting for a 15% dropout rate, the final sample included 46 mother–infant pairs ($n = 73$ each).

Infant development was assessed with the Bayley-III Scales.[15] All tests were administered by two well-trained examiners blind to the study, certified in Bayley-III test procedures and experienced in developmental testing: a specialist pediatrician in infant development and an occupational therapist. The test includes three domains: cognitive, language (receptive and expressive communication), and motor (fine and gross). This Scale comprises 91 items that assess sensory motor development, exploration and manipulation, object relatedness, concept formation, and memory. Each test item has a scale score that determines infant performance. The sum of scores of the three domains classifies performance into one of four categories of development with a mean of 100 and a standard deviation of 15: accelerated development (>115), within normal limits (85–115), at risk (70–84), and delayed (<70).[15]

The growth of infants was evaluated by measuring weight, height, and head circumference. These measurements were used to construct the following indicators: weight-for-age, height-for-age, and head circumference-for-age, according to international reference standards.[18] The operationalization of variables was performed according to the Argentine Pediatrics Society guidelines.[19] In addition, the following maternal variables were evaluated: age (years), educational level (complete schooling in years), number of pregnancies, number of deliveries, type of delivery (vaginal or C-section), body mass index (BMI) for gestational age (using Calvo's gestational weight gain reference charts),[20] and pregestational BMI (pgBMI), estimated with height and weight values registered in the health card before week 12 of gestation. Accordingly, normal pgBMI was 18.5–25 kg/m^2, overweight pgBMI was 25–30 kg/m^2, and obese pgBMI was $\geq$ 30 kg/m^2.[21]

To predict the risk of developing hypertension, BP was assessed during pregnancy. Hypertension in the office setting was defined as BP $\geq$ 140/90 mmHg, resulting from the average of three BP determinations taken by a specially trained nurse after a 5-min resting period, in the sitting position and with the arm at the heart level, using a validated automated oscillometric measuring device with proper arm cuffs (OMRON HEM 705 CP; Omron Corporation, Kyoto, Japan). Ambulatory BP monitoring was performed with Spacelabs 90,207 (Spacelabs Healthcare Company, Issaquah, WA, USA). Daytime and nighttime measurements were scheduled every 15 and 20 min, respectively.

The different types of maternal HDP were defined as gestational hypertension (at least two BP $\geq$ 140/90 mmHg measurements after 20 weeks of gestation), PE (the mentioned BP values together with persistent proteinuria, *i.e.*, > 0.3 g/L in 24-h urine test), and E (the two previously mentioned and seizures).

Statistical analysis

Data were analyzed with the R package version 3.5.1. Kolmogorov–Smirnov test was used to test qualitative variables for normality, expressed as frequency (%), means ± standard deviations and median (interquartile range [IQR]), as appropriate.

Comparison of anthropometric variables between infants born to mothers with and without HDP was performed with Student's *t*-test. Comparison of maternal characteristics was carried out with Mann–Whitney test. The association between the study groups and neurodevelopmental results was made with Fisher test. The adjustment of the odds ratio (OR) for risk or delay in neurodevelopmental tests was made using multiple logistic regression (including all relevant variables) and backward stepwise selection (adjusting for the smallest number of variables) according to

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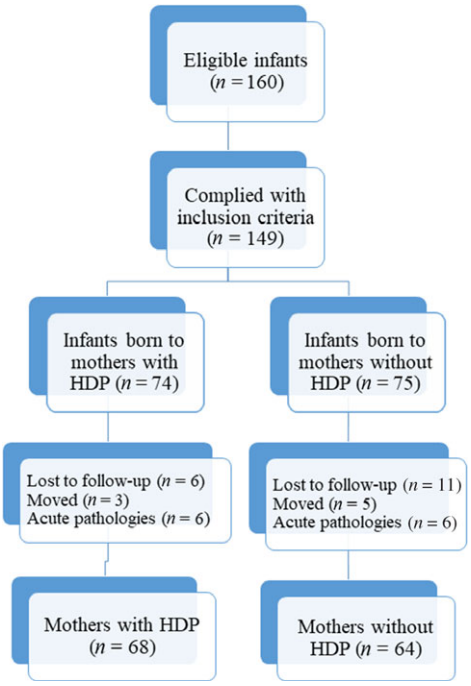

Fig. 1. Flow chart of participant registration and follow-up.

