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The effect of maternal hypertension on mortality in infants 22, 29 weeks gestation

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ABSTRACT

Objective: To evaluate the effect of maternal hypertension on mortality risk prior to discharge, in infants 22 + 0 to 29 + 6 weeks gestational age.

Study design: We evaluated 88,275 North American infants whose births were recorded in Vermont Oxford Network centers between 2008 and 2011 Infants born between 22 + 0 and 29 + 6 weeks gestational age were evaluated in 2-week gestational age cohorts and followed until death or discharge. Logistic regression was used to adjust for birth weight, antenatal steroid exposure, infant sex, maternal race, inborn/outborn, prenatal care and birth year.

Results: 21,896 infants were born to hypertensive mothers; 13% died prior to Neonatal Intensive Care Unit discharge compared to 20% of the 66,379 infants born to mothers without hypertension. After adjustment, infants had significantly lower mortality compared to preterm infants not born to hypertensive mothers, at all gestational ages examined (22/23: odds ratio (OR) = 0.65 (95% Confidence Interval (CI): 0.55, 0.77; 24/25); OR = 0.77 (95% CI: 0.71, 0.84); 26/27: OR = 0.66 (95% CI: 0.59, 0.74); 28/29: OR = 0.58 (95% CI: 0.51, 0.67). Additionally, births associated with maternal hypertension increase dramatically by gestational age, resulting in a larger proportion of births associated with maternal hypertension at later gestational ages.

Conclusions: Preterm birth due to any cause carries significant risk of mortality, especially at the earliest of viable gestational ages. Maternal hypertension independently influences mortality, with lower odds of mortality seen in infants born to hypertensive mothers, after adjustment, and should be taken into consideration as an element in counseling parents.

1. Introduction

Neonatal mortality in the very low birth weight (VLBW) population declined considerably in the early 1990s, but has since leveled off [1–4]. Declines in neonatal mortality rates have been attributed to improvements in prenatal monitoring and perinatal care, including widespread use of surfactant and antenatal steroid therapies [5,6]. However, infants born at the lowest gestational ages (GA) face high rates of mortality and serious morbidities, often with life-long health problems stemming from premature birth [7–9]. In the United States, the preterm delivery rate has increased from 9% in 1981 to 12.5% in 2004; approximately 20% of preterm births occur prior to 31 weeks gestation [10]. Lower GA and lower BW are both associated with increased mortality rates. Between 2000 and 2009, 49.2% of infants recorded in the Vermont Oxford Network (VON) who were born with a birth weight (BW) of 501, 1500 g, died or suffered a severe neonatal morbidity [11].

Hypertension, including diagnoses of chronic and gestational, preeclampsia, eclampsia, and HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets), complicates as many as 15% of pregnancies in the United States [12]. Chronic hypertension, defined as hypertension existing prior to 20 weeks gestation, is

Abbreviations: CI, Confidence Interval; GA, gestational age; IUGR, intrauterine growth restriction; NICU, Neonatal Intensive Care Unit; OR, odds ratio; pPROM, preterm premature rupture of membranes; VON, Vermont Oxford Network; VLBW, very low birth weight.

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associated with adverse pregnancy outcomes including intrauterine growth restriction (IUGR), stillbirth, placental abruption, and premature birth. In 2004, approximately 1.7% of pregnancies were complicated by chronic hypertension [13]. Women with chronic hypertension have an 8-fold higher risk of developing superimposed preeclampsia compared to the general population, and are twice as likely to experience adverse neonatal outcomes [14]. Preeclampsia, characterized by new onset high blood pressure and abnormal laboratory tests, develops after 20 weeks gestation and is a leading cause of both maternal mortality and perinatal morbidity and mortality, affects an additional 3–5% of pregnancies [15]. Whether maternal hypertension affects outcome in preterm infants is debated, with some studies stating hypertension in pregnancy is associated with an increased risk of mortality, while other studies suggest either no association or a decreased risk [16–22]. The VON uses the broad definition of either a singular systolic reading of >140 or diastolic of >90 mmHg to define maternal hypertension in order to pragmatically identify all cases.

We examined the hypothesis that infants born to mothers with hypertension will have a lower mortality rate than infants who are delivered without an association with maternal hypertension, after adjusting for maternal and perinatal covariates. Preterm births are attributed to a short list of generalized causes: spontaneous preterm labor (40–45% of births), preterm premature rupture of membranes (pPROM) (25–30% of births), or delivery for fetal or maternal indications (30–35%), where maternal hypertension is a leading cause. As many as 25–40% of preterm births are attributed to intrauterine infection, particularly those manifesting as spontaneous preterm labor and pPROM, with rates as high as 50% for births occurring prior to 28 weeks GA [23]. In this context, subclinical infection may often contribute a pro-inflammatory uterine environment, such that preterm births of unknown etiology are potentially influenced by subclinical inflammation. This difference likely impacts the risk profile of differing infants, with maternal hypertension having a lower risk of mortality than comparison infants.

