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RESEARCH ARTICLE

Hematological disorders in preterm newborns born to mothers with pregnancy-induced hypertension

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Abstract

Background: *Pregnancy-induced hypertension (PIH) has been related to impaired fetal growth, possibly by affecting hematopoiesis. This study aimed to analyze the most frequent hematological alterations in preterm infants born to mothers with PIH.* **Methods:** *We conducted a cross-sectional study in newborns born to mothers with PIH. We reviewed 130 hemograms of preterm infants: 45 from mothers with PIH, 71 with preeclampsia, and 14 with HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count). Normality, cytosis conditions, or cytopenia values were adjusted for gestational ages. Differences between groups were analyzed with classical and Bayesian statistics (BF01 = null/alternative hypothesis ratio).* **Results:** *Anemia was found in only 1.2% of newborns. In the white blood cell count, the most frequent finding was lymphopenia (56.2%) and monocytosis (38.5%) (p = 0.6, FB01 = 249 y p = 0.81, FB01 = 19.9). Thrombocytopenia was found in 12.5% (p = 0.56, FB01 = 67). No significant differences were observed among PIH groups.* **Conclusions:** *Hematological alterations of newborns born to mothers with PIH are frequent and do not show a distinct pattern related to the severity of the affection in the mother. We recommend a full hematological evaluation in these preterm neonates.*

Keywords: *Pregnancy-induced hypertension. Hemogram. Thrombocytopenia. Preterm newborn.*

Alteraciones hematológicas en recién nacidos pretérmino de madres con enfermedad hipertensiva del embarazo

Resumen

Introducción: *La enfermedad hipertensiva del embarazo (EHE) se ha relacionado con alteraciones en el crecimiento fetal, posiblemente porque afecta la hematopoyesis. El objetivo de este estudio fue analizar las alteraciones hematológicas más frecuentes en los recién nacidos prematuros hijos de madres con EHE.* **Métodos:** *Se llevó a cabo un estudio transversal en recién nacidos de madres con EHE. Se revisaron los hemogramas de 130 neonatos prematuros: 45 madres con hipertensión gestacional, 71 con pre-eclampsia y 14 con síndrome de HELLP (hemólisis, enzimas hepáticas elevadas y bajo recuento de plaquetas). Las cifras de normalidad, condiciones de citosis o citopenia fueron ajustadas a las edades gestacionales. Las diferencias entre los grupos se analizaron con estadística clásica y bayesiana (FB01= relación hipótesis nula/alterna).* **Resultados:** *Se encontró anemia en solo el 1.2% de los recién nacidos. En la serie blanca el hallazgo más frecuente fue la linfopenia (56.2%) y monocitosis (38.5%) (p = 0.6, FB01 = 249 y p = 0.81, FB01 = 19.9). La plaquetopenia se encontró en*

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el 12.5% (p = 0.56, FB01 = 67). No se observaron diferencias significativas entre los grupos de EHE. **Conclusiones:** *Las alteraciones hematológicas en recién nacidos de madres con EHE son frecuentes sin mostrar un patrón distinto con relación a la gravedad del padecimiento de la madre. Aun así, es recomendable la valoración hematológica en estos neonatos.*

Palabras clave: *Hipertensión gestacional. Hemograma. Plaquetopenia. Neonato. Prematuro.*

Introduction

The hypertensive disease is a frequent complication during pregnancy. It is one of the leading causes of maternal and perinatal morbidity and mortality[1-4] and affects approximately 5-10% of pregnancies worldwide. Also, it is more frequent during the first pregnancy and is a risk factor for preterm birth[5].

Although the main cause of this condition is still unknown, it has been related to abnormal trophoblast invasion of the spiral arteries during implantation, leading to reduced placental perfusion, which in turn causes uteroplacental insufficiency and progressive fetal hypoxia from week 20 onwards. This process could explain the complications of the fetus, both during gestation and at birth[2,5,6].

