Maternal Preeclampsia Protects Preterm Infants against Severe Retinopathy of Prematurity

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Objective To study the influence of maternal preeclampsia on the occurrence of retinopathy of prematurity.
Study design A prospective cohort study of 324 preterm neonates with birth weight ≤1500 g and gestational age ≤32 weeks. Multiple maternal and perinatal factors were analyzed for association and confounding by multiple logistic regression analysis.
Results Mean birth weight was 1128 ± 240 g, and mean gestational age 29.7 ± 1.9 weeks. Twenty-four newborns (7.4%) had severe retinopathy of prematurity; 97 had any stage of retinopathy, and 227 had no retinopathy of prematurity. Preeclampsia and complete antenatal steroid treatment course reduced the risk for any stage of retinopathy of prematurity by 60% and 54%, respectively. Preeclampsia reduced the risk for severe retinopathy of prematurity by 80%.
Conclusions Preeclampsia lowered the risk for occurrence of any stage and severe retinopathy of prematurity in very low birth weight infants. *(J Pediatr 2011;158:372-6)*.

Maternal preeclampsia is a frequent cause of prematurity. Retinopathy of prematurity (ROP) remains one of the leading causes of preventable childhood blindness. ROP occurs frequently in middle-income countries where improvements in the perinatal care have increased survival rates of very low birth weight (VLBW) infants. ROP pathogenesis has evolved over 50 years. Initially the uncontrolled use of oxygen therapy was mainly responsible for ROP. More recently, risk factors for ROP are low birth weight and short gestational age.[1] ROP rates differ perhaps related to geographic areas, genetics differences, or environmental susceptibility.[2-7] Many studies have evaluated postnatal factors that contribute to ROP. On the other hand, antenatal or maternal risk factors have been minimally studied.[8,9]

Gotsch et al[10] reported an antiangiogenic state in patients with preeclampsia resulting from changes in the concentrations of circulating angiogenic factors. Because ROP is a vasoproliferative disease, an antiangiogenic state in mothers with preeclampsia might protect the infant for ROP. An association between preeclampsia and ROP has not been reported. We evaluated maternal and perinatal factors for their association with the development of any stage and severe ROP, and if these factors were independent of the birth weight and gestational age.

Methods

A prospective cohort study included all preterm infants screened for ROP with birth weight ≤1500 g and gestational age ≤32 weeks at birth. The mothers were admitted to Hospital de Clínicas de Porto Alegre between October 2002 and July 2009.

The study included all preterm infants screened for ROP who survived until the initial ophthalmologic examination performed between the 4th and 6th week after birth. The infants were examined at 45 weeks postmenstrual age (postmenstrual age = gestational age at birth + weeks of life) or until effective stabilization of retinopathy was achieved after treatment. The data were prospectively collected, and there were no exclusion criteria. All patients had eye examinations, consisting of binocular indirect ophthalmoscopy after pupil dilation in both eyes with 0.5% tropicamide and 2.5% phenylephrine eye drops, with a 28-diopter lens (Nikon, Melville, New York), and a newborn infant eyelid speculum (Alfonso Eye Speculum; Storz, Bausch & Lomb Inc, San Dimas, California). Scleral indentation was performed when necessary. Screening sessions were performed and scheduled according to the Brazilian guidelines to detect and treat ROP. Subsequent examinations were determined by the findings in the first examination.[11,12]

Clinical outcomes included the onset of any stage of ROP and development of ROP requiring treatment. ROP was classified according to the 1984/1987 International Classification of ROP in stages 1 to 5.[13,14] Threshold ROP was defined as 5 contiguous or 8 cumulative clock hours of stage 3 ROP with plus disease in zone I or II,

IVH	Intraventricular hemorrhage
ROP	Retinopathy of prematurity
SGA	Small for gestational age
VEGF	Vascular endothelial growth factor
VLBW	Very low birth weight

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Table I. Univariate analysis of the risk factors for any stage of ROP and for severe ROP

