New-Onset Maternal Gestational Hypertension and Risk of Retinopathy of Prematurity

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Purpose. To evaluate associations between conditions of maternal new-onset gestational hypertension (mHTN) and the features imparting risk of severe retinopathy of prematurity (ROP) in preterm infants.

Methods. Hospital databases and charts of all preterm inborn infants at the University of North Carolina from 1996 to 2007 were retrospectively reviewed. The presence or absence of mHTN (e.g., pre-eclampsia) and infant factors (birthweight, gestational age, erythropoietin use, and zone and stage of ROP) were analyzed for independence of association.

Results. Of the 5143 infants, 323 had ROP and 76 had mothers with mHTN. Infants with ROP were more likely to have mothers with mHTN and to be younger and smaller at birth. At initial examination, more infants of mothers with mHTN had vascularization into the lower zones than did infants of mothers without mHTN ($P < 0.001$). However, at the examination in which the most severe ROP was present, there was no association between mHTN and ROP stage ($P = 0.2342$). Analysis of stage and zone together showed that infants born to mothers with mHTN were more likely to have ROP at initial examination, after adjustment for gestational age, but not for birth weight. The use of erythropoietin was not associated with ROP zone or stage, even after adjustment for maternal condition, infant birth weight, or gestational age.

Conclusions. Although larger avascular areas or higher severity scores were associated with mHTN after adjustment for gestational age at initial examination, no associations were found between mHTN and ROP severity score at the examination when ROP was most severe. There were no associations between ROP severity and treatment with erythropoietin. (*Invest Ophthalmol Vis Sci.* 2010;51:4983–4988) DOI:10.1167/iovs.10-5283

With the increase in preterm births in the United States and throughout the world, retinopathy of prematurity (ROP) has become a leading cause of childhood blindness.[1] It has been recognized that young gestational age and low birth weight are associated with greater risk of severe ROP and blindness, and screening in the United States is thus recommended for preterm infants born at less than 32 weeks' gestational age or less than 1500 g birth weight.[2] In recent studies, however, the greater risk of severe ROP has been associated with not only low birth weight, but also perinatal factors that may lead to poor weight gain after birth.[3]

Conditions of maternal gestational hypertension include pre-eclampsia, eclampsia, and HELLP syndrome (hypertension, elevated liver enzymes, and low platelets). These clinically significant obstetric complications are estimated to affect nearly 5% of all pregnancies and represent a spectrum of clinical signs that include new onset of maternal hypertension, proteinuria, and edema.[4] If not managed properly, these conditions can progress to maternal seizures, antepartum hemorrhage, placenta abruption, coma or death, and premature fetal delivery and/or death. Further, these conditions are associated with low infant birth weight, and pre-eclampsia has been independently associated with growth restriction.[5] Recent studies suggest that mothers with pre-eclampsia have elevated levels of circulating antiangiogenic factors, such as the soluble fms-like tyrosine kinase 1 (s-flt1)[6] and endoglin (a co-receptor of TGFβ1)[7] and reduced levels of bioactive proangiogenic factors, such as vascular endothelial growth factor (VEGF), and placental growth factor (PlGF).[8,9] In addition, prospective studies have demonstrated that altered concentrations of angiogenic factors were sensitive predictors of pre-eclampsia.[6] Since the intrauterine environment is essential for the developing fetus, uteroplacental insufficiency in conditions such as pre-eclampsia may lead to altered fetal vascular programming and both short- and long-term complications.

ROP develops after birth in preterm infants. Repeated longitudinal examinations of the infant fundus are performed to detect either mature retinal vascularization or the development of ROP. The area of retinal vascular development is defined as the zone, with the lowest zone (zone I) being those with the smallest area of vascularized retina and therefore, those with the largest area of avascular retina. At initial examination, retinal vascular development may be incomplete, with no ROP present. However, as developmental angiogenesis proceeds, ROP may manifest as different levels of disease severity.[10] We postulated that conditions of new-onset maternal hypertension (including pre-eclampsia) may increase the severity of ROP by interfering with the infant's retinal vascular development, evidenced as a smaller zone at first examination, and thereby increase the risk of severe ROP, evidenced by higher stage of disease at the examination in which the most severe disease is noted ("worst" examination).

