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Maternal Hypertension Influences Mortality and Severe Morbidity in Infants Born Extremely Preterm

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MATERNAL HYPERTENSION INFLUENCES MORTALITY AND SEVERE
MORBIDITY IN INFANTS BORN EXTREMELY PRETERM

A Dissertation Presented

by

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ABSTRACT

Worldwide, more than 1 million infants die as a result of premature birth. In the United States, where 1 in 10 births occurs preterm, premature birth is the leading cause of infant mortality. Premature infants have high rates of mortality and morbidity, with the highest rates seen in those infants born extremely preterm—prior to 30 weeks gestation. Severe morbidity in these infants often contributes to life-long health problems. Maternal hypertension (HTN) is one contributor to preterm birth and also contributes to fetal growth restriction, resulting in birth weights which are small for gestational age (SGA, and generally within the lowest 10th percentile). Within this high risk population, SGA infants have increased risk of mortality compared to appropriate for gestational age infants. Therefore the impact of maternal HTN on neonatal outcome might be presumed to be negative. Previous studies however, have been contradictory, with both higher and lower rates of infant mortality reported in infants born to mothers with HTN, as well as differing reports analyzing the relationship between serious morbidity and maternal HTN.

Utilizing the Vermont Oxford Network Very Low Birth Weight database, a collaborative database of Level III Neonatal Intensive Care Units across the world, 88,275 North American infants born between 22+0 and 29+6 weeks gestational age between 2008 and 2011 were identified. This dissertation explores the relationship between maternal HTN and gestational age at time of birth within this population, and the reported rates of morbidity and mortality in infants born prior to 30 weeks gestation. The independent contributions of maternal HTN with neonatal morbidity and mortality in our population were estimated using logistic regression and adjusting for factors previously known to be associated with risk, including birth weight, antenatal steroid exposure, infant sex, maternal race/ethnicity, prenatal care, inborn/outborn status, and birth year. We hypothesized that mortality rates would be lower for infants born to mothers with HTN compared to those born due to other factors, when corrected for the noted confounding variables and surviving infants would have better prognoses, as evidenced by lower rates of severe morbidity, including bronchopulmonary dysplasia, intraventricular hemorrhage, periventricular leukomalacia, necrotizing enterocolitis, and infection. Within the higher-risk SGA population, we hypothesized that mortality rates would be higher than observed in appropriately grown infants, but decreased in those born to mothers with HTN, despite the association between maternal HTN and SGA.

This dissertation begins with an explanation of current knowledge about preterm birth, maternal HTN, and their associations. Chapter 2 focuses on the relationship between maternal HTN and infant mortality in extremely preterm infants. Chapter 3 examines the risk associated with severe morbidities in surviving infants. In addition, we also use a combined morbidity risk assessment score which has previously been used to determine future risk of long term disability. In Chapter 4, SGA infants are separately evaluated for their risk of mortality and the association with maternal HTN.

These analyses support the high mortality and morbidity rates seen in extremely preterm infants. Maternal HTN, after adjustment, results in reduced risk of both mortality and severe morbidities in infants compared to infants born to mothers with other underlying contributors to preterm birth. This suggests that clinical practices and parental counseling should reflect differing risk profiles in sub-populations of extremely preterm infants.

CITATIONS

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CHAPTER 1: MATERNAL HYPERTENSION INFLUENCES MORTALITY AND MORBIDITY IN EXTREMELY PRETERM INFANTS

1.1. Preterm Birth

Preterm birth rates in developed countries that track population data, including the United States, United Kingdom, and Scandinavian countries, demonstrate dramatic increases in preterm birth rates over the past 20 years.^{1,2} This is attributed to an increase in multiple births, use of artificial reproductive therapy for conception, an increase in elderly primiparas, as well as changes in clinical practice which result in higher cesarean-sections and better identification of gestational age due to early pregnancy ultrasound dating. It is estimated that 9.6% of all births occur prior to 37 weeks gestation, with 85% of those occurring in Africa and Asia. Additionally, over half a million preterm births occur in each Europe and North America, and 900,000 in Latin America and the Caribbean.³ The observed preterm birth rate in North America was 11.4% of all births in 2014.⁴

Despite comprising a relatively low percentage of total births, more than 28% of neonatal deaths are attributed to preterm birth worldwide.³ This accounts for more than 1 million infant deaths as a result of preterm birth. In the United States, where more than 1 in 10 births occurs preterm, preterm birth is the leading cause of infant mortality, accounting for as much as 75% of perinatal mortality and more than half of morbidity.⁵ The vast majority of preterm births occur at later preterm gestational ages, with rates increasing as gestational age increases. Approximately 20% of preterm births occur prior

to 31 weeks gestation.¹ The highest rates of morbidity and mortality occur in infants born at the earliest gestational ages.

