Original article

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Clinical features, biochemical markers, and acute phase reagents of inflammation in hypertensive crises of pregnancy

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Abstract

***Introduction*: Preeclampsia is a major cause of maternal and fetal morbidity and mortality, accounting for approximately 25% of maternal deaths in Latin America. Preeclampsia is a state of systemic inflammation due to an immunologic imbalance between proinflammatory and regulatory T cells, leading to multiorgan damage.**

***Objective*: To describe the clinical features, biochemical markers, and acute phase reactants of inflammation in hypertensive disorders of pregnancy.**

***Materials and methods*: An observational, cross-sectional, prospective study was conducted in hypertensive pregnant patients hospitalized at the Women's Hospital of Culiacan, Mexico, from March 2021 to January 2022. These patients were classified according to the type of hypertension based on 24-hour urine protein determination. A toxicologic profile including uric acid, lactate dehydrogenase (LDH), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), serum lipids, and total leukocytes was obtained to calculate the neutrophil-lymphocyte ratio of patients in each of the study groups. The body mass index (BMI) was also calculated. Data were analyzed using Stata Intercooled 13.1.**

***Results*: The mean age of the included patients was 25.43±6.5 years, gestational age was 37.35±2.73, 35.9% were primigravida, and 16.07% were adolescents. Among the 397 cases, 23.17% had severe preeclampsia, 24.69% had non-severe pre-eclampsia, 27.2% had gestational hypertension, and 24.94% were healthy controls. Neutrophil-lymphocyte ratio, uric acid, urea, LDH, and CRP were higher in the most severe cases of hypertensive disease. Changes in serum magnesium levels were mainly observed in severe preeclampsia.**

***Conclusions*: In this study, biochemical and inflammatory markers were higher in severe forms of hypertensive disorders of pregnancy.**

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Introduction

Pre-eclampsia is a common cause of maternal and fetal morbidity and mortality. (1) It affects 2-8% of pregnant women worldwide. It accounts for 25% of maternal deaths in Latin America and the Caribbean, a figure that is 9% higher than the rates observed in Africa and Asia. It is the most common but least understood disorder of pregnancy. Pre-eclampsia is a rapidly progressive condition associated with numerous risk factors, particularly genetic factors. (2)

The pathophysiological mechanisms of pre-eclampsia are characterized by a failure of the trophoblastic invasion of the spiral arteries, which may be associated with increased uterine artery vascular resistance and decreased placental perfusion. Typically, hypertension and pre-eclampsia occur in the late second or third trimester of pregnancy. (3-5) In addition, maternal obesity, hypertension, and type 2 diabetes mellitus play an essential role in the development of hypertensive disorders during pregnancy, as do the metabolic abnormalities associated with these risk factors. (6-9) Pre-eclampsia and gestational hypertension share pathophysiological similarities, underscored by comparable effects of oxidative stress, although they diverge due to the lower antioxidant capacity of the latter. The identification of genes associated with these risks remains crucial. (10)

It is unknown how the different types of hypertensive disorders of pregnancy influence systemic inflammation and whether this is manifested by neurological, lipid, hepatic, renal, hematological, and coagulation alterations, most likely due to endothelial dysfunction and/or ischemia at the tissue level. (9) This would indicate that hypertensive disorders of pregnancy have a wide range of manifestations and that we do not yet fully know all the clinical and biochemical characteristics of patients admitted to the obstetric intensive care unit with hypertensive disorders.

This study aimed to describe the clinical and biochemical features and the distribution of inflammatory markers in hypertensive disorders of pregnancy. In addition, we aimed to identify the clinical characteristics associated with admission to the obstetric intensive care unit.

Materials and methods

An observational, cross-sectional, prospective, and descriptive study was conducted by consecutive non-probabilistic sampling in hypertensive pregnant women with a gestational age of more than 20 weeks, hospitalized at the Women's Hospital, Culiacán, Sinaloa, Mexico, from March 2021 to January 2022. Those with gestational age of less than 20 weeks, patients with severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2), sepsis, hematologic disorders, nephropathy, liver disease, and coagulation disorders were excluded.

Study groups

Hypertensive patients with a gestational age of more than 20 weeks were divided into four groups according to 24-hour urine protein determination:

- Group 1 (G1): Healthy pregnant women without hypertension and proteinuria (control group).
- Group 2 (G2): Pregnant women with gestational hypertension with proteinuria <300 mg/dl and systolic blood pressure between 140-160 mmHg and diastolic between 90-110 mmHg.
- Group 3 (G3): Pregnant women with non-severe pre-eclampsia (proteinuria >300 mg/dl without target organ involvement) with systolic blood pressure between 140-160 mmHg and diastolic between 90-110 mmHg.
- Group 4 (G4): Pregnant women with severe pre-eclampsia, with or without proteinuria >300 mg/dl, and systolic blood pressure ≥160 mmHg and diastolic ≥110 mmHg or those with target organ involvement.