Akaike Information Criterion (AIC). Differences were significant at $p < 0.05$.

Results

Of the 160 infants evaluated, 149 complied with the inclusion criteria and were followed up until six months of age. Of these, 68 and 64 infants born to mothers with and without HDP, respectively, completed the study (Fig. 1). The characteristics of mothers with and without HDP are presented in Table 1. It can be seen that median age and number of C-sections were higher in mothers with HDP. The increased rate of scheduled C-sections was due to the maternal condition (73.5% [$n = 50$] gestational hypertension; 11.8% [$n = 8$] chronic hypertension; 10.3% [$n = 7$] PE; and 4.4% [$n = 3$] PE superimposed to chronic hypertension) and to avoid fetal distress. None of the HDP mothers presented E. At the end of pregnancy, the prevalence of overweight and obesity was higher in mothers with than without HDP (overweight, 44.1% vs. 14.3%; obesity, 27.1% vs. 6.1%, respectively) ($p < 0.0001$).

Table 2 shows the general characteristics of infants at birth and at six months of age. Gestational age was 39 and 38 weeks in infants born to mothers without and with HDP, respectively. Differences in the prevalence of preterm infants were not significant. However, weight-for-age *Z*-score was significantly higher in infants born to mothers with HDP at six months of age (0.54 ± 1.01 vs -0.13 ± 0.91; $p = 0.0032$). On the other hand, despite differences found at birth, neither height-for-age nor head circumference-for-age *Z*-scores differed between groups.

Bivariate analysis of Bayley-III results in normal infants and infants at increased risk of neurodevelopmental delay is presented in Table 3. Differences according to age of the infant, type of delivery (C-section vs. vaginal), presence of anemia, maternal age, and schooling were not significant. On the other hand, the association with type of diet (exclusive breastfeeding vs. mixed feeding and mixed feeding vs. only formula) and number of children showed an increased risk of neurodevelopmental delay.

Table 4 shows the adjusted multiple logistic regression model used to assess the association of risk of neurodevelopmental delay with HDP. It included variables that in the bivariate analysis significantly associated with HDP or Bayley-III results (gestational age, exclusive breastfeeding up to six months of age, maternal education, type of delivery, maternal age, and number of children). After applying the stepwise selection process with AIC criteria, we built the final model with the variables number of children and exclusive breastfeeding at six months of age. The prevalence of risk of neurodevelopmental delay was significantly higher in infants born to mothers with HDP at six months of age (OR, 3.71; 95% CI, 1.30; 12.28).

When such prevalence was adjusted for the number of children and breastfeeding up to six months of age, infants born to mothers with HDP were four times more likely to be at risk of neurodevelopmental delay compared with infants born to mothers without HDP. Concerning each component of the Bayley-III test, results showed that infants born to mothers with HDP had a higher prevalence of risk of delay in the language ($p = 0.031$) and motor ($p = 0.036$) domains. However, adjusted OR showed a higher prevalence only in the language domain.

Table 5 shows the unadjusted and adjusted logistic regression model for number of children and breastfeeding up to six months of age. For this analysis, mothers without HDP were the control group, and mothers with HDP were divided into those having chronic hypertension and gestational hypertension. The effect of chronic and gestational hypertension on neurodevelopment remained only in infants born to mothers with gestational hypertension. It should be noted that the number of mothers with chronic hypertension was low, suggesting a lack of statistical power to detect differences.

Discussion

The current study investigated the prevalence of neurodevelopmental disorders in six-month-old infants born to mothers with and without HDP. One of the findings of this study was the detection of nutritional, gynecologycal, obstetric, and age differences between mothers with and without HDP. Our results also showed that the rates of overweight/obesity, number of children, age at delivery, and C-sections were higher in mothers with HDP, whereas gestational age was lower. Similar characteristics have been described in other populations of mothers with HDP, even though under different contexts.[22,23] According to Dude *et al.*, a BMI increase of at least 2 kg/m^2 between deliveries in women without HDP was associated with an increased risk of hypertensive disorder in a subsequent pregnancy.[24]

In our study, birthweight of infants born to mothers with and without HDP was similar, as opposed to the findings of other authors reporting lower birthweight in infants born to mothers with HDP.[25] The different results could be probably due to the fact that we did not include either moderately/extremely preterm or IUGR infants, since these pathologies increase the risk of neurodevelopmental disorders during infancy[13,14] and could have acted as potential confounding factors when evaluating infant development. Regarding postnatal birthweight, our results agree with other reports showing higher weight gain in infants born to mothers with HDP and diabetes.[25,26]