The World Health Organization, the American College of Obstetrics and Gynecology, and the Clinical Practice Guidelines of the Mexican Social Security Institute (IMSS, for its Spanish acronym) classify pregnancy-induced hypertension (PIH) in the following categories[1,3,5,7]:

a) Gestational or arterial hypertension. It occurs after the 20th week of pregnancy or in the first 24 hours after delivery with negative proteinuria and no edema.
b) Preeclampsia. Begins after the 20th week of pregnancy or up to 2 weeks after delivery with blood pressure ≥ 140/90 mmHg, proteinuria > 300 mg/L, elevated serum creatinine (> 30 mg/mmol), and edema.
c) Severe preeclampsia, with blood pressure (systolic/diastolic) ≥ 160/110 mmHg, proteinuria ≥ 2 g/L in 24 hours, oliguria, and target organ involvement (headache, blurred vision, phosphenes, right flank pain, vomiting, papilledema, clonus ≥ 3+, and hepatic hypersensitivity).
d) HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome or complication of severe preeclampsia with the appearance of thrombocytopenia (platelet count < 150,000 mm^3), elevated liver enzymes, and evidence of hemolysis.
e) Eclampsia. Similar to preeclampsia but accompanied by neurological symptoms such as seizures, hyperreflexia, headache, visual disturbances, or coma.

Moreover, preeclampsia fetopathy is defined as the alterations observed in newborns born to mothers with preeclampsia, eclampsia, or HELLP syndrome[5].

The spectrum of neonatal complications is very broad and can range from asymptomatic patients to neonatal death, depending on the severity of the disease. Among the most common complications of the hypertensive disease are low weight for gestational age, intrauterine growth restriction, metabolic disorders (hypo- or hyperglycemia, hypo- or hypermagnesemia, hypocalcemia, and hyperbilirubinemia), respiratory disorders (hyaline membrane syndrome or meconium aspiration syndrome) and hematologic disorders, such as thrombocytopenia, neutropenia, polycythemia, leukopenia, and anemia.

Regarding hematological disorders, an increased risk of thrombocytopenia has been described in these infants, with an incidence between 9-36% of neonates born to mothers with this complication[8], but which can be as high as 47% if there is a history of HELLP syndrome[9]. This thrombocytopenia seems to be related to a decrease in megakaryocyte proliferation and maladaptation of megakaryocytes as a consequence of hypoxia, low birth weight, and prematurity of the neonates[1,4-6]. Furthermore, there is evidence of an effect of fetal hypoxia on increased erythropoietin secretion and increased fetal erythropoiesis. Both are manifested by a 10- to 12-fold increased risk of high hematocrit and polycythemia at birth[1]. As for leukocytes, neutropenia has been reported, attributed to a lower myeloid precursor count with decreased chemotaxis secondary to placental insufficiency, as well as a consequence of early termination of pregnancy. Some authors also report the presence of leukopenia associated with low birth weight[1].

These findings, however, have not been consistent. In other studies, some authors have considered that there is a greater impact on platelets[8,9]; others, on the white blood cells, and others, on the erythrocyte count[1-3]. On this basis, the aim of this study was to analyze the most frequent hematological alterations in preterm neonates born to mothers with PIH.

Methods

We conducted an observational, analytical, and retrospective study, including 130 preterm live newborns (< 37 weeks of gestation (WG)), attended between 2016

and 2018, who met the following selection criteria: maternal history of hypertensive disease of pregnancy or PIH, admitted to our Neonatal Intensive Care Unit (NICU), with complete blood biometry taken within the first 24 hours of life. Neonates with a history of maternal amniotic membrane rupture for more than 12 hours, infants born to mothers with evidence of infection, neonatal sepsis, neonatal jaundice with onset before 12 hours of life, or severe congenital malformations, genetic syndromes, or death were excluded.

The diagnosis and treatment of PIH was performed by the gynecologists in charge of the mother's care based on the Mexican Clinical Practice Guidelines for Obstetric Care. According to the American College of Obstetrics and Gynecology[7], the mothers were classified regarding PIH as A) gestational hypertension; B) preeclampsia (including mild and severe cases); C) HELLP syndrome; and D) eclampsia.

Neonatal blood samples were collected by peripheral venous puncture or during umbilical venous catheter placement and processed with a Beckman Coulter UniCel DxH800 equipment. The definition of the incremental and decremental states for each hematologic line was taken from the gestational age-adjusted criteria[10,11].

