Sepsis and Neutropenia in Very Low Birth Weight Infants Delivered of Mothers with Preeclampsia

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Objective To study the association between maternal preeclampsia and neonatal sepsis in very low birth weight newborns.

Study design We studied all infants with birth weights between 500 g and 1500 g who were admitted to 6 neonatal intensive care units of the Brazilian Network on Neonatal Research for 2 years. Exclusion criteria were major malformations, death in the delivery room, and maternal chronic hypertension. Absolute neutrophil count was performed in the first 72 hours of life.

Results A total of 911 very low birth weight infants (preeclampsia, 308; non-preeclampsia, 603) were included. The preeclampsia group had significantly higher gestational age, more cesarean deliveries, antenatal steroid, central catheters, total parenteral nutrition, and neutropenia, and less rupture of membranes >18 hours and mechanical ventilation. Both groups had similar incidences of early sepsis (4.6% and 4.2% in preeclampsia and non-preeclampsia groups, respectively) and late sepsis (24% and 22.1% in preeclampsia and non- preeclampsia groups, respectively). Vaginal delivery and neutropenia were associated with multiple logistic regressions with early sepsis, and mechanical ventilation, central catheter, and total parenteral nutrition were associated with late sepsis. Death was associated with neutropenia in very preterm infants.

Conclusions Preeclampsia did not increase neonatal sepsis in very low birth weight infants, and death was associated with neutropenia in very preterm infants. *(J Pediatr 2010;157:434-8)*.

Maternal preeclampsia is a frequent cause of very preterm birth,[1] and in developing countries, spontaneous preterm delivery and hypertensive disorders are the most important determinants of perinatal death.[2] Infection is an important cause of serious illness and death for very low birth weight (VLBW) infants (birth weight ≤1500 g).[3]

Reports on the association of sepsis, neutropenia, and gestational hypertensive disorders show conflicting results.[4-9] Some data suggest a high incidence of neutropenia in infants of mothers with preeclampsia and an association with neonatal sepsis. These studies of small patient populations were conducted >10 years ago and included late preterm infants and VLBW infants. The incidence of sepsis in VLBW infants is high,[3] and there are no large studies of the effect of preeclampsia on the incidence of sepsis in VLBW infants. This study of the Brazilian Network on Neonatal Research was undertaken to determine whether there is an association between maternal preeclampsia and neonatal sepsis.

Methods

This multicenter study enrolled VLBW infants born in 6 academic public neonatal intensive care units (NICUs) of the Brazilian Network on Neonatal Research during a period of 2 years. At each NICU, 2 or 3 neonatologists prospectively collected the data on a Web-based data system specially designed for Brazilian Neonatal Research Network. The study was approved by the ethical committee of each participant NICU and by the ethical committee of the Hospital de Clinicas de Porto Alegre, Porto Alegre, Brazil, the leading center for this study.

Preterm infants born with birth weights from 500 to 1500 g from January 2006 to December 2007 were included. We did not include infants with major congenital anomalies, infants who died in the delivery room, and infants whose mothers had chronic hypertension without preeclampsia during the gestational period.

ANC	Absolute neutrophil count
NICHD	National Institute of Child Health and Human Development
NICU	Neonatal intensive care unit
rhG-CSF	Recombinant human granulocyte colony-stimulating factor
VLBW	Very low birth weight

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VLBW infants were divided in preeclamptic (delivered of mothers with preeclampsia) and control (all the neonates without maternal preeclampsia) groups. Diagnosis of maternal preeclampsia was arterial hypertension (blood pressure ≥140 mm Hg systolic, ≥90 mm Hg diastolic, or both) developing after 20 weeks gestation with proteinuria >300 mg in a 24-hour urine sample and edema with no other cause for the symptoms.[10]

Data obtained for all infants included: birth weight, gestational age, mode of delivery, small for gestational age, sex, antenatal use of corticosteroid, time of rupture of membranes, Apgar score at 5 minutes of life, total parenteral nutrition use, percutaneous central catheter use, use of mechanical ventilation, post-natal use of corticosteroid, Score for Neonatal Acute Physiology-Perinatal Extension-II, first total absolute neutrophil count (ANC) in the first 72 hours of life, early-onset and late-onset sepsis, and death during hospital stay. The complete blood count was obtained as deemed necessary by the clinicians caring for the infants. The ANCs were performed with a Sysmex 2100 instrument (TOA Medical Eletronic, Kobe, Japan).

