Brain and brain blood vessels histological description in autopsies of fetuses/neonates born to mothers with hypertension during pregnancy. A case–control study

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Summary

Background Children born to women with hypertension during pregnancy have a two to threefold increased risk of developing cognitive disorders compared to children born to women without hypertension. However, structural changes in the central nervous system of these children remain poorly understood. We aim to compare the brain histological findings from autopsies of neonates and fetuses born to women with and without hypertension during pregnancy.

Methods This retrospective case–control study includes brain histological samples from autopsies of neonates and fetuses born to women with (n = 22) and without (n = 15) hypertension during pregnancy, obtained from biobanks associated with the University Hospital San Ignacio (HUSI), Bogotá, Colombia, between 2007 and 2022. Hypertension during pregnancy was diagnosed following American College of Obstetricians and Gynecologists (ACOG) guidelines. Matched criteria included similar maternal pre-pregnancy morbidity, gestational ages at delivery, fetal sex, and availability of similar histological samples of fetal/neonatal brains. Clinical data were recorded, and two diagnosed-blinded pathologists analyzed all slides.

Findings Ninety-three percent (14/15) of fetuses/neonates born to women with hypertension during pregnancy were born after preeclamptic pregnancies. Histological findings were described for the frontotemporal cortex (97%, 36/37) and meninges (81%, 30/37). Fetuses/neonates born to women with hypertension during pregnancy were smaller (p = 0.030), had a lower gestational age at death (p = 0.047), and were more frequently stillborn. Autopsy records revealed higher maternal vascular malperfusion in women with hypertension during pregnancy (p < 0.0001). Subarachnoid hemorrhage was more common in fetuses/neonates born to women with hypertension during pregnancy (p = 0.036). Other frequent findings included neuropil edema, congested meninges, hypoxic-ischemic encephalopathy, subdural hematoma, venous sinus thrombosis, hemoventricle, and necrotic foci. However, no significant endothelial or vascular wall changes were noted. "Prominent and congested" capillaries were observed only in fetuses/neonates born to women without hypertension.

Interpretation The findings suggest increased cerebrovascular vulnerability in fetuses and neonates exposed to maternal hypertension during pregnancy, with a higher incidence of subarachnoid hemorrhage. While no vascular wall changes were identified, fewer brain capillary alterations were noted in those born to women with hypertension during pregnancy.

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Keywords: Brain; Fetal development; Hypertensive disorders of pregnancy; Histological evaluation; Brain angiogenesis; Human; Neonates; Preeclampsia

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Translation: For the translation of the abstract see the Supplementary Materials section.

Research in context

Evidence before this study

Hypertensive disorders of pregnancy, such as preeclampsia, are known to increase the risk of cognitive impairments in children born to affected mothers, with studies showing a two to threefold increase in risk compared to children born to women without hypertension in pregnancy. However, the structural and histological changes in the brains of these children remain poorly understood. Most available research focuses on clinical outcomes in neonates and infants, including hypoxic-ischemic encephalopathy and cerebrovascular complications. These studies primarily address neonatal brain development but provide limited insights into the underlying histopathological changes associated with maternal hypertension during pregnancy.

A literature search was conducted in PubMed and Google Scholar using terms such as "hypertensive diseases of pregnancy," "neonatal brain," "fetal brain development," and "histological evaluation." Studies were limited to autopsy-based histological analyses and clinical research from 1980 to 2023. Despite the wealth of data on hypertensive pregnancies and fetal outcomes, there is limited research on the direct histopathological examination of fetal and neonatal brains from pregnancies complicated by hypertension. One earlier study, conducted by Hadi in 1984, identified accelerated cerebral maturation in preterm infants exposed to chronic maternal hypertension. However, this study focused on brain maturation without delving into other structural or vascular changes.

Our study aims to address this gap by examining brain histological samples from fetuses and neonates born to women with hypertension during pregnancy. Based on histological analysis of brain samples from deceased fetuses/newborns born to women with hypertension in pregnancy, particularly preeclampsia, this investigation provides new insights into potential microscopic and morphological cerebrovascular vulnerabilities present in those babies. Therefore, our research seeks to clarify the specific structural changes that may contribute to adverse neurological outcomes in these children.

Added value of this study

This study advances the understanding of how maternal hypertension during pregnancy (HDP) affects fetal and neonatal brain structure by providing a detailed histopathological comparison between affected (cases) and unaffected (control) groups. We used a robust protocol led by medical pathologists who analyzed, in a blind manner, brain samples belonging to matched cases and controls. This study was also aimed to evaluate brain vascular alterations. Our study revealed a significantly higher frequency of maternal vascular malperfusion diagnoses in autopsies of fetuses/neonates born to women with HDP compared to those born to women without HDP. Fetuses/neonates born to women with HDP exhibited subarachnoid hemorrhage more frequently than those born to women without HDP. Even though we did not identify any apparent histological alterations in the endothelium or vascular wall of the brain blood vessels, it was remarkable that fetuses/neonates born to women without HDP exclusively presented "prominent and congestive" capillaries. By focusing on brain histology, this study fills a critical gap in the literature, offering new evidence on the impact of maternal HDP on the developing brain and contributing valuable data for further research in this field.

Implications of all the available evidence

This study provides novel insights into the histological cerebral findings in fetuses and neonates born to mothers with HDP compared to those born to normotensive pregnancies. It is the first Latin American study and constitutes one of the few available studies worldwide analyzing the brain after fetal/neonatal death, considering a previous maternal diagnosis of HDP. The observed histological differences remark on the potential effect of HDP on brain development, reinforcing the importance of monitoring and managing HDP to mitigate its potential adverse effects. These insights can inform clinical practices and policies aimed at improving pregnancy outcomes and guiding future research to explore long-term neurological and cognitive consequences for children born to mothers with HDP.