Maternal stress, depression, smoking, alcohol, and drug use, intrauterine infection, and disease, both chronic and acute, have been identified as predictors of preterm birth. Fetal health, including growth restriction, congenital malformations, and multiple gestation also contribute to preterm birth rates. Spontaneous preterm labor is responsible for approximately 40-45% of births, preterm premature rupture of membranes (pPROM) another 25-30% of births, and delivery for fetal or maternal indications accounts for the remaining 30-35% of preterm births.⁶ Of the approximately 13 million preterm births, up to 20% are due to hypertensive issues of pregnancy, including over 100,000 in the United States each year.⁷ While it is well known that pPROM and many preterm labors are caused by maternal infection, it has been suggested that far more pregnancies are complicated by bacteremia than have been reported previously.⁶ As many as 25-40% of preterm births are currently attributed to intrauterine infection, with rates as high as 50% for births occurring prior to 28 weeks GA.⁸ In this context, subclinical infection may contribute a pro-inflammatory uterine environment, such that spontaneous preterm births of unknown etiology are potentially influenced by subclinical inflammation. The earlier preterm labor occurs, the higher the frequency of intrauterine infection, with most spontaneous births prior to 24 weeks gestation associated with histologic chorioamnionitis, but only about 10% of those occurring at 35-36 weeks gestation.⁹ Histologic chorioamnionitis has been identified in 60-90% of all preterm deliveries.¹⁰ Fetal infection, reported in 33% of fetuses with amniotic fluid

cultures positive for bacterial infection, is also highly associated with preterm labor, fetal and neonatal morbidity, and long term disability.¹¹

The March of Dimes has reported annual expenses of \$16.9 billion for neonatal care, \$611 million for early intervention services, and another \$1.1 billion for special education services for infants and children who are born preterm.¹² A second estimate calculated the United States national expenditure in 2005 to be \$26.2 billion in medical, educational, and lost productivity expenses.⁴ Preterm birth is clearly a concern in terms of both infant morbidity and mortality, but also one which should be considered in terms of economic impact.¹³

1.2. Maternal Hypertension

Hypertensive disorders of pregnancy are a significant cause of maternal and fetal morbidity and mortality across the world. As many as 1:100 deliveries in developing countries are complicated by eclampsia, the presence of seizures in a women with preeclampsia, significantly contributing to high maternal mortality rates. In the developed world, hypertensive disorders of pregnancy account for a large proportion of preterm births. Access to medical care drives this discrepancy. Annually, over a half million women die of pregnancy-related deaths; approximately 76,000, or 12% of these are attributed to hypertensive issues.¹⁴ In addition, it is estimated that approximately 500,000 newborns and fetuses die due to complications of preeclampsia.¹⁵

Hypertension complicates approximately 10% of pregnancies in the United States annually. Several separate diagnoses, including chronic hypertension, gestational hypertension, preeclampsia, eclampsia, and HELLP syndrome are included in the overall

prevalence of hypertensive disorders of pregnancy.¹⁶ Preeclampsia affects 3-5% of pregnancies and is diagnosed as new-onset hypertension and abnormal laboratory tests or other evidence of end-organ injury occurring after 20 weeks gestation.¹⁷ It is a leading cause of both maternal mortality and perinatal morbidity and mortality, affects an additional 5-8% of pregnancies.¹⁹ HELLP syndrome often has rapid onset, and the associated multi-organ involvement contributes to a high maternal mortality rate of 0.5-14%, and perinatal demise of between 25 and 50% of fetuses and neonates.¹⁸ There is some debate over whether HELLP syndrome should be included in the diagnosis of preeclampsia, or whether development follows a separate physiologic pathway which presents similarly. With HELLP syndrome, symptoms include Hemolysis, Elevated Liver enzymes, and Low Platelet counts, which demonstrate that the disease states has progressed to the point of multiple system failure. Chronic hypertension is defined as hypertension existing prior to 20 weeks gestation, and is associated with adverse pregnancy outcomes, including IUGR, stillbirth, placental abruption, and preterm birth. In 2004, approximately 1.7% of pregnancies were complicated by chronic hypertension.²⁰ Chronic hypertension is associated with increased risk of developing superimposed preeclampsia, intrauterine growth syndrome, and stillbirth, with as many as 28 out of 1,000 chronically hypertensive women experiencing a perinatal death.²¹