Gestational age was evaluated by using the date of the last menstrual period and confirmed with early obstetrical ultrasound scanning and neonatal clinical examination. Small for gestational age was defined as a birth weight <10th percentile.[11] Sepsis was diagnosed on the basis of the presence of clinical findings and positive results on blood culture tests in the first 72 hours of life for early-onset sepsis or after 72 hours of life for late-onset sepsis. The diagnosis of clinical sepsis was based on the presence of ≥3 of these symptoms: apnea, difficult breathing, cyanosis, tachycardia or bradycardia, perfusion deficit, or shock; irritability, lethargy, hypotonia, and seizures; abdominal distention, vomiting, dietary intolerance, gastric residue, hepatomegaly, idiopathic jaundice, thermal instability, petechiae, or purpura; and a general poor appearance. The diagnosis of pneumonia was based on Centers for Disease Control criteria for clinically defined pneumonia in children <1 year old.[12] Infants were considered to have neutropenia when the total ANC was <1500/mm^3 in the first 72 hours, according to Mouzinho et al.[13]

Statistical Analysis

Descriptive analyses were performed with demographic and clinical variables of all patients. Continuous variables were described as means plus or minus SD, and categorical variables were described as number and percentage. Comparisons between groups were performed with the 2-tailed χ^2 test for categorical variables and Student *t* test for continuous variables. Univariate analysis was performed, and the presence of preeclampsia and other clinical significant variables with a *P* value <.05 were included in multiple logistic regression models. Differences were considered significant when *P* values were <.05. Statistical analysis was performed with SPSS for Windows version 13.0 (Statistical Package for Social Sciences; SPSS Inc., Chicago, Illinois).

Results

A total of 911 infants fulfilled the criteria for inclusion in the study; the mean gestational age and birth weight of the studied population were 30.2 ± 2.8 weeks and 1072 ± 274 g. Preeclamptic and control groups included 308 and 603 newborn infants, respectively.

Of the 911 patients, 727 (79.8%) underwent the first ANC in the first 24 hours, 125 (13.7%) underwent the first ANC between 24 and 72 hours, and 59 (6.4%; 22 and 37 preeclamptic and control groups, respectively) did not undergo a total ANC in the first 72 hours.

Table I. Demographic and clinical characteristics of the study population

	Preeclampsia group	Control group	*P* value
n	308	603	
Gestational age (weeks)	30.8 ± 2.5	29.9 ± 3.0	.0001
Birth weight (grams)	1077 ± 280	1063 ± 260	.48
Vaginal delivery	27 (8.9%)	285 (46.3%)	.0001
Small for gestational age	232 (75.3%)	290 (48.1%)	.0001
Male	157 (51%)	292 (48.4%)	.241
Antenatal corticosteroid	185 (60.1%)	270 (44.7%)	.0001
Rupture of membranes >18 hours	12 (3.9%)	141 (23.4%)	.0001
Apgar score at 5 minutes	9 (7-9)	8 (7-9)	.001
Mechanical ventilation	185 (60.1%)	423 (70.1%)	.003
Total parenteral nutrition	283 (91.9%)	511(84.5%)	.002
Central catheter	217 (70.5%)	364 (60.4%)	.002
Post natal corticosteroid	23 (7.5%)	29 (4.8)	.071
SNAPPE II	13 (5-31)	17 (5-36)	.088
Neutropenia (<1500 neutrophil)	52 (16.9%)	65 (10.8%)	.008
Early onset sepsis	14 (4.6%)	25 (4.2%)	.863
Late onset sepsis	74 (24.0%)	133 (22.1%)	.505
Pneumonia	45 (14.6%)	109 (18%)	.187
Death	66 (21.4%)	165 (27.4%)	.054

Values expressed as mean ± SD, median (p25-p75), absolute number (%) with Student *t* test, χ^2, and Mann-Whitney test.

Table II. Sepsis, death, and neutropenia in neonates in preeclamptic and control groups according to stratification by gestational age

	Preeclampsia group	Control group	*P* value
Early-onset sepsis			
≤27 weeks	1/29	6/138	.826
28-31 weeks	7/153	18/291	.489
≥32 weeks	6/126	1/174	.044
Late-onset sepsis			
≤27 weeks	9/29	34/138	.233
28-31 weeks	46/153	77/291	.483
≥32 weeks	19/126	22/174	.157
Pneumonia			
≤27 weeks	6/29	22/138	.583
28-31 weeks	32/153	71/291	.410
≥32 weeks	7/126	16/174	.281
Death			
≤27 weeks	21/29	85/138	.271
28-31 weeks	35/153	69/291	.643
≥32 weeks	10/126	11/174	.589
Neutropenia			
≤27 weeks	10/25	18/125	.003
28-31 weeks	29/147	33/283	.024
≥32 weeks	13/114	14/158	.489

n/total with χ^2 and Fisher exact tests.