Maternal and perinatal variables	No ROP (n = 227)	Any stage ROP (n = 97)	*P* value for any stage ROP	No ROP plus ROP 1 and 2 (n = 300)	Severe ROP (n = 24)	*P* value for severe ROP
Maternal age	27.6 ± 7.3	26.2 ± 7.6	.138	27.1 ± 7.4	28.4 ± 7.4	.414
Antenatal steroid treatment	105 (46.3%)	32 (33.0%)	.037	126 (42.0%)	11 (45.8%)	.880
Preeclampsia	78 (34.4%)	14 (14.4%)	<.001	90 (30.0%)	2 (8.3%)	.042
Essential hypertension	31 (13.7%)	4 (4.1%)	.019	33 (11.0%)	2 (8.3%)	.950
Prior premature birth	18 (7.9%)	6 (6.2%)	.751	23 (7.7%)	1 (4.2%)	.822
Number of prenatal attendances	274 ± 3	274 ± 3	.530	274 ± 3	274 ± 3	.894
Vaginal delivery	49 (21.6%)	32 (33.0%)	.042	74 (24.7%)	7 (29.2%)	.806
Gestational age (weeks)	30.0 ± 1.7	28.9 ± 2.1	<.001	29.8 ± 1.8	27.9 ± 2.2	<.001
Birth weight (grams)	1170 ± 220	1028 ± 255	<.001	1145 ± 232	908 ± 232	<.001
Apgar score at 5th min	7.8 ± 1.8	7.7 ± 1.5	.697	7.8 ± 1.7	7.6 ± 1.7	.582
Small for gestational age	103 (45.4%)	33 (34.0%)	.076	127 (42.3%)	9 (37.5%)	.805
Male sex	108 (47.6%)	34 (35.1%)	.050	131 (43.7%)	11 (45.8%)	1.000
Multiple gestation	42 (18.5%)	22 (22.7%)	.476	59 (19.7%)	5 (20.8%)	1.000
Oxygen therapy in nasal CPAP	182 (80.2%)	76 (78.4%)	.823	238 (79.3)	20 (83.3%)	.838
Oxygen therapy in mechanical ventilation	109 (48.0%)	59 (60.8%)	.046	153 (51.0%)	15 (62.5%)	.383
Indomethacin	66 (29.1%)	41 (42.3%)	.029	98 (32.7%)	9 (37.5%)	.796
Surfactant	108 (47.6%)	52 (53.6%)	.383	146 (48.7%)	14 (58.3%)	.484
Erythropoietin	192 (85.0%)	79 (81.4%)	.534	251 (83.9%)	20 (83.3%)	1.000
Blood transfusion	122 (53.7%)	80 (82.5%)	<.001	178 (59.3%)	24 (100.0%)	<.001
Any grade of intraventricular hemorrhage	33 (14.5%)	24 (24.7%)	.040	49 (16.3%)	8 (14.0%)	.049
Sepsis	149 (65.6%)	72 (74.2%)	.164	202 (67.3%)	19 (79.2%)	.382
Meningitis	16 (7.0%)	5 (5.2%)	.698	18 (6.0%)	3 (12.5%)	.416
Persistent ductus arteriosus	23 (10.1%)	17 (17.5%)	.095	37 (12.3%)	3 (12.5%)	1.000

N (%); mean ± standard deviation.
Obs: If Bonferroni corrections for multiples variables were applied the new corrected *P* value for significance should be $P < .002$.
CPAP, continuous positive airway pressure.

according to the Multicenter Trial of Cryotherapy for Retinopathy of Prematurity.[15] During data collection, the Revisited International Classification of ROP was published. Subsequently all treated patients had a retrospective ROP classification according to this new classification.[16] All treatments were performed at threshold ROP. Severe ROP meant treatable ROP at any stage 3 with plus, or threshold ROP, and stages 4 or 5. All eye examinations were performed by a single author.