Blood pressure measurement

Blood pressure was measured with an automated sphygmomanometer (BEURER GmbH, Söflinger Str. Ulm, Germany). Measurements were taken more than 2 times within the first 4 hours after admission, and those with systolic blood pressure (SBP) ≥140 mmHg and diastolic blood pressure (DBP) ≥90 mmHg were considered hypertensive.

Glycosylated hemoglobin (HbA1c), urea, creatinine, uric acid, lactate dehydrogenase (LDH), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), cholesterol, triglycerides, hemoglobin, and total leukocytes were obtained from all patients.

Statistical analysis

Data were organized and entered into a database containing quantitative and qualitative variables, from which means, medians, standard deviations, and 95% confidence intervals (95% CI) were obtained. ANOVA and Pearson's chi-squared were used to determine differences in means, and logistic regression analysis was used to assess the degree of association between qualitative variables. A p-value<0.05 was considered statistically significant. Data were analyzed using Stata Intercooled 13.1.

Results

The mean age of the patients included in the study was 25.43±6.5 years (median=25), with a mean gestational age of 37.35±2.73 weeks (median=38). Among the included patients, 35.9% were primigravida, and 16.07% were adolescents. Of the total 397 pregnant women, 92 (23.17%) had severe pre-eclampsia, 98 (24.69%) had non-severe pre-eclampsia, 108 (27.2%) had gestational hypertension, and 99 (24.94%) were classified as healthy controls.

The mean values of laboratory parameters were as follows: mean hemoglobin 11.99 g/dl, platelet count 223,692/mm^3, leukocyte count 12,095/mm^3, LDH 217.31±140 IU/l, uric acid 5.02±1.38 mg/dl, CRP of 16.4±24 mg/dl, ESR 38.32±17 mm/h, NLR (neutrophil-to-lymphocyte ratio) 3.7±1.8, 24-hour proteinuria 932.51±1772.7 mg/dl/24 hours, and creatinine 0.7±2.31 mg/dl (Table 1).

In hypertensive patients, LDH correlated significantly with CRP ($r=0.3717$, $p<0.05$), magnesium ($r=0.15$, $p<0.01$), uric acid ($r=0.13$, $p=0.02$), NLR ($r=0.1398$, $p=0.0174$), and body mass index (BMI) ($r=-0.1545$, $p=0.0103$).

Mean arterial pressure (MAP) correlated significantly with CRP ($p=0.00766$) and magnesium levels (0.17, $p=0.0047$); CRP correlated with LDH (0.3717, $p<0.05$), with MAP (-0.1581, $p=0.0066$); uric acid associated with LDH (0.1328, $p=0.0268$) and magnesium (0.1310, $p=0.0380$).

The frequency of thrombocytopenia in healthy and hypertensive patients was 3.05%, hyperuricemia in 63.12%, neurological abnormalities in 31.97%, and hepatic abnormalities in 10.69% (Table 2).

Among the patients admitted to the intensive care unit (ICU), 48.5% had an NLR greater than 4, 40.2% had severe pre-eclampsia, 33.67% had non-severe pre-eclampsia, and 28.97% had gestational hypertension.

There was a total of 34 (8.2%) admissions to the obstetric intensive care unit; 31 cases were attributed to severe pre-eclampsia and 2 to non-severe pre-eclampsia. Characteristics of hypertensive pregnant women associated with ICU admission included thrombocytopenia (OR=44.62; 95% CI 11.3-175.7), MAP>124 mmHg (OR=9.55; 95% CI 4.2-21.6), transaminitis (OR=9.22; 95% CI 4.01-21.24), neurological abnormalities (OR=3.14; 95% CI 1.47-6.72), NLR>5 (OR=3.15; 95% CI 1.50-6.60), and hyperuricemia (OR=2.79; 95% CI 1.10 -7.03).

Discussion

The most common form of hypertensive disease of pregnancy we found was gestational hypertension. Severe pre-eclampsia was observed mainly in primigravida, with a mean age of 25 years. Most of the biochemical abnormalities were observed in patients with severe pre-eclampsia. These included significant elevations in lactate dehydrogenase, uric acid, urea, C-reactive protein, magnesium, NLR, cholesterol, and triglycerides. These abnormalities were most commonly observed during the third trimester of pregnancy. Other investigators have reported that triglycerides, adiponectin, and leptin are higher in women with pre-eclampsia than in healthy women. (11)

LDH showed a weak correlation with CRP in all groups studied; however, it showed a positive correlation, specifically with magnesium, in cases of severe pre-eclampsia. This has been reported in previous studies. (12-14)

LDH is an enzyme in cellular metabolism and is ubiquitous in cells and tissues. It consists of five different isoenzymes, variations that can calibrate the level of cell death and, consequently, the severity of the disease. These levels may fluctuate throughout the stages of pregnancy. Still, specific isoenzymes may be elevated in severe forms due to their different metabolic activities under aerobic and anaerobic conditions, which affect lactic acid metabolism. LDH is a commonly used marker in diagnosing pre-eclampsia. (10,11)

In our study, patients with severe forms of pre-eclampsia had the most severe biochemical abnormalities. Uric acid, urea, LDH, and CRP levels were higher in these patients, indicating a higher degree of cell and/or tissue damage. Furthermore, we observed that these biomarkers correlated better with BMI in patients with gestational hypertension and non-severe pre-eclampsia. This confirms that obesity influences the pathophysiological mechanisms of hypertension more in these cases than in the severe form (15,16).