To investigate, we evaluated associations between the presence of maternal gestational conditions of hypertension (pre-eclampsia, eclampsia, or HELLP syndrome) and infant ROP. The few studies in which these possible associations have been investigated have reported conflicting conclusions.[11,12] We explored these relationships further in a sample of infants larger than that studied in other efforts[11,12] and born and cared for at one institution. We also evaluated the effect of recombinant erythropoietin, used for anemia of prematurity,[13,14] since, contradictory to recent clinical studies that report a positive association of severe ROP with erythropoietin administra-

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tion,[15,16] murine models of oxygen-induced retinopathy show that erythropoietin has a protective effect if administered before a hyperoxic insult.[17]

METHODS

Design and Infant Data Collection

This clinical study was approved by the University of North Carolina (UNC) at Chapel Hill School of Medicine's Committee on the Protection of the Rights of Human Subjects and Institutional Review Board, and all research adhered to the tenets of the Declaration of Helsinki.

This study was a retrospective review of hospital records for all preterm infants born at UNC from April 1996 to October 2007. Only infants born at 37 weeks' gestation or less were screened for analysis, since this is the maximum gestational age that most pregnancies are allowed to reach before delivery if the mother has a maternal gestational condition of hypertension. Existing hospital databases from the UNC Neonatal Critical Care Center (NCCC) and Labor and Delivery Unit and infant medical records were reviewed.

Eye examinations in the UNC NCCC were performed, based on the published screening recommendations for ROP,[2] including screening all infants born smaller than 1500 g or at a gestational age of 30 weeks or less, as well as selected infants between 1500 and 2000 g birth weight or a gestational age of more than 30 weeks who had an unstable clinical course.[2] In infants born earlier than or at 27 weeks' gestation, the initial examination was performed at 31 weeks' postgestational age. For infants older than 27 weeks' gestational age, the initial examination was performed 4 weeks after birth. For infants with unstable courses, the initial examination was sometimes postponed to 6 weeks after birth. All screened infants had examinations performed before discharge from the hospital.

For funduscopic examination, infants underwent pupillary dilation with an ophthalmic solution of cyclopentolate and phenylephrine (Cyclomydril; Alcon Laboratories, Forth Worth, TX) and indirect ophthalmoscopy with scleral depression at the bedside.[2,10] Follow-up examinations were based on the presence of ROP and performed as recommended.[10,18] The date and results of the examination in which the most advanced ROP (highest stage) was observed that developed during the infant's course in the NCCC was designated the worst examination.

The severity of ROP was based on the International Classification of ROP (ICROP).[19] The zone of ROP indicates the extent of intraretinal vascularization that occurs during retinal vascular development. Zone I comprised a circle centered on the optic nerve that had a radius equal to twice the distance from the optic nerve to the fovea and had the greatest area of avascular retina. Zone II was a circle centered on the optic nerve, the radius of which equaled the distance from the optic nerve to the nasal ora serrata, and zone III was the remaining temporal crescent. For the purpose of analysis in this study, we expanded the ICROP classification and designated eyes with mature vascularization as zone IV. The stage of ROP reflected the level of severity of disease. For analysis, we expanded the ICROP classification and designated no ROP as stage 0. Stage 1 was a line; stage 2 a ridge; stage 3 intravitreous neovascularization; and stages 4 and 5 incomplete and complete retinal detachment, respectively.

Data from the initial examinations of the infants were collected from their hospital charts, since the data were not available in the NCCC database. Data from follow-up examinations were included in the NCCC database and were used for abstracting data for the worst examinations, except for three infants who met the screening criteria but did not have recorded birth weights. Infant birth weight and gestational age were common to both examinations. For the initial examination, the ROP zone and stage of the eye with the lower zone were recorded. For the worst examination, the zones and stages of both eyes were reviewed, and the worse stage and lower zone of either eye was recorded for each infant from hospital databases. Infants who did not meet the criteria for ROP screening were assigned zone IV, stage 0. Whether an infant had received erythropoietin treatment was included with the data collected on the worst examination. Before January 2004, infant oxygen saturations were kept between 98% and 100%, as best as possible, whereas after January 1, 2004, saturations were maintained at 90% to 96% in infants less than 31 weeks' postgestational age. Approximately 25% of the total number of study subjects, and 31% of infants found to have the potential for ROP, were born after 2004 and were managed with these updated oxygen administration protocols.

Data on maternal diagnosis was also obtained from the NCCC database. Maternal care for new onset maternal gestational hypertension (pre-eclampsia, eclampsia, and HELLP syndrome) had been provided by the UNC neonatology teams as soon as the mothers were identified. All infants studied were born at UNC.