Introduction

Hypertension during pregnancy is a human syndrome associated with high maternal and infant morbidity and mortality worldwide,[1] especially in low and middle-income countries such as Colombia.[2] One of the most epidemiological and clinically representative hypertension during pregnancy condition is preeclampsia, which is defined as the presence of *de novo* hypertension (blood pressure ≥140 mmHg systolic or ≥ 90 mmHg diastolic) after 20 weeks of gestation accompanied by proteinuria and/or evidence of maternal organ injury.[3,4] Preeclampsia affects 3–5% of pregnancies. It is responsible for more than 70,000 deaths annually worldwide,[5] which corresponds to 14% of all maternal deaths.[6] In contrast, the risk of neonatal mortality[7] and infant death[8] were nearly double in recent studies.

In addition, epidemiological evidence reports that fetal/neonatal brains are at a high risk of damage, including a two-to-five-fold increased risk of perinatal stroke when their mothers undergo hypertension in pregnancy.[9] Also, the rate of neonatal encephalopathy is six-fold higher with preeclampsia.[10] Moreover, preeclampsia constitutes an independent risk factor for cognitive disorders in their children,[11–24] such as cerebral palsy, impaired neurological development, developmental delays at the age of 5 years, and poor cognitive

development, among others.[11,25,26] Despite this epidemiological evidence, the causality and nature of brain alterations are unknown.

In severe preeclampsia, the fetus compensates placental insufficiency by redistributing blood to the brain, a protective process known as 'fetal brain sparing'.[27] Whether this adaptation continues post-birth remains unclear. Animal studies in mice reported reduced brain perfusion[28] and angiogenesis[29] in five-day-old mouse pups (P5) from a preeclampsia-like syndrome, which were associated with elevated levels of hypoxia-inducible factor alpha (HIF-1α) in the brain cortex, suggesting that vascular compromise and subsequent hypoxia may persist after birth. Supporting this idea, children (10 years old) born to mothers with preeclampsia presented a reduced vascular diameter at the cerebral level, which may lead to reduced blood flow in the parietal and occipital cortex when those children performed a functional test.[30] It is plausible that early impairment of brain vascular function, resulting in hypoxia, may induce structural alterations in the brain. This could account for the increased cerebrovascular and cognitive risks observed later in life in children born to mother with preeclampsia.

Analyzing brain structural and functional changes in offspring from preeclampsia is challenging in humans. Animal models have documented brain structural and functional alterations in offspring of preeclampsia-like syndrome, both neonatally and in adulthood.[31–33] These preclinical findings are supported by human studies in children (aged ten years) born to preeclamptic mothers, reporting enlarged volumes in at least five brain regions (cerebellum, temporal lobe, brain stem, and bilateral amygdalae),[30] which were further associated with impaired neuronal networking.[34] However, there is limited information on brain analysis in fetuses/newborns born to women with hypertension in pregnancy. A retrospective study published in the 80s, which analyzed autopsies of 23 preterm infants born to pregnant women with hypertension in pregnancy, reported that the majority (17 fetuses) exhibited 'accelerated cerebral maturation' two weeks or more in advance of gestational age.[35] No reports analyze *ex vivo* cerebral circulation in fetuses/infants whose mothers had hypertension in pregnancy.

Therefore, we aim to compare the histological findings in the brain and brain vessels in autopsies of neonates and fetuses who were born to mothers with and without hypertension during pregnancy.

Methods

Patients and sample availability

This retrospective study received approval from the Ethical Committee of Hospital Universitario San Ignacio (HUSI), Bogota, Colombia (ref # FM-CIE 0769-20). Due to retrospective and without intervention study, in a highly relevant area that lacks information, and to avoid reviving traumatic experiences in the parents after child death, the Ethical Committee approved informed consent dispense. The Ethical Committee also considered that all parents previously signed their authorization to perform the necropsies and use the material for teaching and future research.

We conducted a comprehensive review of clinical histories and final autopsy reports for all fetal/neonatal autopsies performed in the pathology department of San Ignacio University Hospital from 2007 to 2022. Initially, 275 medical records were identified. The selection criteria included fetuses/neonates born to women with hypertension in pregnancy, gestational age greater than 20 weeks, absence of severe maceration, no suspicion of chromosomal abnormalities, absence of central nervous system malformations, and no maternal history of mental illness or psychoactive substance use. Stillbirth was defined as the death of a baby before or during birth after 28 weeks of gestation, and neonatal death as the death of a baby within the first 28 days of life.

Hypertension during pregnancy was diagnosed according to the ACOG guideline, 2013.[3] Preeclampsia was diagnosed using high blood pressure (>140/90 mm Hg) after 20 weeks of pregnancy and at least one of the following findings: protein in the urine (proteinuria), low blood platelet count, elevated liver enzymes, pulmonary edema, neurological symptoms or echographic signs of uteroplacental dysfunction. Subsequently, a matched group of fetuses/neonates born to women without hypertension were chosen from autopsies. Matched criteria included similar maternal pre-pregnancy morbidity, gestational ages at delivery, fetal sex, and availability of similar histological samples of fetal/neonatal brains.

Sixty-six candidates were obtained for the study, with 25 fetal/neonatal brains in the hypertension in pregnancy group and 41 in the normotensive pregnancy group. Considering that by national regulations, paraffin blocks must be preserved (at 10–20 °C) for up to 15 years, the request was made for the histology slides and paraffin blocks for each of the 66 candidates from the external and internal hospital biobanks. Once it arrived, the available material was examined to identify the availability of central nervous system samples. Then, we included 15 fetal/neonatal brains samples from the hypertension in pregnancy group, and 22 from the normotensive pregnancy group (see Figure S1).

Anatomic-pathologic analysis

Two pathologists (JG, JAF) analyzed all fetal/neonates brain samples, which included the brain cortex, hippocampus, basal ganglia, cerebellum, and brain stem. Pathologists conducted simultaneous reading sessions using a multi-head microscope. All analyses were blinded, with samples randomly selected and morphological

and pathological findings recorded immediately. A template of histological findings, previously designed in the RedCAP database, was used. Each sample was assigned a coded number, later linked to the corresponding clinical information.