Magnesium levels correlated with LDH and CRP in cases with severe pre-eclampsia. This has been reported in other studies and attributed to hypomagnesemia promoting oxidative stress and systemic inflammation. (8,17)

Of the ICU admissions, 93% were for severe pre-eclampsia and the remainder for non-severe pre-eclampsia. Most of these patients had biochemical evidence of hyperuricemia as well as neurological abnormalities, MAP greater than 120 mmHg, impaired liver function, and thrombocytopenia.

Conclusions

There was a significant correlation between BMI and gestational hypertension and non-severe pre-eclampsia. LDH, CRP, magnesium, NLR, and uric acid correlated with disease severity in our cohort. Obesity prevention and better control of pregestational and prenatal weight may reduce the incidence of these clinical conditions.

Table 1. Clinical and biochemical characteristics in patients with hypertensive disease of pregnancy

Characteristics (mean)	Healthy (n=95)	Gestational hypertension (n=107)	Non-severe preeclampsia (n=97)	Severe preeclampsia (n=90)	p-value
Age (years)	25.15	25.98	25.81	24.67	0.4794
Weeks of gestation	38.85[a]	37.15	37.08[a,c]	36.28[a,d]	0.0000*
Number of prenatal consultations	-	6.35	5.90	5.88	0.3533
Mean arterial pressure	85.34[a]	104.20[a,b]	107.30[b,c]	114.82[b,c]	0.0000*
Glycosylated hemoglobin	5.70	5.70	6.49	5.55	0.2268
Lactic acid dehydrogenase (IU/l)	-	192.85[b]	190.5[b,c]	272.42[b,c,d]	0.0000*
Creatinine (mg/dl)	0.57	0.56	1.04	0.63	0.4092
Urea (mg/dl)	16.60[a]	16.54[b]	16.90[c]	22.24[a,b,c,d]	0.0000*
Uric acid (mg/dl)	-	4.80[b]	4.90	5.35[b,d]	0.0180
C-reactive protein	-	15.9	13.13	20.54	0.0928
Erythrocyte sedimentation rate (mm/h)	-	39.11	38	38.19	0.9481
Cholesterol (mg/dl)	-	239.82	232.26	246.05	0.4700
Triglycerides (mg/dl)	-	302.25	280.17	302.13	0.6973
Proteinuria in 24 hrs	-	225.04[b]	600.5[c]	1998.9[b,c,d]	0.0000*
Calcium (mEq/l)	-	9.13	8.96	9.66	0.6600
Magnesium (mEq/l)	-	1.79[b]	1.78[c]	2.25[b,c,d]	0.000*
Hemoglobin	12.09	11.93	12	11.96	0.8431
Leukocytes	13,880.83	11,651.30	11,419.5	11,490.87	0.2757
Neutrophil-lymphocyte ratio	3.41[a]	3.39[b]	3.64[c]	4.46[a,b,c,d]	0.0001*
Platelets	227,865.26	227,185.19	229,712.24	208,869.57	0.1353
Fibrinogen (mg/dl)	663.69	704.83	713.99	694.97	0.3909
Body mass index (kg/m^2)	30.27[a]	32.07[b]	33.19[b,c]	31.52[d]	0.0226

Legend: [a]Healthy; [b]Gestational hypertension; [c]Non-severe preeclampsia; [d]Severe preeclampsia; *Statistically significant at 5%.

Table 2. Comorbid conditions/history of patients with hypertensive diseases of pregnancy

Characteristics (number of cases)	Healthy (n=95)	Gestational hyper-tension (n=107)	Non-severe preeclampsia (n=97)	Severe preeclamsia (n=90)	p-value
Primigravida	25	3.4	36	45	0.008
Adolescent	6	19	20	18	0.016
Neurological abnormal-ities	0	45	28	52	0.000*
Thrombocytopenia	1	0	1	10	0.000*
Previous preeclampsia	0	14	11	13	0.002*
Chronic hypertension	4	17	13	9	0.040*
Elevated liver enzymes	0	4	7	20	0.000*
Uric acid ≥4.5 mg/dl	-	61	52	65	0.049*
Caesarean section	6	54	57	84	0.000*
Urinary tract infection	0	42	43	35	0.735
Cervicovaginitis	0	9	10	8	0.885
Admission to obstetric ICU	1	0	2	31	0.000*
BMI>30	43	58	59	43	0.300
Pregestational diabetes mellitus	0	3	6	1	0.145
Gestational diabetes mellitus	0	18	13	3	0.009*

Legend: ICU=obstetric intensive care unit; BMI=body mass index; *Statistically significant at 5%.

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