Somatometry (weight and height) of each patient was obtained at birth. In addition, the ABO blood group and Rh factor of the binomial were obtained to rule out the possibility of blood incompatibility.

This project was approved by the research and ethics committee of our hospital. It was considered a risk-free study, and all information was handled with anonymity and confidentiality.

Statistical analysis

Qualitative data were summarized as simple and relative frequencies in percentages. Given the number of patients, quantitative variables were summarized as medians and minimum and maximum values. Comparison of proportions and medians was performed using classical and nonparametric statistics (χ^2 and Kruskal-Wallis tests) according to the type of variables. Statistical significance was considered with a p-value < 0.05.

The hypotheses of equality (null H) versus difference (alternative H) were tested with Bayesian statistics. Evidence was considered with the Bayes' factor (null relative to alternative (BF01)). Values from 1 to 3 were defined as anecdotal evidence; from 3 to 10 as moderate evidence; from 10 to 100 as strong evidence, and > 100 as extreme evidence in favor of the null hypothesis. Similarly, 1 to 0.3 was defined as anecdotal; 0.29 to 0.1 as moderate; 0.09 to 0.01 as strong; and < 0.01 as extreme in favor of the alternative hypothesis[12]. An equal probability distribution between the two hypotheses was considered *a priori* (*a priori* uninformative, concentration 1), by default JASP (Jeffreys's Amazing Statistics Program).

Results

Data were collected from 130 neonates born to mothers with the hypertensive disease during pregnancy. There were no patients with severe preeclampsia or eclampsia. We found gestational hypertension in 45 cases (34.6%), preeclampsia in 71 (54.6%), and HELLP syndrome in 14 (10.7%) (Table 1).

Among the groups of neonates, we found differences in the averages (medians) of their weights (statistically significant difference and with still anecdotal evidence in favor of the alternative hypothesis), where the smallest group was that of mothers with preeclampsia (< 200 g). Neither height nor gestational age was different, both with moderate evidence in favor of equality.

Regarding the history of membrane rupture < 12 hours as a risk factor for infection, the events were infrequent (only three cases) and with no differences among groups (extreme evidence in favor of the null hypothesis).

Regarding ABO and Rh group incompatibility, no differences were found compared with the hypertension groups (Table 1).

In the hematological analysis of the neonates (Table 2), we found no polycythemia. The most frequent finding was anemia (in two patients), with extreme evidence in favor of equal proportions.

Regarding white blood cells, we found an alteration in the total count in 10 patients (7.7%), nine with an increase and one with a decrease in the number of white cells (Table 2). However, in the analysis of the proportions of the different cells, we found lymphopenia in 56.2% (73/130) (considered < 40% of the total white blood cell count, adjusted for gestational age), neutrophilia in 43.1% (56/130) and monocytosis in 38.5% (50/130)[11]. For all these alterations, extreme evidence in favor of the null hypothesis of equality between groups was obtained.

Finally, we found alterations in the platelet count in 20 neonates (15.4%), of whom four had thrombocytosis and 16 thrombocytopenia (mild in twelve, from 100 to 150 thousand platelets, and moderate in four neonates,

Table 1. Characteristics of neonates according to the type of pregnancy-induced hypertension

Newborn variable	Gestational hypertension (n = 45)	Preeclampsia (n = 71)	HELLP syndrome (n = 14)	*p*-value and Bayes' factor null/alternative (01)
Female gender	27 (60%)	40 (56%)	5 (35.7%)	$p = 0.27^{+}$ $BF_{01} = 3.7$
Gestational age (weeks*)	33 (29-36)	33 (28-36)	33 (29-35)	$p = 0.83^{++}$ $BF_{01} = 8.1$
Birth weight (g)	1835 (960-3545)	1640 (530-3710)	1815 (1290-2300)	$p = 0.02^{++}$ $BF_{01} = 0.4$
Height at birth (cm)	44.5(35-50)	43(28-51)	44(33-47)	$p = 0.04^{++}$ $BF_{01} = 0.96$
Pre-birth ROM < 12h	1 (2.2%)	2 (2.8%)	0	$p = 0.81^{+}$ $BF_{01} = 118$
Blood group O or Rh incompatibility[a]	10/42 (23.8%)	21/63 (33.3%)	4/14 (28.6%)	$p = 0.57^{++}$ $BF_{01} = 8.4$