Each brain sample was composed of slides stained with routine staining (Hematoxylin and Eosin Stain (H&E)). We evaluated the presence of clinically relevant histological findings including subarachnoid hemorrhage, intraparenchymal hemorrhage, hypoxic-ischemic encephalopathy, subdural hematoma, foci of necrosis, vascular congestion thrombosis of the longitudinal venous sinus, immaturity, neuronal apoptosis, gliosis, hemorrhage, vascular changes in endothelium, vascular, perivascular changes, thrombus, and karyorrhexis (Figure S2). Also, unusual findings not listed above were included in our database. All findings were recorded as dichotomic variables.

Maternal and perinatal clinical data were also recorded in the same RedCap database. This information included maternal age, gestational age, weight, prepregnancy comorbidities, pregnancy complications, neonates' sex, neonates' complications, vitality, type of delivery, days of hospitalization, suspected perinatal asphyxia, hypothermia protocol, and life span.

Finally, the diagnoses reported at the moment of the autopsy were recorded. Those reports included the presence of caput, cord alterations, maternal vascular malperfusion (i.e., uteroplacental blood flow impairments), fetal vascular malperfusion, multiple visceral hemorrhages, minor malformations, signs of hypoxia, postmortem infectious processes, congenital disabilities, chorioamnionitis, diffuse alveolar damage, necrotizing enterocolitis, aspiration of amniotic fluid and disseminated intravascular coagulation.

Statistical analysis

Quantitative variables are presented as mean ± standard deviation, while qualitative variables are in percentages considering their respective groups. Quantitative variables were compared through non-parametric statistics using the Mann–Whitney test. Qualitative variables were compared using the Chi-square test. Statistical analyses were performed using GraphPad Prism 9.00 (GraphPad Software, San Diego, California, USA). $p < 0.05$ was considered statistically significant.

Role of the funding source

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Results

Clinical characteristics and sample availability

We report clinical findings and brain histological alterations from 37 fetuses and neonates, divided into 22 fetal/neonatal brains samples of babies born to women without hypertension in pregnancy and 15 born to women with hypertension in pregnancy (Figure S1).

Considering the respective group, 80% (12/15) and 27% (6/22) of the women with and women without hypertension in pregnancy, respectively, showed comorbidities before pregnancy. Despite that, there were no statistical differences between pregnant women with and without hypertension in pregnancy in the analyzed maternal parameters, including age, prepregnancy morbidity (i.e., history of hypertension, diabetes mellitus, hyperthyroidism, obesity, or autoimmune disease), gestational age at delivery, history of infection, or rate of cesarean section (Table S1). There were no cases of gestational diabetes. Despite that, we acknowledge that none of the births recorded in the study occurred after 40 weeks of gestation. Furthermore, in agreement with the selection criteria, none of the pregnant women without hypertension in pregnancy had any diagnosis of hypertension. In contrast, preeclampsia was the most representative diagnosis in pregnant women with hypertension in pregnancy (93%, 14/15). These results evidence suitable case–control matching from the maternal diagnosis point of view.

There were no male/female ratio differences between fetal/neonates born to women with or without hypertension in pregnancy (Table 1). Percentage of stillbirth and neonatal death (up to 28 days) were 41% (9/22) and 73% (11/15), and 59% (13/22) and 27% (4/15) in the group without hypertension in pregnancy and hypertension in pregnancy, respectively. Fetal/neonates in the group of hypertension in pregnancy were smaller and with lower gestational age at decease than in the group without hypertension in pregnancy ($p < 0.05$ in all comparisons). Intrauterine growth restriction was documented in 5% of the population belonging to the women with hypertension in pregnancy.

Despite that, cerebral parameters, including cephalic perimeter, crown-rump length, head circumference/crown-rump length ratio, and cephalic weight, were not statistically different between fetuses/neonates born to women with or without hypertension in pregnancy. Perinatal asphyxia was less likely to be diagnosed in the group of hypertension in pregnancy than in the group without hypertension in pregnancy (13% (2/15) versus 36% (8/22), respectively, $p = 0.0002$). Only one child born to women with hypertension in pregnancy was exposed to hypothermia, whereas six were in the group without hypertension in pregnancy ($p = 0.002$). Non-

Characteristics	Without hypertension during pregnancy (n = 22)	With hypertension during pregnancy (n = 15)	p
Male, n (%)	11 (50)	9 (60)	0.54
Female, n (%)	11 (50)	6 (40)	
Stillbirth, n (%)	9 (41)	11 (73)	0.052
Neonatal death, n (%)	13 (59)	4 (27)	
Gestational age at decease (weeks, mean ± SD)	**31.1 ± 7.4**	**26.6 ± 5.9**	**0.047**
Newborn weight (g, mean ± SD)	**2138.0 ± 1739.0**	**995.9 ± 950.8**	**0.030**
Newborn height (cm, mean ± SD)	**40.4 ± 10.2**	**32.4 ± 8.2**	**0.016**
Cephalic perimeter (cm, mean ± SD)	27.2 ± 7.0	22.8 ± 5.1	0.076
Crown-rump length (cm, mean ± SD)	27.0 ± 7.2	22.4 ± 6.2	0.051
Head circumference/crown-rump length (mean ± SD)	1.0 ± 0.1	1.0 ± 0.1	>0.99
Cephalic weight (g, mean ± SD)	565.8 ± 1007.0	237.3 ± 255.4	0.26
Perinatal asphyxia, n (%)	**8 (36)**	**2 (13)**	**0.0002**
Hypothermia, n (%)	**6 (27)**	**1 (7)**	**0.0002**

SD, standard deviation. Statistically significant differences are heighted in bold letters.

Table 1: **Characteristics of fetal/newborn born to women with and without hypertension during.**

reassuring fetal status was documented in only two individuals of the entire population, one in each comparative group.

In addition, and compatible with maternal diagnosis, 87% (13/15) of fetuses/neonates born to women with hypertension in pregnancy showed signs of maternal vascular malperfusion, which was significantly higher than in the group without hypertension in pregnancy (18% (4/22), $p < 0.0001$). Most of the fetuses/neonates born to women with hypertension in pregnancy (73 versus 45%, $p = 0.09$) showed multiple visceral hemorrhages. Nevertheless, there were no differences in umbilical cord alterations, fetal signs of malperfusion (including signs of hypoxia), infection process, or minor malformations between comparative groups with or without hypertension in pregnancy. Still, various diagnoses were also found in the group without hypertension in pregnancy, including chorioamnionitis, other alterations not cataloged in our database, and necrotizing enterocolitis, among others (Table 2).