Maternal variables were age, number of prenatal visits, use of antenatal steroid, occurrence of preeclampsia, essential hypertension, type of delivery, and previous preterm birth. Antenatal steroid treatment was defined as the completion of 2 doses of betamethasone 24 hours apart or 4 doses of dexamethasone given 12 hours apart more than 24 hours before delivery. The diagnosis of preeclampsia required arterial hypertension (blood pressure ≥140 mm Hg systolic and ≥90 mm Hg diastolic) developing after 20 weeks gestation and proteinuria >300 mg in a 24-hour urine sample in the absence of previous hypertension or kidney disease.[17]

Postnatal variables were birth weight, gestational age (evaluated by obstetric history, early obstetric ultrasound, and confirmed by newborn infant clinical examination), small for gestational age (SGA) (<10th percentile), sex, single or multiple gestations, Apgar score at 5 minutes, oxygen therapy by nasal continuous positive airway pressure or mechanical ventilation, erythropoietin, indomethacin, surfactant, blood transfusions, and presence of sepsis, meningitis, persistent ductus arteriosus, and any grade of intraventricular hemorrhage (IVH) diagnosed by cerebral ultrasonography. Sepsis and meningitis were defined by clinical examination and/or microbiological culture. Clinical sepsis was based on the presence of three or more of the following: apnea, difficult breathing, cyanosis, tachycardia, or bradycardia, shock; irritability, lethargy, hypotonia, and seizures; abdominal distention, vomiting, dietary intolerance, gastric residue, hepatomegaly, idiopathic jaundice, thermal instability, petechiae, or purpura; and general poor appearance.

Statistical Analyses

We used SPSS software (version 14.0 for Windows; SPSS Inc, Chicago, Illinois). Student's *t* test, χ^2 and Mann-Whitney test were used to compare patients with versus without ROP. We included clinical variables that were statistically significantly associated with ROP ($P < .05$) in multiple logistic regression models. Bonferroni correction for the *P* value was not used in this study. The study protocol was approved by the Research Ethics Committee of Hospital de Clínicas de Porto Alegre.

Results

During the period of the study 515 patients with birth weight ≤ 1500 g and gestational age ≤32 weeks were admitted to the neonatal intensive care unit. Before the initial ophthalmologic examination, 158 died. Of the 357 surviving VLBW infants, 324 (91%) were included in the study. The infants had a mean birth weight 1.128 ± 240 g and a mean gestational age 29.7 ± 1.9 weeks. One hundred forty-two (43.8%) were male, and 136 were SGA (42%). One hundred thirty-seven (42.3%) received a complete antenatal steroid course, 222 (75.5%) were delivered by cesarean-section, and 92 (28.4%) had maternal preeclampsia. Mean gestational

ages of newborns delivered of non-preeclamptic and preeclamptic mothers were similar (29.6 ± 1.9 weeks and 30.0 ± 1.6 weeks, respectively; $P = .95$).

We diagnosed any stage of ROP in 97 (29.9%) patients: 41 stage 1, 32 stage 2, 22 stage 3, 1 stage 4, and 1 stage 5. Severe ROP developed in 24 patients, and 22 were from nonpreeclamptic pregnancies ($P = .024$). Only 23 patients were treated by transpupillary diode laser photocoagulation for threshold ROP; one had progression to stage 4A ROP despite two laser photocoagulation treatments. This patient required scleral buckle to stop ROP progression. One patient missed the treatment appointment and developed stage 5. None of the treated patients had ROP in zone 1.

After univariate analysis any stage of ROP was associated with less antenatal steroid treatment, less maternal preeclampsia, and essential hypertension. Lower gestational age and birth weight, use of mechanical ventilation, indomethacin, blood transfusions, and any grade of IVH were associated with more ROP (**Table I**). By univariate analysis VLBW infants with severe ROP had less maternal preeclampsia, lower gestational age and birth weight, more blood transfusions, and more any grade of IVH (**Table I**).

Variables included in the multiple logistic regression model for any stage of ROP were gestational age and SGA, maternal preeclampsia, antenatal steroid treatment, essential hypertension, any stage of intraventricular hemorrhage, mechanical ventilation, indomethacin, blood transfusion, and vaginal delivery. Low gestational age and blood transfusion were significant risk factors; maternal preeclampsia; and antenatal steroid treatment reduced risk by 60% and 54%, respectively (**Table II**). Variables included in a multiple logistic regression model for severe ROP were gestational age and SGA, maternal preeclampsia, any stage of intraventricular hemorrhage, and blood transfusion. Low gestational and SGA were risk factors; and maternal preeclampsia reduced risk by 80% (**Table II**).