Definitions of Variables

A dichotomous outcome variable was used to describe the presence or potential to develop ROP versus the absence of ROP, for the descriptive statistics. Infants were classified as having ROP if either eye had stage 1 or greater ROP or had incomplete retinal vascularization, (zone < IV). Only infants with stage 0 and zone IV ROP in both eyes were grouped into the category of having no ROP. Therefore, some infants with stage 0 ROP were grouped with those having ROP, because they had the potential to develop ROP as long as their retinas were incompletely vascularized. Infants were also categorized by whether they had been born to mothers having a condition of new-onset gestational hypertension (i.e., pre-eclampsia, eclampsia, or HELLP syndrome) (yes/no) and whether they received erythropoietin therapy (yes/no). Infant birth weight was categorized as follows: ≤700 g, >700 and ≤1000 g, and >1000 g. Gestational age was categorized as ≤27 weeks versus >27 weeks.

Subsequent exploratory analyses were conducted with an ordinal outcome variable that combined zone and stage into a ROP severity score for each infant. The categories for this variable are presented in Table 1. Having stage 0 and zone IV denoted the least severe, and having stage 2 or 3 in either zone I or II denoted having the greatest severity of ROP.

Statistical Analysis

Differences in percentages (or means) of birth weights or gestational ages in each category were assessed between groups of infants with and without ROP using binomial tests and *t*-tests. For assessing associations between the presence or absence of gestational hypertension or previous erythropoietin therapy and the outcomes of zone, stage, and the ROP severity score, Mantel-Haenszel raw mean score statistics were calculated and χ^2 tests performed on these statistics. When considering multivariate analyses, which adjusted for birth weight or gestational age, Extended Mantel-Haenszel raw mean score statistics were used. In calculating these statistics, modified ridit scores were used, because the outcome categories were not thought to be equally spaced. All tests were two-sided with $\alpha = 0.05$ (SAS 9.2; SAS Institute, Cary, NC).

TABLE 1. Categorization of Stage and Zone into Ordinal ROP Severity Variables

	Stage 0 (no ROP)	Stage 1	Stage 2	Stage 3
Zone IV (fully vascularized)	1	X	X	X
Zone III	2	2	2	2
Zone II	3	3	4	4
Zone I	3	3	4	4

Level 1 is least severe, and level 4 is most severe. X, no Zone IV eyes had any stage of ROP by definition.

TABLE 2. Characteristics of the Study Population

	Initial Examination (n = 4993)				Worst Examination (n = 5140)			
	ROP (n = 175)		No ROP (n = 4818)		ROP (n = 322)		No ROP (n = 4818)	
	mHTN (n = 52)	No mHTN (n = 123)	mHTN (n = 912)	No mHTN (n = 3906)	mHTN (n = 76)	No mHTN (n = 246)	mHTN (n = 912)	No mHTN (n = 3906)
Birth weight, g								
≤700	20 (39)	25 (20)	36 (4)	132 (3)	27 (36)	54 (22)	36 (4)	132 (3)
>700 to ≤1000	22 (42)	57 (46)	94 (10)	205 (5)	36 (47)	117 (48)	94 (10)	205 (5)
>1000	10 (19)	41 (33)	782 (86)	3569 (91)	13 (17)	75 (30)	782 (86)	3569 (91)
Mean (SD)	823 (291.41)	948 (276.60)	1725 (699.82)	2145 (798.41)	815 (264.80)	930 (305.39)	1725 (699.82)	2145 (798.41)
	Initial Examination (n = 4996)				Worst Examination (n = 5143)			
	ROP (n = 176)		No ROP (n = 4820)		ROP (n = 323)		No ROP (n = 4820)	
	mHTN (n = 52)	No mHTN (n = 124)	mHTN (n = 912)	No mHTN (n = 3908)	mHTN (n = 76)	No mHTN (n = 247)	mHTN (n = 912)	No mHTN (n = 3908)
Gestational age, wk								
≤27	22 (42)	83 (67)	60 (7)	317 (8)	34 (45)	165 (67)	60 (7)	317 (8)
>27	30 (58)	41 (33)	852 (93)	3591 (92)	42 (55)	82 (33)	852 (93)	3591 (92)
Mean (SD)	28 (2.44)	27 (2.40)	32 (2.92)	33 (3.49)	28 (2.00)	27 (2.53)	32 (2.92)	33 (3.49)
Erythropoietin received								
Yes	14 (73)	37 (30)	—	—	22 (29)	67 (27)	—	—
No	38 (27)	87 (70)	—	—	54 (71)	180 (73)	—	—

Data are expressed as n (%), except where noted. mHTN, maternal new-onset gestational hypertension.