In both groups, the frontotemporal cortex and the meninges were the brain areas most frequently available for evaluation, with 97% and 81% availability rates across the entire analysis group. A similarly high proportion of these tissue samples was observed in both fetuses/neonates born to women with and without hypertension in pregnancy (see Table S2). However, in fetuses/neonates born to women with hypertension in pregnancy, the hippocampus and cerebellum were available in only 20% (3/15) of individuals, compared to 50% (11/22) and 59% (13/22) in the group without hypertension in pregnancy. Additionally, the brain stem and hippocampus were available in 20% and 50% of fetuses/neonates born to women with or without hypertension in pregnancy, respectively (See Table S2).

We evaluated the weight of the brain in 76% (28/37) of the included samples. Among these, only 36% had an appropriate weight for gestational age, with equal distribution in both comparative groups with and without hypertension in pregnancy. Additionally, 11% of the brains in the overall group had a lower-than-expected weight, with fetuses/neonates born to women with hypertension in pregnancy representing twice as many as the group without hypertension in pregnancy. Conversely, in the group with greater-than-estimated weight, two-thirds were fetuses/neonates born to women without hypertension in pregnancy, and one-third were born to women with hypertension in pregnancy (73% versus 27%).

Characteristics	Without hypertension during pregnancy (n = 22)	With hypertension during pregnancy (n = 15)	p
Umbilical cord alterations, n (%)	3 (14)	4 (27)	0.32
Maternal vascular malperfusion, n (%)	**4 (18)**	**13 (87)**	**<0.0001**
Fetal vascular malperfusion, n (%)	4 (18)	4 (27)	0.53
Multiple visceral hemorrhages, n (%)	10 (45)	11 (73)	0.092
Minor malformations, n (%)	7 (32)	7 (47)	0.36
Signs of hypoxia, n (%)	9 (41)	4 (27)	0.37
Infectious processes, n (%)	4 (18)	2 (13)	0.69
Chorioamnionitis, n (%)	8 (36)	–	–
Diffuse alveolar damage, n (%)	2 (9)	–	–
Necrotizing enterocolitis, n (%)	3 (13.6)	–	–
Amniotic liquid aspiration, n (%)	1 (4.5)	–	–
Disseminated intravascular coagulation, n (%)	4 (18)	–	–
Other alterations, n (%)	12 (54.5)	4 (27)	0.092

Statistically significant differences are heighted in bold letters.

Table 2: **Fetal/newborn anatomopathological diagnosis at decease.**

	Without hypertension during pregnancy (n = 22)	With hypertension during pregnancy (n = 15)
General findings		
Subarachnoid hemorrhage, n (%)	**7 (32)**	**10 (67)**[a]
Intraparenchymal hemorrhage, n (%)	4 (18)	3 (20)
Neuropil edema, n (%)	–	3 (20)
Congestive meninges, n (%)	1 (4.5)	–
Interventricular hemorrhage, n (%)	1 (4.5)	1 (7)
Hypoxic ischemic encephalopathy, n (%)	1 (4.5)	–
Subdural hematoma, n (%)	3 (14)	–
Vascular congestion, n (%)	4 (18)	1 (7)
Longitudinal venous sinus thrombosis, n (%)	2 (9)	–
Hemoventricle, n (%)	2 (9)	–
Immaturity, n (%)	2 (9)	2 (13)
Foci of necrosis, n (%)	1 (4.5)	–
Frontotemporal cortex		
Neuronal apoptosis, n (%)	1 (4.5)	–
Gliosis, n (%)	3 (14)	3 (20)
Neuropil calcifications/mineralization, n (%)	1 (4.5)	1 (7)
Hemorrhage, n (%)	3 (14)	3 (20)
Vascular changes (thrombi), n (%)	1 (4.5)	–
Karyorrhexis, n (%)	–	1 (7)
Other, n (%)	4 (18)	1 (7)
Other brain areas		
Neuronal apoptosis, n (%)	1 (4.5)	–
Gliosis, n (%)	3 (14)	2 (13)
Hemorrhage, n (%)	6 (27)	2 (13)
Vascular changes (perivascular), n (%)	1 (4.5)	–
Other, n (%)	7 (32)	2 (13)

Statistically significant differences are heighted in bold letters. [a]The absolute difference in the proportion of subarachnoid hemorrhage was 35% (95% CI 1.68%, 61.0%) and a p-value of 0.036.

Table 3: **Histological findings in brain slices of fetus/newborn born to women with and without hypertension during pregnancy.**

Histopathological findings

The most frequent general histopathological analysis was the presence of subarachnoid hemorrhage, documented in 46% (17/37) of all brains; from them, the majority belong to the fetuses/neonates born to women with hypertension in pregnancy. The absolute difference in the proportion of subarachnoid hemorrhage was 35% (95% CI 1.68%, 61.0%) and a p-value of 0.036. The presence of edema of the neuropil was a unique finding discovered in 20% of hypertension in pregnancy group. In addition, congestive meninges, hypoxic-ischemic encephalopathy, subdural hematoma, longitudinal venous sinus thrombosis, hemoventricle, and necrosis foci were most likely found in fetuses/neonates born to women with hypertension in pregnancy.

In the frontotemporal cortex, hemorrhage and gliosis were the most frequent diagnoses, occurring in 17% (6/37) of all samples examined, with no significant differences between both comparative groups. Congestive and prominent vasculature were diagnosed in only 14% of the cortices examined, with fetuses/neonates born to women without hypertension in pregnancy the most diagnosed with this alteration. Karyorrhexis was exclusively observed in fetuses/neonates born to women with hypertension during pregnancy, while neuronal apoptosis was identified in the group without hypertension in pregnancy. Other diagnoses not initially described were more likely present in pregnant women without hypertension in pregnancy, although they were not statistically significant (see Table 3).