2. Materials and methods

Infants born at GA 22 + 0 to 29 + 6 were identified as a part of the VON VLBW database. The VLBW database is a data repository, begun in 1990, in which all reporting centers within the VON submit observational clinical care and outcome data for infants born in or transferred to member centers, between 401 and 1500 g or 22 + 0 and 29 + 6 weeks GA [24]. Beginning in 2008, the first obstetric factors, including dichotomous variables for maternal hypertension and diagnosis of chorioamnionitis were collected [25]. For this reason this analysis is limited to births occurring during calendar years 2008 through 2011. Inclusion was limited to infants born in the 667 North American centers. Infants from multiple gestations were excluded as multiple gestation is a risk factor for both preterm birth and maternal hypertension, likely due to different maternal physiologic adaptations specific to pregnancy of multiple gestations. As mortality was our primary outcome of interest, infants with chromosomal abnormalities and birth defects with associated high rates of mortality were excluded ($n = 4288$) [26]. The University of Vermont Institutional Review Board approved the database for research purposes.

The VON database defines maternal hypertension as a single reading above 140 systolic or 90 diastolic, prior to or during the pregnancy that is identified in the maternal medical record at the time of delivery presentation. These cases may or may not have had other diagnostic criteria of preeclampsia, such as proteinuria or other end-organ involvement. Mortality is defined as death prior to hospital discharge. Infants born in VON centers are classified as inborn. Those born elsewhere and transferred to a VON reporting center within the first 28 days of life are classified as outborn. All transferred infants are tracked for survival status until final hospital discharge. Antenatal steroid administration is coded when dosing was administered at any time prior to delivery. Prenatal care refers to documentation of any prenatal visits.

Differences in initial demographic characteristics between infants born to hypertensive mothers versus those born to non-hypertensive mothers were examined using chi square tests and *t*-tests. GA cohorts were created in 2-week increments: 22/23, 24/25, 26/27, and 28/29 to account for differences in developmental maturity and obstetric management practices with advancing gestation. Observed mortality rates between infants born to mothers with and without hypertension were compared within each GA cohort. Logistic regression was used to estimate the independent effect of hypertension on infant mortality. Additional covariates in the model were infant sex, maternal race, inborn/outborn status, antenatal steroid exposure, prenatal care, and BW. These covariates were chosen due to their association with mortality and prior inclusion in VON models [11,27]. Standardized rates of mortality were computed based on the derived logistic regression model. These estimates represent the rates that would be observed in infants born to hypertensive mothers and the comparison group if the two groups had identical covariate distributions equivalent to the population used to derive the model. All regression analyses were based on generalized estimating equations (GEE) that accounted for the clustering of infants within hospital [28]. Odds ratios are reported with 95% Confidence Intervals (CI). All analyses were performed using SAS Statistical Software Version 9.3 (SAS Institute, Cary, NC) with statistical significance determined using $\alpha = .05$.

3. Results

Infants identified from the VON VLWB database as having been born between 22 + 0 and 29 + 6 weeks GA between 2008 and 2011 yielded a study population of 88,275 infants. They were evenly distributed by birth year. The population was skewed toward more mature infants, as evidenced by higher GA, with 3.2% of births occurring at 22 weeks, 7.1% at 23 weeks, 11.3% at 24 weeks, 12.4% at 25 weeks, 13.7% at 26 weeks, 15.6% at 27 weeks, 17.7% at 28 weeks, and 19.1% at 28 weeks. Infants born to hypertensive mothers included 21,896 infants, approximately 25% of the total, with representative rates increasing with increasing GA (Fig. 1).

Infants born to hypertensive mothers were significantly smaller than infants born to non-hypertensive mothers in all GA cohorts (22/23: mean HTN = 500.1 ± 124.6, no HTN = 558.4 ± 98.7 g; 24/25: HTN = 605.4 ± 163.0, no HTN = 732.8 ± 134.4; 26/27: HTN = 785.8 ± 186.1, no HTN = 967.5 ± 181.4; 28/29: HTN = 1040.3 ± 226.3, no HTN = 1244.8 ± 232.2 g (all p's < .001) (Table 1).

Univariate analyses indicated odds of mortality for HTN infants relative to other infants as being GA dependent, with a reduced rate of mortality at 22/23 weeks (OR 0.82, 95% CI 0.71, 0.97), increased risk of mortality at 24/25 weeks (OR 1.26, 95% CI 1.17, 1.36), increased risk at 26/27 (OR 1.10, 95% CI 1.00, 0.20), and reduced odds at 28/29 weeks (OR 0.88, 95% CI 0.77, 0.99). Delivery room deaths accounted for 54.6% of deaths at 22/23 week, 10.9% of 24/25 week, 6.1% of 26/27 week, and 6.4% of 28/29 week infants. Adjusting by BW alone resulted in a reduced odds estimate of mortality at all GAs (Table 2).

Multivariate analysis allowed for a more complete risk assessment adjusting for the many factors known to contribute to neonatal mortality: BW, infant sex, maternal race, inborn/outborn, antenatal steroids, and prenatal care. Omission of BW from our logistic models resulted in projected ORs of mortality prior to