*Median (minimum-maximum); $^{+}\chi^2$ with Yates's correction; $^{++}$Kruskal-Wallis.
[a]Blood group of 11 mothers was not available. Previous concentration = 1.
BF_{01}: Bayes' factor, null relative to alternative hypothesis; ROM: rupture of membranes.

from 50 to 100 thousand platelets). Also, the proportion of thrombocytopenia increased with the severity of hypertension (6.7% in gestational hypertension, 14.1% in preeclampsia, and 21.3% in HELLP syndrome, χ^2 trend p = 0.05).

All neonates were discharged alive and without apparent sequelae.

Discussion

Our main hypothesis was to find thrombocytopenia as the most frequent hematological alteration in infants born to mothers with hypertensive disease of pregnancy. We found thrombocytopenia in 12.3% of the studied neonates.

Furthermore, thrombocytopenia seemed to increase according to the severity of the maternal hypertensive state, showing a higher proportion in newborns born to mothers with preeclampsia. However, for more severe situations (HELLP syndrome or eclampsia), this relationship was not evident due to its low incidence, probably associated with better prenatal control and timely care in our institution. This observation is consistent with the study by Okoye et al., who found a higher proportion of thrombocytopenia in neonates born to mothers with PIH compared to infants born to healthy mothers (38% vs. 8%)[1]. However, these authors did not report on the degree of thrombocytopenia, which is considered mild (150,000 to 100,000), moderate (100,000 to 50,000), and severe (< 50,000) according to the platelet count[10,11]. Conversely, Bayoumi et al. reported thrombocytopenia degrees: mild in 13% of neonates born to mothers with PIH compared to 2% in the control group[13]. Tsao et al. also estimated a 36% incidence of mild thrombocytopenia in neonates with the same condition[9]. Finally, in a study by Raizada et al., no statistically significant relationship was detected between the neonatal platelet count and the severity of maternal hypertensive disease[14,15].

As the pathogenesis of thrombocytopenia secondary to hypertensive disease of pregnancy is not yet fully understood, several theories have been proposed. Roberts and Murray postulated that fetal hypoxia has a direct depressive effect on megakaryocytopoiesis and platelet production[16,17]. Castle et al. attribute this to impaired megakaryocyte formation and increased platelet activation mediated by cytokines, thrombopoietin, and interleukin-6 as a consequence of the proinflammatory state in preeclampsia, leading to increased platelet aggregation and destruction, thus reducing platelet counts[17,18]. McDonald et al. suggest the hypothesis—supported by an *in vitro* study—that stem cells compete during fetal hypoxia caused by maternal preeclampsia. In this regard, erythropoietin is increased in the fetus, generating thrombocytopenia by suppressing the megakaryocytic cell line because erythrocytes and megakaryocytes share the same precursor[17,19].

Another factor associated with thrombocytopenia is low birth weight. Chaurasiya et al. found that neonates

Table 2. Blood count alterations in newborns according to the type of pregnancy-induced hypertension