In the remaining brain areas that were analyzed, histological findings were less prevalent. Nonetheless, the most frequent observation was gliosis in the hippocampus, present in 29% (11/37) of all available samples. Notably, 75% of these gliosis were observed in fetuses/neonates born to women without hypertension in pregnancy. The two most common findings in the basal ganglia were hemorrhages and thrombi, each occurring in 9% of the samples and exclusively within the group without hypertension in pregnancy. Conversely, 5% of the examined samples documented gliosis in the basal ganglia, occurring solely in the group of hypertension in pregnancy.

Hemorrhage was the most frequently observed finding in the cerebellum, present in 34% (13/37) of all examined samples. Of these, 80% were in the group without hypertension in pregnancy and 20% in the hypertension in pregnancy group.

The only documented findings in the brainstem were hemorrhage (n = 1) and prominent vascular structures with congestion (n = 1), each observed in 7% of the samples.

Analysis of the brain blood vessels

Since we focused on brain blood vessels, we searched for endothelial or vascular signs of damage. However, we could not identify any apparent histological alterations in the endothelium or the vascular wall in any analyzed samples. Despite that, we found that some brains had capillary vasculature that we called "prominent and congestive," categorized as "other findings" in the blind analysis. Interestingly, those alterations were present only in fetuses/neonates born to women without hypertension in pregnancy (Fig. 1).

Discussion

In the present study, we presented data from 37 available autopsies in our institution according to the selection criteria. Fifteen (40%) corresponded to fetuses/neonates born to mothers who presented hypertension in pregnancy; most of them were born after a preeclamptic pregnancy. Women without hypertension in pregnancy (n = 22, 60% of the studied group) exhibited similar maternal pre-pregnancy morbidity, gestational age at delivery, way of delivery, and fetal/neonatal sex than women with hypertension in pregnancy. Most of

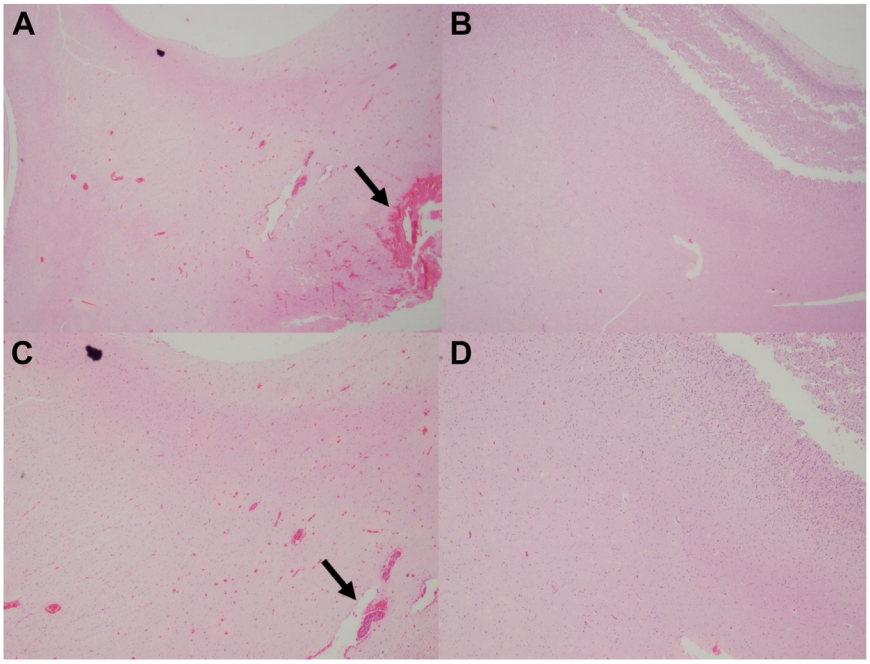

Fig. 1: **Representative images of capillary vasculature structures identified as "prominent and congestive."** **A** (2×) and **C** (4×) are representative images from the frontotemporal cortex observed in autopsies of neonates born to women without hypertension in pregnancy, showing congestive prominent vasculature (arrows). **B** (2×) and **D** (4×) show representative images of the frontotemporal cortex observed in autopsies of neonates born to pregnant women with hypertension.

the babies who died and underwent autopsy were stillborn; most of them belonged to the hypertension in pregnancy group, who also exhibited maternal vascular malperfusion. Despite our meticulosity, we only observed differences in the rate of subarachnoid hemorrhage, a diagnosis more likely found in the group of hypertension in pregnancy. Also, no significant differences between fetuses/neonates born to women with and without hypertension in pregnancy were found in the eight histological and conventional parameters analyzed in their brain samples. Although some particularities were found in each comparative group, they deserve further investigation. Importantly, we could not identify any apparent histological alterations in the endothelium or the vascular wall in any analyzed samples. Therefore, our pioneering findings in Latin American samples suggest a potential vulnerability in cerebrovascular integrity in fetuses and neonates exposed to maternal hypertension, as indicated by the increased incidence of subarachnoid hemorrhage.

Brain circulation was our focus

How preeclampsia affects offspring neurodevelopment is not well understood. Current theories suggest that neurological and cognitive impairments may stem from neuroinflammation or disrupted cerebrovascular function.[36] One of our focuses of interest in this analysis was brain circulation, considering the hypothesis that placental alterations observed in preeclampsia may drive impairments in brain formation/function.[37,38] We have hypothesized, based on our preclinical findings,[28,29] that placental adaptations occurring in preeclampsia may release anti-angiogenic factors toward the fetal circulation capable of impairing angiogenesis and brain blood vessels, which in turn may lead to structural and functional alterations in the brain.[39] In this regard, brain hemorrhages and the presence of thrombosis were more common in fetuses/neonates born to women with hypertension in pregnancy than those born to women without hypertension in pregnancy. Brain hemorrhages, including subarachnoid hemorrhage, are also found in prematurity and patients with chronic hypoxia, as in fetuses/neonates born to women with hypertension in pregnancy.[40] We also describe some brain capillary abnormalities identified as "prominent and congestive", which were more likely present in the group without hypertension in pregnancy.