Table II. Adjusted logistic regression for any stage and for severe ROP

	OR	95% CI	*P* value
For any stage of ROP			
Gestational age (weeks)	0.779	0.656-0.925	.004
Maternal preeclampsia	0.406	0.202-0.817	.012
Antenatal steroid treatment	0.559	0.320-0.978	.042
Essential hypertension	0.459	0.147-1.431	.180
Any grade of intraventricular hemorrhage	1.251	0.628-2.492	.524
Use of oxygen in mechanical ventilation	1.202	0.668-2.162	.539
Use of indomethacin	1.434	0.793-2.595	.233
Blood transfusion	2.901	1.533-5.490	.001
Vaginal delivery	0.712	0.388-1.307	.272
Small for gestational age	1.399	0.727-2.693	.315
For severe ROP			
Gestational age (weeks)	0.561	0.427-0.738	<.001
Maternal preeclampsia	0.202	0.043-0.944	.042
Any stage of intraventricular hemorrhage	1.936	0.708-5.294	.198
Blood transfusion	3.012	0.826-10.985	.095
Small for gestational age	4.377	1.348-14.208	.014

Discussion

The incidence of any stage of ROP and severe ROP was 29.9% and 7.4%, respectively. This ROP rate is low, even for countries with established standards of excellence in perinatal care.[18,19] Complete antenatal steroid treatment and maternal preeclampsia were protective factors for any stage of ROP, and maternal preeclampsia was the only significant protective factor for severe ROP needing treatment in VLBW infants.

The high prevalence of SGA in our study was the result of using birth weight as a cutoff point even for newborns with 32 weeks' gestational age. In this study, SGA was not independently associated with development of any stage of ROP (**Table II**) as we previously reported.[20] It was, however, independently associated with severe ROP (**Table II**), as reported by others.[21,22]

Low gestational age and birth weight was associated with ROP in most studies. Both are considered the most important risk factors for ROP in different populations and in different countries.[1,23] Our results agree; they also provide information about antenatal risk factors that associate with ROP. Preeclampsia or antenatal steroid treatment was protective from any stage ROP.

Preeclampsia is linked to maternal and perinatal rates of mortality, morbidity, and prematurity.[24] Holmström et al,[25] in a population-based study, reported that maternal preeclampsia was less frequent in the non-ROP group, but the difference was not statistically significant. Seibert and Linderkamp[9] reported that maternal preeclampsia and lung maturation induced with antenatal betamethasone were associated with lower incidence of ROP. They suggested that maternal preeclampsia and hypertension mature VLBW infants and maternal stress increases cortisol.[9] A retrospective study included maternal preeclampsia as a main risk factor for development of ROP, although none of the newborns delivered by preeclamptic mothers needed surgical treatment.[26] The Italian ROP Study Group reported the importance of antenatal steroid treatment for respiratory distress syndrome in VLBW infants and the highly significant protective effect of this therapy for ROP.[27] Improvement of respiratory function would decrease the need of oxygen therapy and secondarily the occurrence of ROP. Our data showed decreased development of ROP in VLBW infants delivered by preeclamptic mothers or after antenatal steroid therapy, independently of oxygen therapy. We suggest that intrauterine stress matures neonatal retinal vasculature preventing ROP.