Risk factors for the development of preeclampsia include nulliparity, obesity, extremes in maternal age, multiple gestations, diabetes, underlying chronic hypertension or renal disease, and a family history of cardiac disorders or preeclampsia.²²⁻²⁵ Many studies have addressed an underlying familial predisposition in the development of preeclampsia.²⁶⁻²⁹ Physiologically, reduced plasma volume, increased pulse pressure, and

increased sympathetic response have been identified as clinical precursors to preeclampsia and there is evidence they are altered prior to pregnancy in those who subsequently develop preeclampsia.³⁰ There is also strong evidence that familial preeclampsia is associated with increased long term risk for the subsequent development of hypertension and ischemic cardiovascular disease outside pregnancy. Women who develop severe preeclampsia, especially early-onset, have a much higher rate of having family members who have had early-onset cardiovascular disease of any type.³¹

Historically, eclampsia was recognized and described by Hippocrates over 2,500 years ago. The word “eclampsia” translates to seizures, and preeclampsia means “before seizure.” In Hippocrates’ Coan Prognosis, the description of headaches, combined with heaviness and seizures, were considered to be serious.³² Until the late 1700s, preeclampsia and eclampsia were repeatedly described, but knowledge about the disease was limited. By the mid-1800s, proteinuria and severe edema were recognized as danger signs for the development of preeclampsia/eclampsia. It was not until the 1960s that science began to compare preeclamptic pregnancies to normal in order to understand the differences in order to determine causation. Since that time, there have been countless theories about the cause of preeclampsia, however causation remains unknown.

Researchers have evaluated the possibilities of uterine ischemia, overactive inflammatory processes, angiogenesis, prostacyclin, endothelial dysfunction, nutritional deficiency, placental disease, hemodynamic vascular injury, preexisting maternal conditions and physiology, immune reaction, and genetics as causes of preeclampsia.^{14,33,34} There is a general consensus that placental dysfunction contributes to the development of preeclampsia, but the definitive trigger has yet to be identified.

Unfortunately, as with the cause of preeclampsia, evidence about possible treatments is also limited. Traditionally when preeclampsia was suspected or a pregnant woman appeared to be at high risk of progressing to preeclampsia, women were placed on bed rest, despite no evidence that restriction of movement prevents preeclampsia development or worsening. Low-dose aspirin in early pregnancy has shown limited effectiveness, reducing the risk of preeclampsia by only 10% in women with at least one risk factor.^{14,33} The use of magnesium sulfate is well established and accepted for the prevention of seizures, and may provide neuroprotection for neonates.¹⁶ This treatment, while very successful at lowering blood pressure, is a muscle relaxant and increases risk of hemorrhage following delivery.

Antihypertensive medications are often employed to prevent stroke and delay delivery in order to optimize fetal development. Until recently, clinical guidelines suggested immediate delivery for preeclampsia was the only option to prevent further health issues, regardless of disease severity. Within the last decade, physicians have been moving towards more frequent use of expectant management, including regular monitoring and observation instead of immediate delivery at time of diagnosis. While emergency cesarean was long considered the necessary route of delivery, there has also been a movement toward induction of vaginal delivery, with constant blood pressure monitoring for both mother and fetus to ensure safety during delivery. The current protocol for delivery is to terminate pregnancies that have not reached viability when maternal status is life threatening and to deliver those that are over 37 weeks of gestation.¹⁷ Between this time frame, doctors do their best to allow the fetus to mature,

with a goal of maintaining the pregnancy until at least 34 weeks. However, if preterm labor or other complications develop, the fetus will be delivered.