In addition, changes in the endothelial cells or at the vascular wall were complex to detect in the histological samples. Indeed, none were reported in the blind analysis performed in this study. Despite that, and considering evidence from our group showing defects in the brain circulation in pups of the preeclampsia-like syndrome, characterized by reduced angiogenesis[29] associated with reduced brain perfusion and hypoxia,[28]

we are conducting additional analysis of the brain circulation in these human brains.

Preeclampsia and brain alterations in offspring

The death of a baby is one of the most devasting emotions for parents, clinicians, and the whole society. Indeed, fetal/neonatal mortality is a measurement included as a significant health indicator in any country. The World Health Organization (WHO) reports that premature birth, low birth weight, infections, asphyxia, and birth trauma account for about 80% of newborn deaths globally.[41] Preeclampsia and severe hypertension in pregnancy increase the risk for stillbirth (30% increase) and fetal and neonatal mortality (twofold),[7] yet a reduced risk was reported with mild hypertension.[42]

Interestingly, gestational age and birth weight moderate these relationships.[10] Since our study includes stillbirth and newborns who died, it is not possible to completely elucidate differences between fetuses/neonates born to women with or without hypertension. Especially, when autopsy stillbirth brains have described a range of pathologies limited to acute abnormalities such as severe congestion, white matter edema, and neuronal karyorrhexis (pontosubicular necrosis with or without neuronal karyorrhexis at other sites),[43] hemorrhage and acute neuronal necrosis.[44] We also acknowledge that there were differences in the frequency of stillbirth, neonatal death, and, therefore, gestational age at deceases in the comparative groups with and without hypertension in pregnancy. These differences may confound our results in the analysis of the brain.

We also indicate that we have extended clinical data from mothers and babies, which allows us to establish some comparisons in a scenario where there needs to be more information regarding the analysis of the brain in babies from preeclampsia. As far as we know, only one study has detailed autopsy in babies born to women with hypertension in pregnancy.[35] In this old report from the 80s, they report that most of the preterm infants born to women with hypertension in pregnancy exhibited signs of accelerated cerebral maturation two weeks or more in advance of gestational age. It is hard to compare this evidence with our report (see below). Therefore, we encourage future studies to deeply analyze specific damage markers to the neurovascular unit (endothelium, pericytes, microglia, neurons) in human samples.

Fetal and neonatal deaths can result from various factors, including genetic conditions, infections, placental abnormalities, and fetal–maternal hemorrhage. However, many cases are not thoroughly evaluated for underlying causes. Perinatal autopsy and placental examination are among the most valuable tools for investigating fetal death. In this regard, we describe that placentas were studied whenever available at the institution. As expected, women with hypertension in pregnancy presented findings of maternal vascular malperfusion, which agree with a previous report showing placental anomalies as the most important cause of perinatal mortality.[45] In addition, the autopsy report indicated that one of the most frequently documented findings in both comparative groups with and without hypertension in pregnancy was multiple visceral hemorrhages, with fetuses/neonates born to women with hypertension in pregnancy tending to exhibit it more frequently than those born to women without hypertension in pregnancy. The presence of changes due to hypoxia was the most important cause of death in both groups.

In the only report we found regarding the analysis of the fetuses/neonates born to women with hypertension in pregnancy, authors indicate that most of the affected fetuses/neonates showed accelerated gestational gyral pattern age of more than two weeks than their clinical gestational age.[35] This study does not include a comparative group without hypertension in pregnancy, so it is impossible to make a real contrast with our findings. Despite that, this author reports that microscopic examination of the brain (and lung, kidneys, and placentas) showed normal findings. However, there was no clear description of which signs of abnormalities were analyzed in this study. Conversely, we generate several methodological advantages, including a matched comparative group including fetuses/neonates born to women without hypertension in pregnancy, blind analysis for at least two pathologists, and protocolized records of the findings. A detailed description of the clinical records of both mothers and babies complements these strengths.

The brain cortex is one of the areas more prone to hypoxia-mediated damage.[46] Fortunately, frontotemporal cortex was available in almost all analyzed fetuses/neonates. However, due to sample size, we could not detect any statistically significant differences between fetuses/neonates born to women with and without hypertension in pregnancy in this area.

When considering the brain findings, it is especially striking that the brains of the fetuses/neonates born to pregnant women without hypertension in pregnancy impress with a more significant number of general findings compared to the hypertension in pregnancy group in the different categories and areas identified, especially regarding the presence of hemorrhage and gliosis. We consider this finding to be expected since it is impossible to find normal brains as “controls” since all constitute deceased babies. Therefore, it is expected that they will have changes secondary to the complications that led to their death. An effort was made to choose cases of ascending infection due to the rapid outcome, which could interfere less with possible structural changes in the brain. We also acknowledge that despite this effort, the unfound differences between fetuses/neonates born to women with and without hypertension in pregnancy are also limited by a lack of appropriate comparative groups. Access to fetuses/neonates’ brains without brain affection is impossible to get

in an anatomopathological unit or they are ethically and socially restricted.

We acknowledge the limitations of this study, particularly those related to its retrospective nature and potential confounding factors, such as small sample size and the lack of consideration for confounding variables like ethnicity, cause of death, gestational age, pregnancy complications, and the need for neonatal intensive care. Differences in stillbirth frequency and age at death also pose significant limitations. Nonetheless, including these autopsy samples was necessary to gain insight into this underexplored area. On the other hand, the absence of significant histological changes in the frontotemporal cortex, meninges, and vascular walls suggests the possibility of more subtle or functional alterations rather than gross structural changes. Two independent pathologists conducted a masked analysis and recorded all data immediately to overcome observer potential bias. In addition, our results underscore the need for advanced detection methods beyond routine histology to uncover potential alterations.

In conclusion, this study is the first in Latin America to explore potential histological differences in autopsies of fetuses/neonates born to women with hypertension in pregnancy. Thus, these fetuses/neonates exhibited a higher incidence of subarachnoid hemorrhage and distinct histological features in brain regions like the frontotemporal cortex. However, no significant histological alterations were found in the examined brain areas, including the frontotemporal cortex and meninges, nor in the endothelium or vascular walls when we compared them with fetuses/neonates born to women without hypertension. While some "prominent and congestive" brain capillary abnormalities were noted only in fetuses/neonates born to women without hypertension in pregnancy. These findings highlight the complexity of analyzing fetuses'/neonates' brains to elucidate the impact of hypertension in pregnancy. We encourage multicentric studies that combine functional studies with noninvasive structural brain alterations to better understand the potential negative impact of hypertension in pregnancy on brain development.