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Table 1. Characteristics of mothers with and without HDP

	Mothers without HDP $n = 64$	Mothers with HDP $n = 68$	p value
Age (years)	26 (21–30)	31 (25–34.25)	0.001
Schooling (years)	12 (8–12)	12 (7.75–12)	0.787
Number of children	2 (1–3)	2.5 (2–3)	0.009
Number of pregnancies	2 (1–3)	3 (2–4)	0.002
pgBMI	23.61 (21.64–25.82)	30.17 (25.39–34.70)	<0.001
Gestational weight gain	12.00 (8.00–15.00)	11.50 (6.77–16.00)	0.998
C-section (%)	27 (42.2)	50 (73.5)	<0.001

Results are presented as median and IQR.

Table 2. Characteristics of infants born to mothers with and without HDP at birth and at six months of age

	Without HDP ($n = 64$) n (%)	With HDP ($n = 68$) n (%)	p value
Sex (female)	28 (43.8)	31 (45.6)	0.862
At birth			
Weight (g)*	3235 (2943.8–3616.3)	3110 (2837.5–3542.5)	0.209
Height (cm)	50.22 ± 2.28	49.15 ± 2.03	0.017
Head circumference (cm)*	35 (34.5–36)	35 (34–36)	0.299
Gestational age (weeks)*	39 (38–39)	38 (37–39)	0.001
Preterm (36 weeks)	3 (4.7)	9 (13.4)	0.129
At six months			
Weight (g)	7156.1 ± 799.8	7594.2 ± 969.9	0.032
Height (cm)	64.9 ± 2.3	64.8 ± 2.4	0.776
Head circumference (cm)*	43.3 (43–44)	43.2 (42.8–44.1)	0.874
Weight-for-age *Z*-score	0.25 ± 0.97	0.37 ± 0.98	0.646
Height-for-age *Z*-score	0.04 ± 0.93	−0.17 ± 1.07	0.227
BMI *Z*-score	0.31 ± 1.12	062 ± 0.93	0.103
Anemia (Hb < 11 g/dL) (%)	12 (31.6)	24 (46.2)	0.195
Type of feed			0.102
Exclusive breastfeeding (%)	18 (48.7)	24 (60)	
Mixed feeding (%)	11 (29.7)	12 (30)	
Exclusive formula feeding (%)	8 (21.6)	4 (10)	

Results are presented as the mean ± standard error of the mean, *median, and IQR and percentage (%).

The prevalence of risk of infant neurodevelopmental delay at six months assessed by Bayley-III was three times higher in HDP infants. Although the benefits of breastfeeding for neurodevelopment have been well-established through the evaluation of performance with different tests,[27] results of the multivariate analysis adjusted for exclusive breastfeeding at six months of age and number of children indicated that infants born to mothers with HDP maintained increased odds of neurodevelopmental delay as compared with those born to mothers without HDP.

To our knowledge, the assessment of neurodevelopmental disorders in infants born to mothers with HDP at six months of age has been scarcely reported. A recent cohort study conducted in Wuhan, China, evaluating mothers and six-month-old infants with the Chinese version of the Gesell Developmental Schedules suggests that HDP associates with a higher risk of neurodevelopmental disorders in the infant.[28] The same as in our study, the motor and language domains were the most affected ones. However, when we adjusted for exclusive breastfeeding at six months and number of children, only the language domain was affected. On the other hand, Chen *et al.* found a significant association between the social behavior and adaptability domain of infants born to mother with chronic hypertension as compared with gestational hypertension.[28] Our findings are consistent with results of other authors who also reported infant neurodevelopmental disorders at two years of age using the Bayley-III Scale in a cohort study of 1,008 infants born to hypertensive mothers.[29]

Long-term trials using other infant neurodevelopmental assessment scales have found similar results. For instance, the use of the Ages and Stages Questionnaire (ASQ) in a prospective study to examine neurodevelopmental performance in children of women

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Table 3. Bivariate analysis of the results obtained with Bayley III Scale