RESULTS

During the study period, 4996 preterm infants where identified as having an initial examination, and 5143 infants were identified as having a worst examination. At the time of their initial examination, 176 (3.5%) of 4996 infants were classified as having ROP. Of these 176 infants with ROP, 52 (29.5%) were born to mothers with new-onset gestational hypertension that included a diagnosis of preeclampsia, eclampsia, or HELLP syndrome.

At the time of their worst examination, 323 (6.3%) of 5143 infants were classified as having ROP. Of these 323 infants with ROP, 76 (24%) were born to mothers with new-onset gestational hypertension that included a diagnosis of preeclampsia, eclampsia, or HELLP syndrome. The remaining 4820 infants had fully vascularized retinas and were classified as not having ROP (Table 2).

The majority of the infants, particularly infants with ROP, were <30 weeks' gestational age (>73% of infants; data not shown). Among mothers who had new-onset gestational hypertension, the percentage of infants of gestational age ≤27 weeks was greater among infants with ROP than among those without ROP at the initial examination (42% vs. 7%, $P < 0.001$; Table 2). Among mothers who did not have new-onset gestational hypertension, the percentage of infants with gestational age ≤27 weeks was also greater among infants with ROP than without ROP at the initial examination (67% vs. 8%, $P < 0.001$). In addition, mean gestational ages were lower in infants with ROP than in those without at the initial examination, both in infants from mothers with new-onset gestational hypertension (28 vs. 32, $P < 0.001$) and in infants from mothers without gestational hypertension (27 vs. 33, $P < 0.001$). Similar relationships were observed at the time of the worst examination (Table 2).

Among mothers who had new-onset gestational hypertension, the percentage of infants with birth weight ≤700 g was greater among infants with ROP than among those without ROP at the initial examination (39% vs. 4%, $P < 0.001$; Table 2). Among mothers who did not have new-onset gestational hypertension, the percentage of infants with birth weight ≤700 g was also greater among infants with ROP than without ROP at the initial examination (20% vs. 3%, $P < 0.001$). In addition, mean birth weights were lower in infants with ROP than without ROP at the initial examination for both infants from mothers with new-onset gestational hypertension (823 g vs. 1725 g, $P < 0.001$) and infants from mothers without gestational hypertension (948 g vs. 2145 g, $P < 0.001$). A similar relationship was observed for birth weights between 700 and 1000 g, as well as at the worst examination (Table 2).

To examine the effect of new-onset maternal gestational hypertension on ROP severity, we first looked at whether maternal hypertension was associated with lower zone at the initial examination (Table 3). The percentages of infants with lower zone tended to be slightly higher (e.g., 2% vs. 1% for zone I, 3% vs. 2% for zone II) if they were born to mothers with gestational hypertension than if they were born to mothers without gestational hypertension ($P < 0.001$). Statistical significance remained after adjustment for gestational age categories, with the association being stronger in infants >27 weeks than in infants ≤27 weeks (data not shown). However, after adjustment for birth weight categories, the association became nonsignificant ($P = 0.2273$). Examination of only those infants

TABLE 3. Infants in Each Zone at Initial Examination by Maternal New-Onset Hypertension Status

	I	II	III	IV	Total
Hypertension	19 (2)	33 (3)	0 (0)	912 (95)	964
No hypertension	40 (1)	74 (2)	10 (0)	3908 (97)	4032

Data are expressed as frequencies (percentages) in each zone. Unadjusted, $P < 0.001$; after adjustment for birth weight categories, $P = 0.2273$; after adjustment for gestational age categories, $P < 0.001$.

Table 4. Infants with Zone < IV in Each Stage ROP at Worst Examination by Maternal New-Onset Hypertension Status

	0	1	2	3	Total
Hypertension	3 (5)	25 (38)	27 (42)	10 (15)	65
No hypertension	12 (6)	55 (28)	88 (45)	40 (21)	195

Data are expressed as frequencies (percentages) at each stage. Unadjusted, $P = 0.2342$; after adjustment for birth weight categories, $P = 0.0130$; after adjustment for gestational age categories, $P = 0.8237$.

<32 weeks or <1500 g birth weight ($n = 1728$) showed in a similar distribution of zones: 89% for zone IV and maternal hypertension versus 90% for zone IV and no maternal hypertension. This association was not significant ($P = 0.3262$; data not shown).