Contributors

CE conceptualized the manuscript, funding acquisition, investigation, project administration, supervision, validation, writing. MO was the leading pathologist of this project, data curation, formal analysis, methodology. JG, JAF, and MO performed all blind pathological analyses, data curation, formal analysis, methodology. JG prepared the draft of the manuscript. JG and CE prepare tables and figures. JAF and MO critically edited the manuscript. All co-authors approved the final version of this manuscript.

Data sharing statement

Data are available upon request to Dr. Carlos Escudero and Dr. Mercedes Olaya.

Editorial disclaimer

The translation of the Summary was submitted by the authors, and we reproduce it as supplied. It has not been peer reviewed. Our editorial processes have only been applied to the original version in English, which should serve as a reference for this manuscript.

Declaration of interests

The authors do not have any commercial conflicts of interest to declare. However, we initially submitted the manuscript to fulfill all the requirements for Dr. Johana Gonzalez's thesis defense as a pathologist.

We used Grammarly, a typing assistant based on Artificial Intelligence, to check English texts for grammar, clarity, and engagement.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lana.2024.100955.

References

1 Duley L. The global impact of pre-eclampsia and eclampsia. *Semin Perinatol*. 2009;33:130–137.
2 Narváez Diaz N. Informe de evento morbilidad materna extrema, Colombia, 2017. In: *Pública Proceso de Vigilancia y Analisis de Riesgo de Salud Pública*. Colombia: Instituto Nacional de Salud. FOR-R02. 4000-001; 2017:1–17. https://www.ins.gov.co/buscador-eventos/Informesdeevento/MORBILIDAD%20MATERNA%20EXTREMA%202017.pdf. Accessed November 2021.
3 ACOG, Pregnancy. TFoHi. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' task force on hypertension in pregnancy. *Obstet Gynecol*. 2013;122(5):1122–1131.
4 ACOG practice bulletin No. 202: gestational hypertension and preeclampsia. *Obstet Gynecol*. 2019;133(1):1. https://doi.org/10.1097/AOG.0000000000003018.
5 Brown MA, Magee LA, Kenny LC, et al. Hypertensive disorders of pregnancy. *Hypertension*. 2018;72:24–43.
6 Say L, Chou D, Gemmill A, et al. Global causes of maternal death: a WHO systematic analysis. *Lancet Global Health*. 2014;2(6):e323–e333. https://doi.org/10.1016/S2214-109X(14)70227-X.
7 Basso O, Rasmussen S, Weinberg CR, Wilcox AJ, Irgens LM, Skjaerven R. Trends in fetal and infant survival following preeclampsia. *JAMA*. 2006;296(11):1357–1362.
8 Greene T, Hartnett ME. Programming error led to underestimate of effect sizes in study of association of maternal preeclampsia and risk of infant retinopathy of prematurity. *JAMA Ophthalmol*. 2019;137(1):119. https://doi.org/10.1001/jamaophthalmol.2018.5055.
9 Li C, Miao JK, Xu Y, et al. Prenatal, perinatal and neonatal risk factors for perinatal arterial ischaemic stroke: a systematic review and meta-analysis. *Eur J Neurol*. 2017;24(8):1006–1015.
10 Korzeniewski SJ, Sutton E, Escudero C, Roberts JM. The Global Pregnancy Collaboration (CoLab) symposium on short- and long-term outcomes in offspring whose mothers had preeclampsia: a scoping review of clinical evidence. *Front Med (Lausanne)*. 2022;9:984291. https://doi.org/10.3389/fmed.2022.984291.
11 Figueiro-Filho EA, Croy BA, Reynolds JN, et al. Diffusion tensor imaging of white matter in children born from preeclamptic gestations. *AJNR Am J Neuroradiol*. 2017;38(4):801–806.
12 Alsnes IV, Janszky I, Asvold BO, Okland I, Forman MR, Vatten LJ. Maternal preeclampsia and androgens in the offspring around puberty: a follow-up study. *PLoS One*. 2016;11(12):e0167714. https://doi.org/10.1371/journal.pone.0167714.
13 Ratsep MT, Hickman AF, Croy BA. The Elsevier trophoblast research award lecture: impacts of placental growth factor and preeclampsia on brain development, behaviour, and cognition. *Placenta*. 2016;48(Suppl 1):S40–S46.
14 Ratsep MT, Hickman AF, Maser B, et al. Impact of preeclampsia on cognitive function in the offspring. *Behav Brain Res*. 2016;302:175–181.
15 Pinheiro TV, Brunetto S, Ramos JG, Bernardi JR, Goldani MZ. Hypertensive disorders during pregnancy and health outcomes in the offspring: a systematic review. *J Dev Orig Health Dis*. 2016;7(4):391–407.

16 Escudero C, Roberts JM, Myatt L, Feoktistov I. Impaired adenosine-mediated angiogenesis in preeclampsia: potential implications for fetal programming. *Front Pharmacol*. 2014;5:134. https://doi.org/10.3389/fphar.2014.00134.

17 Davis EF, Lazdam M, Lewandowski AJ, et al. Cardiovascular risk factors in children and young adults born to preeclamptic pregnancies: a systematic review. *Pediatrics*. 2012;129(6):e1552–e1561. https://doi.org/10.1542/peds.2011-3093.

18 Tuovinen S, Raikkonen K, Pesonen AK, et al. Hypertensive disorders in pregnancy and risk of severe mental disorders in the offspring in adulthood: the Helsinki Birth Cohort Study. *J Psychiatr Res*. 2012;46(3):303–310.

19 Wu CS, Nohr EA, Bech BH, Vestergaard M, Catov JM, Olsen J. Diseases in children born to mothers with preeclampsia: a population-based sibling cohort study. *Am J Obstet Gynecol*. 2011;204(2):157.e1–157.e5. https://doi.org/10.1016/j.ajog.2010.08.046.