	Bayley III Scale		
	Normal ($n = 107$)	Risk/delay ($n = 25$)	p value
Birthweight	3220 (2917.5–3620)	3100 (2760–3350)	0.210
Gestational age	38 (37–39)	38 (37–39)	0.322
Maternal age	27 (23.25–33)	31 (24–34)	0.345
Maternal education (years)	12 (8–12)	11 (6–12)	0.083
Number of children	2 (1–3)	3 (2–3)	**0.024**
Interpregnancy interval	79 (38–108)	62 (36–101.3)	0.599
Sex (female) (%)	52 (48.6)	7 (28.0)	0.076
Preterm (36 weeks) (%)	9 (8.5)	3 (12.0)	0.699
C-section (%)	61 (57.0)	16 (64.0)	0.653
Exclusive breastfeeding at six months (%)	64 (59.8)	3 (13.0)	< **0.001**
Overweight/obesity at the end of pregnancy (%)	41/87 (47.1)	11/21 (52.4)	0.808
Infant anemia (%)	30/70 (42.9)	6/20 (30.0)	0.438

Statistically significant results are presented in bold.
Results are expressed as median and IQR and frequency (%).

Table 4. Association between hypertensive disorder of pregnancy and infant neurodevelopment at six months

	Neurodevelopmental risk/delay *n* (%)	p	OR	95% CI	Adjusted OR*	95% CI
General result						
Without HDP	6/64 (9.4)			Reference		Reference
With HDP	19/68 (27.9)	**0.008**	**3.75**	**(1.46; 10.96)**	**3.97**	**(1.33; 13.86)**
Language domain						
Without HDP	2/64 (3.1)	**0.031**		Reference		Reference
With HDP	10/68 (14.7)		**5.34**	**(1.34; 35.73)**	**6.58**	**(1.30; 60.39)**
Cognitive domain						
Without HDP	2/64 (3.1)	0.166		Reference		Reference
With HDP	7/68 (10.3)		3.56	(0.82; 24.52)	2.86	(0.56; 23.39)
Motor domain						
Without HDP	6/64 (9.4)	**0.036**		Reference		Reference
With HDP	16/68 (23.5)		**2.97**	**(1.13; 8.81)**	2.91	(0.97; 10.04)

Statistically significant results are presented in bold.
*OR adjusted for number of children and exclusive breastfeeding at six months of life.

with severe PE until age 5 showed that babies born to PE mothers failed at least one category at year 1, while the number of ASQ categories failed at year 2 was significantly greater.[12] In another prospective follow-up study, neurodevelopmental outcome in children born to mothers with early and severe hypertensive complications of pregnancy was assessed at the age of 4.5 years using the Revised Amsterdam Child Intelligence Test.[30] The results of the mentioned study showed more cognitive problems in this cohort of children, with a mean intelligence quotient of eight points, lower than in the normal population.[30] A prospective cohort study conducted in China using the Chinese Wechsler Young Children Scale of Intelligence showed that the offspring of mothers with severe PE had 2.86 higher prevalence of intellectual disability than infants born to normotensive mothers.[31]

A case-control study of children aged 24–60 months found association between severe PE, autism spectrum disorder and many forms of developmental delay, as confirmed by the Mullen Scales of Early Learning and the Vineland Adaptive Behavior Scales.[32] A systematic review including 45 observational studies reported a significant association of gestational hypertension with lower cognitive function and higher BP in the offspring.[33]

In our study, language was the most affected domain according to the Bayley-III Scale. The low language performance at six months of age currently found might be indicative of the risk for developing later language disorders. In this sense, the Western Australian Pregnancy Cohort (Raine) Study[34] of 1389 children born to mothers with HBP or PE at 10 years of age assessed verbal and nonverbal ability with the Peabody Picture Vocabulary Test-Revised and the Ravens Colored Progressive Matrices, respectively, and compared such ability with that of infants born to normotensive women. The authors concluded that HBP and PE were risk factors for reductions in the verbal ability of children.[34] On the other hand, a

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Table 5. Association between the different types of HDP and infant neurodevelopment at six months