At the time of the worst examination, we found there to be no association between maternal hypertension and ROP stage in infants who had zone < IV ($P = 0.2342$, Table 4). There was no statistical evidence for the association after adjustment for gestational age ($P = 0.8237$). However, after adjustment for birth weight, marginal statistical significance was achieved ($P = 0.0130$), with the strength of the association between maternal hypertension and ROP being primarily due to an observed association in infants weighing >700 and ≤1000 g at birth (data not shown).

We further explored the association between new-onset maternal gestational hypertension and ROP severity by using a severity score that combined zone and stage (Table 1). At the time of the initial examination, we found there to be an association between gestational hypertension and ROP severity ($P < 0.001$). The association remained after adjustment for gestational age, but no evidence of an association was found after adjustment for birth weight ($P = 0.6786$). Using the ROP severity score at the time of the worst examination, we did not find any evidence of an association between gestational hypertension and ROP severity ($P = 0.2024$) as well as after adjustment for gestational age ($P = 0.6555$) or birth weight ($P = 0.2643$).

Tables 5 and 6 display the percentages of infants in each zone (for the initial examination) and with each ROP disease stage (for the worst examination), by whether the infant received erythropoietin therapy. Whereas there appeared to be a slightly higher percentage of infants in zone I in the erythropoietin group compared with the group that did not receive erythropoietin (16% vs. 10%), there was no evidence of an overall association between erythropoietin treatment and zone at the initial examination ($P = 0.3735$). When the analysis was limited to infants with zone < IV at the worst examination, there was no evidence that erythropoietin therapy was associated with ROP disease stage ($P = 0.8478$). When ROP severity score was taken as the outcome, the lack of statistical association persisted ($P = 0.8104$). Adjustment for each of birth weight, gestational age, and gestational hypertension alone did not change the results appreciably (data not shown).

Table 5. Infants in Each Zone at Worst Examination by Erythropoietin Therapy Status

	I	II	III	IV	Total
EPO	9 (10)	55 (62)	8 (9)	17 (19)	89
No EPO	38 (16)	135 (58)	15 (6)	46 (20)	234

Data are expressed as frequencies (percentages) in each zone. Unadjusted, $P = 0.3735$.

Table 6. Infants with Zone < IV in Each Stage ROP at Worst Examination by Erythropoietin Therapy Status

	0	1	2	3	Total
Erythropoietin	3 (4)	23 (32)	32 (45)	14 (19)	72
No erythropoietin	12 (7)	57 (30)	83 (44)	36 (19)	188

Data are expressed as frequencies (percentages) at each stage. Unadjusted, $P = 0.8478$.

Discussion

Uteroplacental insufficiency present in pregnant women with pre-eclampsia, eclampsia, or HELLP syndrome may lead to vascular compromise in the developing fetus.[4,20] Few studies have been performed to determine the associations of these conditions with ROP severity, and the reports are conflicting. Shah et al.[11] reported that maternal pre-eclampsia was predictive of ROP in very-low-birth weight infants, whereas Seiberth and Linderkamp[12] reported maternal pre-eclampsia was associated with reduced incidence rates of ROP. Therefore, it remains unclear if conditions of new-onset maternal hypertension affect the fetus' developing retinal vasculature and lead to ROP. To explore this, we reviewed all infants at our institution who were born prematurely at <37 weeks of gestation over the course of 11 years. Among them, we found a rare patient cohort of 76 infants, revealing an incidence rate of approximately 7 infants per year.

In pre-eclampsia, maternal antiangiogenic factors have been reported to be elevated and proangiogenic growth factors to be reduced.[4,21,22] One antiangiogenic factor that has been studied is s-flt-1, a soluble splice variant of vascular endothelial growth factor receptor 1 (VEGFR1). s-flt-1 can bind VEGF and prevent it from signaling through its receptors.[22] Some of the symptoms associated with pre-eclampsia are similar to the side effects reported from systemic inhibition of VEGF—namely, hypertension, proteinuria, and vascular events.[23] Angiogenesis is necessary for fetal vasculogenesis, angiogenesis, and development. Elevated maternal s-flt-1 could interfere with infant development, including retinal vascular development, if s-flt-1 were to cross into the fetal circulation at an effective concentration. In the retina, this may manifest as larger areas of peripheral avascular retina (i.e., lower zones) on initial examinations and higher stages and more severe ROP at later examinations when ROP develops. It remains unclear to what extent elevated maternal levels of antiangiogenic factors, including s-flt-1, can cross through the placenta and into the fetal circulation. Pregnant rodents treated with s-flt-1 as a means to model manifestations of preeclampsia yielded mixed results.[24–26] Offspring demonstrated mild growth retardation, but these effects were limited to male mice, and treatment did not affect vascular patterning and development in neonatal mice.[25] However, lower concentrations of s-flt-1 may also have more profound effects on retinal vessels, which are small and support a complex, developing retinal structure, particularly in preterm infants.