20 Jayet PY, Rimoldi SF, Stuber T, et al. Pulmonary and systemic vascular dysfunction in young offspring of mothers with preeclampsia. *Circulation*. 2010;122(5):488–494.

21 Wu CS, Nohr EA, Bech BH, Vestergaard M, Catov JM, Olsen J. Health of children born to mothers who had preeclampsia: a population-based cohort study. *Am J Obstet Gynecol*. 2009;201(3):269.e1–269.e10. https://doi.org/10.1016/j.ajog.2009.06.060.

22 Robinson M, Mattes E, Oddy WH, et al. Hypertensive diseases of pregnancy and the development of behavioral problems in childhood and adolescence: the Western Australian Pregnancy Cohort Study. *J Pediatr*. 2009;154(2):218–224.

23 Wu CS, Sun Y, Vestergaard M, et al. Preeclampsia and risk for epilepsy in offspring. *Pediatrics*. 2008;122(5):1072–1078.

24 Tenhola S, Rahiala E, Martikainen A, Halonen P, Voutilainen R. Blood pressure, serum lipids, fasting insulin, and adrenal hormones in 12-year-old children born with maternal preeclampsia. *J Clin Endocrinol Metabol*. 2003;88(3):1217–1222.

25 Maher GM, O'Keeffe GW, Kearney PM, et al. Association of hypertensive disorders of pregnancy with risk of neurodevelopmental disorders in offspring: a systematic review and meta-analysis. *JAMA Psychiatr*. 2018;75(8):809–819.

26 Figueiro-Filho EA, Mak LE, Reynolds JN, et al. Neurological function in children born to preeclamptic and hypertensive mothers - a systematic review. *Pregnancy Hypertens*. 2017;10:1–6.

27 Tanis JC, Boelen MR, Schmitz DM, et al. Correlation between Doppler flow patterns in growth-restricted fetuses and neonatal circulation. *Ultrasound Obstet Gynecol*. 2016;48(2):210–216.

28 Lara E, Rivera N, Gonzalez-Bernal A, et al. Abnormal cerebral microvascular perfusion and reactivity in female offspring of reduced uterine perfusion pressure (RUPP) mice model. *J Cerebr Blood Flow Metabol*. 2022;42(12):2318–2332.

29 Troncoso F, Sandoval H, Ibanez B, et al. Reduced brain cortex angiogenesis in the offspring of the preeclampsia-like syndrome. *Hypertension*. 2023;80(12):2559–2571.

30 Ratsep MT, Paolozza A, Hickman AF, et al. Brain structural and vascular anatomy is altered in offspring of pre-eclamptic pregnancies: a pilot study. *AJNR Am J Neuroradiol*. 2016;37(5):939–945.

31 Tachibana R, Umekawa T, Yoshikawa K, et al. Tadalafil treatment in mice for preeclampsia with fetal growth restriction has neurobenefic effects in offspring through modulating prenatal hypoxic conditions. *Sci Rep*. 2019;9(1):234. https://doi.org/10.1038/s41598-018-36084-x.

32 Liu X, Zhao W, Liu H, et al. Developmental and functional brain impairment in offspring from preeclampsia-like rats. *Mol Neurobiol*. 2016;53(2):1009–1019.

33 Carver AR, Andrikopoulou M, Lei J, et al. Maternal pravastatin prevents altered fetal brain development in a preeclamptic CD-1 mouse model. *PLoS One*. 2014;9(6):e100873. https://doi.org/10.1371/journal.pone.0100873.

34 Mak LE, Croy BA, Kay V, et al. Resting-state functional connectivity in children born from gestations complicated by preeclampsia: a pilot study cohort. *Pregnancy Hypertens*. 2018;12:23–28.

35 Hadi HA. Fetal cerebral maturation in hypertensive disorders of pregnancy. *Obstet Gynecol*. 1984;63(2):214–219.

36 Escudero C, Kupka E, Ibanez B, et al. Brain vascular dysfunction in mothers and their children exposed to preeclampsia. *Hypertension*. 2023;80(2):242–256.

37 Gardella B, Dominoni M, Scatigno AL, et al. What is known about neuroplacentology in fetal growth restriction and in preterm infants: a narrative review of literature. *Front Endocrinol*. 2022;13:936171. https://doi.org/10.3389/fendo.2022.936171.

38 Kratimenos P, Penn AA. Placental programming of neuropsychiatric disease. *Pediatr Res*. 2019;86(2):157–164.

39 Lara E, Acurio J, Leon J, Penny J, Torres-Vergara P, Escudero C. Are the cognitive alterations present in children born from preeclamptic pregnancies the result of impaired angiogenesis? Focus on the potential role of the VEGF family. *Front Physiol*. 2018;9:1591.

40 Brown WR. Association of preterm birth with brain malformations. *Pediatr Res*. 2009;65(6):642–646.

41 World Health Organization. Newborn mortality. https://www.who.int/news-room/fact-sheets/detail/newborn-mortality; 2014. Accessed September 2023.

42 Razak A, Florendo-Chin A, Banfield L, et al. Pregnancy-induced hypertension and neonatal outcomes: a systematic review and meta-analysis. *J Perinatol*. 2018;38(1):46–53.

43 Chang KT, Keating S, Costa S, Machin G, Kingdom J, Shannon P. Third-trimester stillbirths: correlative neuropathology and placental pathology. *Pediatr Dev Pathol*. 2011;14(5):345–352.

44 Ernst LM, Bit-Ivan EN, Miller ES, Minturn L, Bigio EH, Weese-Mayer DE. Stillbirth: correlations between brain injury and placental pathology. *Pediatr Dev Pathol*. 2016;19(3):237–243.

45 Pinar H, Goldenberg RL, Koch MA, et al. Placental findings in singleton stillbirths. *Obstet Gynecol*. 2014;123(2 Pt 1):325–336.

46 Miller SL, Huppi PS, Mallard C. The consequences of fetal growth restriction on brain structure and neurodevelopmental outcome. *J Physiol*. 2016;594(4):807–823.