While the acute effects of preeclampsia are easier to quantify, a great deal of current research is outlining the future health risks for both mother and offspring. The risk of recurrence in subsequent pregnancies ranges from 20-75%, depending on severity and stage of disease onset. Up to 20% of women whose previous pregnancy was affected by preeclampsia go on to develop chronic hypertension or microalbuminuria. In addition, mothers who suffer a preeclamptic pregnancy have a high rate of future cardiovascular disease. The severity of hypertensive disease during pregnancy is also predictive of early onset cardiovascular disease, with women who develop severe preeclampsia early in pregnancy having the highest incidence of early-onset cardiovascular disease. Women who develop severe preeclampsia, especially early-onset, also have a much higher rate of having family members who have had early-onset cardiovascular disease of any type.³¹

Maternal hypertension is associated with adverse pregnancy outcomes including maternal and fetal death, intrauterine growth restriction, and preterm birth.³⁵ For preterm infants born to hypertensive mothers, there are conflicting reports on the outcome status of these infants. Several studies have reported that infants born to hypertensive mothers suffer from higher rates of morbidities and developmental disability, while other studies report the opposite effect.

Understanding maternal contributions to infant susceptibility is important, and the association between maternal hypertension, preterm birth, and perinatal mortality, and subsequent development of severe morbidities is not well understood.

1.3. Infant Mortality

In 2013, the March of Dimes reported 107 deaths out of 100,000 live births occur preterm or are classified as low birth weight.⁴ Improvements in perinatal survival have been steady since the early 1990s, however infants born at the lowest gestational ages still face high rates of morbidity and mortality.³⁶⁻³⁸ A combination of improved prenatal and perinatal care, including surfactant and antenatal steroid therapies, have greatly increased survival.^{39,40} Survival rates are highly dependent on gestational age at birth. Lower gestational age and birth weight are attributed to higher mortality rates; 92.6% of infants born at 22 weeks gestation, and 60.5% born at 23 weeks died in the United States, with decreasing mortality as gestational age increased (Figure 1.1).⁴¹

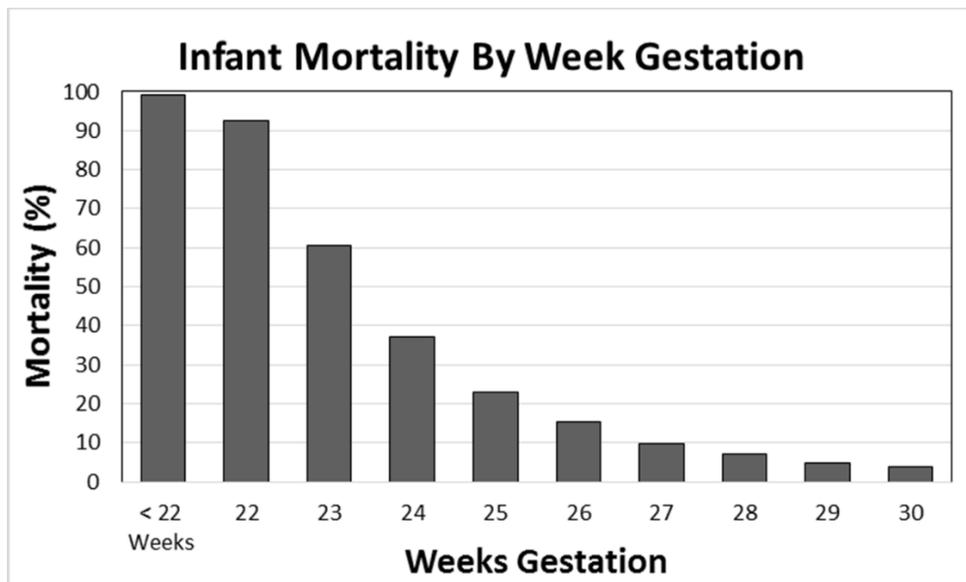


Figure 1.1: Infant mortality by week gestation. Data from the Vermont Oxford Network, 2012.

Lucey et al. reported that within the Vermont Oxford Network between 1996 and 2000, 4172 infants were born with birth weights between 401 and 500 grams. The mortality rate for these fetal infants was 83%, with high morbidity was seen in

survivors.⁴² Also using the Vermont Oxford Network Very Low Birth Weight Database, Horbar et al. compared mortality between 2000 and 2009, reporting a decrease in overall mortality in 501 to 1500 gram infants by 2009. Despite a reduced mortality rate, 49.2% of all included infants and 89.2% of very low birth weight infants either died or developed severe neonatal morbidity in 2009.⁴³ Similar results were recently published by the Neonatal Institute of Child Health and Human Development Neonatal Research Network, reporting an overall decline in mortality across time, among 22+0 and 28+6 week gestational age infants born between 2000 and 2011.⁴⁴ Between 2000 and 2011, mortality rates due to specific morbidities have changed, at least in part related to changes in treatment. There has been a shift from morbidities related to pulmonary issues, infection, central nervous system injury, and immaturity occurring less frequently than at previous points in time, with an increase in necrotizing enterocolitis.⁴⁴