A hypothesis for the pathogenesis of preeclampsia is the "ischemic model"; a reduced placental blood flow causes decreased fetal growth and intrauterine growth restriction[28,29] in patients who are likely to have development of ROP, peripheral retinal vessel growth, or are totally interrupted after premature birth, resulting in a nonvascular and hypoxic peripheral retina (phase 1 of ROP). The proliferative phase of disease occurs because of ischemia. Lack of retinal perfusion in the early phase of ROP determines the subsequent degree of neovascularization, i.e., the severity of disease.[30] Vascular

endothelial growth factor (VEGF) is a potent angiogenic factor necessary for normal growth of blood vessels that is associated with undesired retinal neovascularization.[31] The hyperoxia experienced by the neonate after a preterm birth promotes a reduction in VEGF expression and induces a vaso-obliteration state due to endothelial cell apoptosis. As the retina matures and becomes hypoxic because of vascular growth interruption, VEGF level increases progressively to cause the undesired retinal neovascularization (phase 2 of ROP). Inhibition of VEGF at this phase cannot prevent retinal neovascularization proving that ROP is a multifactorial disease.[31-33]

Gotsch et al[10] reported an antiangiogenic state in patients with preeclampsia. They detected changes in the circulating angiogenic factors concentrations, especially soluble Tie-2. ROP is a vasoproliferative disease and an antiangiogenic state in maternal preeclampsia could protect from ROP. We found that maternal preeclampsia was a protective factor for ROP that reduced the need for laser treatment. We speculate that some antiangiogenic factor produced by preeclamptic mother may cross the placenta barrier to the fetus. As with maternal antibody, it could remain circulating and acting on the retina for several months. There is a temporal sequence of abnormal Doppler changes in the peripheral and central circulatory systems of the fetus delivered of preeclamptic mothers, and those changes also occur in cerebral circulation and retinal vessels.[34] We suggest that those circulatory changes plus modifications of factors involved in angiogenesis could prevent the development of ROP in preterm infants.

The limitation of our study is the lack of information on retinal circulatory changes that may occur in very preterm infants delivered of preeclamptic mothers. Normal blood flow velocity and Doppler indexes of the ophthalmic arteries from birth to hospital discharge of inborn infants with birth weights between 500 and 1500 g and gestational age $\leq$ 32 weeks were just published and could be used as standard for the study population.[35] The importance of our study is the demonstration that VLBW infants delivered by preeclamptic mothers have 60% reduction in risk for any stage of ROP, and 80% reduction in risk for severe ROP. ■

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50 Years Ago in *THE JOURNAL OF PEDIATRICS*

Turner's Syndrome in the Male

Steiker DD, Mellman MJ, Bongionvanni AM, Eberlein WR, Leboeuf G. J Pediatr 1961;58:321-9

Although described clinically more than two decades earlier, the recognition that most patients with Turner syndrome (TS) were "chromatin negative" emerged only 7 years before this report. Using the "nuclear sexing" system, the interpretation of the absence of Barr bodies (sex chromatin), based on the 1947 Jost experiments in rabbits, was that individuals with TS were genetic males who had undergone prenatal castration resulting in female genitalia and gonadal dysgenesis. Demonstration of the 45, X karyotype and admonition that such persons be considered female with an abnormal genotype rather than a "chromosomal male" or case of "sex reversal" appeared only 2 years before Steiker et al reported their five cases of apparent TS in males. Thus, it is easy to understand their confusion regarding the relationship between these boys and the classic triad of sexual infantilism, congenital webbed neck, and cubitus valgus that comprised the initial description of girls with TS. Not only is a female phenotype now part of its definition, but the manifestations of TS are believed to be primarily caused by haploinsufficiency of one or more of the multitude of genes on the X chromosome, such as SHOX.

A likely candidate for what was presumed male Turner syndrome is Noonan syndrome, which is caused by PTPN11 deletions in ~50% of cases. Although one or more of the five boys probably had Noonan syndrome, it is unlikely that they all did, given the disparate phenotypes. Distinguishing among children with overlapping features such as short stature, abnormal auricles, high arched palate, low posterior hairline, and short or webbed neck was surely a challenge 50 years ago, and, despite advances in molecular and clinical genetics, sometimes remains one to this day. The authors are to be commended for attempting to reconcile a bewildering set of observations, causing them to go so far as to suggest that the features of TS were unrelated to the emblematic chromosomal pattern. This insinuation might seem preposterous to us today, but we should remember the importance of an open mind and consider every conceivable explanation for our findings until the inexorable process of scientific discovery allows the "truth" to become illuminated.

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