Postgestational age has been closely correlated with severity of ROP[27] regardless of infant gestational age or birth weight. Infants born at 27 weeks' gestation or younger usually have their first examinations performed at 31 weeks' postgestational age, whereas those born at or older than 28 weeks gestation are examined at older ages, based on guidelines.[2] Infants born to mothers with conditions of new-onset gestational hypertension were more likely to have lower zones on initial examinations than infants born to mothers without new-onset gestational hypertension. After adjustment for gestational age but not birth weight, a significant association was still found be-

tween greater infant severity score and maternal diagnosis of new-onset gestational hypertension at the initial examination. These results support the hypothesis that maternal conditions leading to pre-eclampsia are associated with a greater potential for infants to develop ROP. Still, it does not show an association independent of low birth weight. However, at the worst examination, no significant associations were found between severity of ROP and maternal condition in unadjusted analyses or analyses adjusted for birth weight or gestational age.

Recombinant erythropoietin has been used to treat anemia of prematurity[13,14] and has been associated with increased risk of severe ROP.[15,16] However, erythropoietin has also been shown to reduce avascular retina if given before a hyperoxic insult in a mouse model of oxygen-induced retinopathy.[17] Therefore, we sought to determine whether there is an association between erythropoietin use and the severity of ROP in infants born to mothers with new-onset gestational hypertension. However, we found no associations between the use of erythropoietin and ROP severity, even after accounting for maternal condition.

Other investigators have suggested that in response to a hypoxic intrauterine environment from reduced levels of circulating proangiogenic growth factors in pre-eclampsia, the development of the fetal retinal vasculature may actually be accelerated. Hadi and Hobbs[28] demonstrated that when infants are under chronic intrauterine stress, either from maternal hypertension or pre-eclampsia, there is accelerated maturation of the tunica vasculosa of the lens in the anterior compartment. It was hypothesized that hypoxia-mediated stabilization of transcription factors, such as hypoxia-inducible factor (HIF)-1α, led to increased fetal expression of molecules, such as VEGF, erythropoietin, and glucose transporter-1.[29] These and other factors were then postulated to accelerate the maturation of the retinal vasculature, thus reducing the potential for ROP to develop. Our results at the time points of retinal examination did not provide support for accelerated vascularization.

This was a retrospective study of a rare patient cohort of infants with ROP born to mothers with new-onset gestational hypertension. The low numbers of infants with ROP born to mothers with new-onset gestational hypertension may have limited the power of the analysis. Not all initial examination records were accessible through existing databases and patient hospital charts; however, care was taken to consider the analyses of initial and worst examinations separately. ROP was classified based on stages and zones abstracted from retinal drawings without the benefit of wide-angle fundus imaging. The study may also have had unrecognized confounding variables because of the long duration of the study period from 1996 to 2007, during which significant advances were made in the screening and treatment algorithms for both maternal gestational hypertension and infant ROP. One change was in infant oxygen saturation. The number of infants born to mothers with new-onset maternal hypertension in these subgroups, defined by oxygen protocol, was too small for meaningful analyses. The effect of oxygen should be addressed in larger studies. All study participants were from a single tertiary center, and therefore treatments of both new-onset maternal hypertension and preterm infants were initiated at the time of diagnosis, and little variability within the individual neonatologists' practices was anticipated. Finally, our study grouped maternal pre-eclampsia, eclampsia, and HELLP syndrome under the same disease category to obtain a large enough study sample for analysis. A more precise analysis would stratify infants to each of these conditions; however, this would have further limited the sample size and decreased the power.

In conclusion, the results of this study indicate that conditions of new-onset maternal gestational hypertension, such as pre-eclampsia, were associated with lower zone at initial examinations for ROP but were not associated with an increased severity of ROP at the worst examination. Furthermore, the use of erythropoietin did not have an effect on ROP severity, even when maternal condition was considered. Future studies of larger databases are needed and may provide greater insight into the relationships of these maternal conditions and severity of infant ROP.

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