	Neurodevelopmental risk/delay *n* (%)	p	OR	95% CI	Adjusted OR	95% CI
General result						
Without HDP	6/64 (9.4)	**0.019**	reference		reference	
Gestational hypertension	16/57 (28.1)		**3.77**	**(1.42; 11.27)**	**3.87**	**(1.26; 13.83)**
Chronic hypertension	3/11 (27.3)		3.62	(0.67; 16.98)	4.58	(0.71; 28.34)
Language domain						
Without HDP	2/64 (3.1)	**0.035**	reference		reference	
Gestational hypertension	8/57 (14)		**5.06**	**(1.20; 34.56)**	**6.08**	**(1.15; 57.05)**
Chronic hypertension	2/11 (18.2)		6.89	(0.75; 63.70)	9.32	(0.82; 125.51)
Cognitive domain						
Without HDP	2/64 (3.1)	0.182	reference		reference	
Gestational hypertension	6/57 (10.5)		3.65	(0.80; 25.63)	2.82	(0.52; 23.76)
Chronic hypertension	1/11 (9.1)		3.10	(0.14; 35.44)	3.07	(0.13; 42.65)
Motor domain						
Without HDP	6/64 (9.4)	0.061	reference		reference	
Gestational hypertension	14/57 (24.6)		**3.15**	**(1.16; 9.50)**	3.01	(0.98; 10.64)
Chronic hypertension	2/11 (18.2)		2.15	(0.29; 11.15)	2.38	(0.28; 15.02)

Results are presented as percentage, OR, 95% CI, and adjusted OR for number of children and exclusive breastfeeding at six months of life. Statistically significant results are presented in bold.

nationwide study carried out in Iceland found a minimal or no effect of maternal PE/E on children's academic performance (4th, 7th, and 10th grades) at ages 9–15 years.[35] This study compared children born to mothers with PE/E with children of normotensive mothers using mandatory tests in the language arts and mathematics.[35] It should nevertheless be noted that the last assessment tool cannot be compared with the previously mentioned ones, which apply standardized and specific scales.

Experimental and clinical research has shown that PE increases the morbidity and mortality of both the fetus and the pregnant woman. Although PE pathogenesis has not yet been fully understood, growing evidence suggests that aberrations in angiogenic factor levels and coagulopathy account for PE clinical manifestations.[36] In these target organs, endothelial injury is the common nominator of tissue damage, interfering with their normal function.[36] A study performed in a rat model concluded that PE would impair neuronal signaling through demyelination, greatly contributing to long-term sensorimotor and cognitive deficit.[37] Another study aimed at determining whether microstructural properties (myelination patterns and white matter connectivity) differed between PE offspring and matched typical children demonstrated marked differences between groups in anomalies in the caudate nucleus, superior longitudinal fasciculus, and cingulate gyrus.[38] The authors concluded that the analysis of brain magnetic resonance imaging datasets from PE children suggested that the intellectual deviations reported in individuals born to PE mothers were due to neurologic differences.[38]

The strength of our study lies in the multiple analysis of risk factors for neurodevelopmental delay in the offspring adjusted for potential confounders, that is, infants less than 36 weeks of gestation or with IUGR, who were not included in the model. At the same time, one of the limitations of our study was the lack of registry of data on medication of mothers with HDP, which can overestimate or underestimate the strong association between their offspring and neurocognitive development.

Conclusion

The current results show that babies born to mothers with HDP at 36 weeks of gestation or greater and without IUGR had a higher prevalence and almost three times increased risk of neurodevelopmental delay at six months of age than infants born to mothers without HDP. Considering the high prevalence of neurodevelopmental disorders in infants born to mothers with HDP, early detection and timely interventions are essential for improving long-term neurocognitive outcomes.

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Conflicts of interest. None.

Ethical standards. The study protocol was approved by IDIP's Institutional Research Review Board on May 16, 2018. All procedures contributing to this work complied with the ethical standards laid down in the 1964 Declaration of Helsinki and successive revisions and amendments. Written informed consent was obtained from parents and/or tutors of the participating infants before enrolment in the study and in the presence of a witness.

Authors' contributions. Initial conception or design: M.S., A.R., F.R., A.V., V.F., H.F.G.; final design: M.S., A.R., F.R., A.V., V.F., H.F.G., W.E., P.C., M.S.; data acquisition: M.S., A.R., F.R., W.E., P.C., M.S.; analysis or interpretation: M.S., A.R., F.R., V.F., H.F.G.; drafting the article: M.S., A.R., F.R., A.V., V.F., W.E., M.S., P.C., H.F.G.; critically revising the article: M.S., A.R., F.R., A.V., V.F., W.E., M.S., P.C., H.F.G. All authors have read and approved the final article.

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