Variable	Gestational hypertension (n = 45)	Preeclampsia (n = 71)	HELLP syndrome (n = 14)	Total (n = 130)	Classical and Bayesian significance
Red blood cells					
Anemia (Hb)	2.2% (1)	1.4% (1)	0	1.5% (2)	p = 0.83
Low htc	2.2% (1)	1.4% (1)	0	1.5% (2)	BF_{01} = 144.5
Polycythemia	0	0	0		
Leukocytes					
Leukocytosis	6.7% (3)	7.1% (5)	7.2% (1)	6.9% (9)	p = 0.92+
Leukopenia	0	1.4% (1)	0	0.8% (1)	BF_{01} = 2526
Normal	93.3% (42)	91.5% (65)	92.8% (13)	92.3% (120)	
Neutrophils					
Neutrophilia	44.4% (20)	40.9% (29)	50% (7)	43.1% (56)	p = 0.97+
Neutropenia	8.9% (4)	8.4% (6)	7.1% (1)	8.5% (11)	BF_{01} = 118
Normal	46.7 (21)	50.7% (36)	42.9% (6)	48.4% (63)	
Bands					
Bandemia	2.2% (1)	2.8% (2)	0	2.3% (3)	p = 0.81+
Normal	97.8% (44)	97.2% (69)	100% (14)	97.7% (127)	BF_{01} = 118.5
Lymphocytes					
Lymphocytosis	0	2.8% (2)	0	1.5% (2)	p = 0.62+
Lymphopenia	53.3% (24)	59.1% (42)	50% (7)	56.2% (73)	BF_{01} = 249
Normal	46.7% (21)	38.1% (27)	50% (7)	42.3% (55)	
Monocytes					
Monocytosis	42.2% (19)	36.6% (26)	35.7% (5)	38.5% (50)	p = 0.81+
Normal	57.8% (26)	63.4% (45)	64.3% (9)	61.5% (80)	BF_{01} = 19.9
Eosinophils					
Eosinophilia	2.2% (1)	2.8% (2)	0	2.3% (3)	p = 0.87+
Eosinopenia	0	1.4% (1)	0	0.8% (1)	BF_{01} = 6695
Normal	97.8% (44)	95.8% (68)	100% (14)	96.9% (126)	
Platelets					
Thrombocytosis	4.4% (2)	1.4% (1)	7.1% (1)	3.1% (4)	p = 0.36+
Thrombocytopenia	6.7% (3)	14.1% (10)	21.3% (3)	12.3% (16)	BF_{01} = 67
Normal	88.9% (40)	84.5% (60)	71.4% (10)	84.6% (110)	

+χ^2 with Yates's correction.
BF_{01}: Bayes' factor, null relative to alternative hypothesis; Hb: hemoglobin; htc: hematocrit.

with low birth weight born to PIH mothers had a 5-fold increased risk of severe thrombocytopenia compared to neonates with adequate birth weight; thus, the authors showed a relationship between prematurity, low birth weight, and thrombocytopenia[15]. The risk of thrombocytopenia has been estimated at values ranging from 2.5 times by Robert and Murray[15,16] to 4.5 times by Bhat and Cherian[8,15]. Finally, Tsao et al. found a significant relationship between extremely low birth weight, PIH, and thrombocytopenia[9,15]. This relationship has been attributed to the pathogenesis of PIH, explaining that inadequate placental implantation generates insufficient blood perfusion that prevents adequate nutrient supply, affecting homeostasis and fetal growth. In our study, we observed the impact on the weight of newborns born to mothers with PIH, especially in mothers with preeclampsia, although the relationship between low birth weight and thrombocytopenia was not analyzed.

As for the other blood cell series, we did not find any alterations related to the red blood cells in this study. Furthermore, no neonate showed evidence of hemolysis, despite having analyzed maternal-fetal compatibility of the ABO and Rh groups. Also, no polycythemia associated with chronic fetal hypoxia due to PIH was observed. This last situation has been reported in previous studies, although with low frequencies[5,9].

Regarding white blood cells, we did not find alterations in the total counts of the patients. However, we observed an alteration in the proportion (percentage) of monocytes (relative monocytosis > 7% of the total white blood cells)[11]. This finding could be explained by the use of steroids as pulmonary maturation agents when it is necessary to terminate pregnancy[1].

The strengths of this study are the availability of hematological studies in all neonates born to mothers with PIH and the homogeneity of the method in the hemogram analysis.

The main limitation of this study was the sample size, as it was insufficient for a more detailed analysis of both blood cell subpopulations and the degree of severity of thrombocytopenia, low birth weight, and hypertensive disease of pregnancy. In addition, the impact of lung maturation factors, the timing of their application, and gestational age at the time of PIH diagnosis should be studied in the future.

In conclusion, we can state that hypertensive disease during pregnancy may increase the risk of alterations in the platelets of neonates at birth, particularly those related to mild to moderate thrombocytopenia. In this study, no alterations in red blood cells or white blood cells were observed.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. This study involved a retrospective review of medical records, for which approval was obtained from a formally constituted review board (Institutional Review Board or Institutional Ethics Committee).

Conflicts of interest

The authors declare no conflict of interest.

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