Despite momentous improvements in perinatology over the last decades, mortality rates in extremely preterm infants remain high.^{37,43,45-48} Many factors contribute to survival, including immaturity, race, birth weight, infant sex, access to high level medical care, and clinical course.⁴⁸⁻⁵³ It is becoming clear that obstetric factors also have a large role in influencing postnatal outcome.⁵⁴ As few as half of deaths in singleton preterm infants may be due to prematurity, while the remaining factors are the result of pathologies contributing to preterm birth, including underlying maternal infection and disease.⁵⁵ This dissertation investigates the effect of maternal hypertension on neonatal morbidity and mortality rates.

There are conflicting reports on the effect of maternal hypertension on the outcome of preterm infants. Deaths <12 hours after birth have been reported to be less

likely in infants born to hypertensive mothers, though early deaths are as much an indication of clinical management as physiology.⁴⁸ Buchbinder et al. reports that infants born to mothers with severe gestational hypertension have lower birth weights, more infants who are classified as small for gestational age, as well as higher preterm birth rates at both 37 and 35 weeks when compared to women with mild preeclampsia and those who were normotensive.⁵⁶ There were no differences observed in mortality.⁵⁶ This differs from several studies reporting that hypertension in pregnancy is associated with increased fetal, perinatal, and neonatal death.⁵⁷⁻⁶¹ In a study of Italian infants born between 23 to 31 weeks gestation, a marginally higher mortality (OR: 1.4, 95% CI: 1.0 to 2.0) was reported after adjustment for covariates in infants born to mothers with “disorders of placentations,” a descriptor including growth restriction, and maternal hypertension, when compared to those born to mothers with presumed infection/inflammation.⁶² A sub-analysis, restricting inclusion to only infants with identified maternal hypertension or clinical chorioamnionitis yielded similar overall results, but varied by gestational age.⁶² They reported a gestational age dependent relationship, demonstrating increased mortality in infants born to mothers with hypertension prior to 28 weeks, but increased mortality in infants born to mothers with chorioamnionitis after 28 weeks gestation.⁶² Other studies have found no association or lower risk of infant mortality.⁶³ Evans et al. reported a highly significant decrease in the risk of infant mortality (OR=0.46, 95% CI: 0.36 to 0.50) in infants born at less than 32 weeks gestational age or with birth weights of <1500 grams in Australia and New Zealand level III Neonatal Intensive Care Units.¹⁷ In 2006, Chen reported reduced early and late neonatal mortality when comparing infants born to mothers with hypertension to

those born to normotensive mothers in both early preterm (OR= 0.59, 95% CI: 0.56 to 0.63) and late preterm infants (OR= 0.80, 95% CI: 0.73 to 0.87), but an increased risk of mortality in term infants (OR= 1.08, 95% CI: 1.02 to 1.14) born to mothers with hypertension.⁶⁴ Similarly, Bastek reported lower mortality in infants born to mothers with hypertension when born at low gestational ages, but increased risk in term infants.⁶⁵

Two arguments have been presented to explain the mechanism in which maternal hypertension may result in lower mortality risk. The first suggests that hypertension in pregnancy encourages fetal development in the face of uteroplacental dysfunction by allowing for improved fetal nutrition in the presence of increased uteroplacental blood flow.⁶⁸ The second argument suggests that it is not the “protective” effect of hypertension, but the deleterious effects of the “other” etiologies of preterm birth which increases risk of serious morbidities, including periventricular leukomalacia and intraventricular hemorrhage. Many factors contribute to infant development, both in utero and after delivery, and these all play a role in mortality risk and potential for morbidities to occur. While preterm birth itself is a risk factor for infant mortality and morbidity, the interplay between maternal and fetal factors, both pre- and post-natal, as well as those occurring due to medical practice, all influence outcome (Table 1.2). However, the important take away message of this dissertation is not that infants born to hypertensive mothers have lower rates of mortality than other infants, but that mechanistically, there are likely other factors, including underlying maternal infection and inflammation, which acts mechanistically to worsen outcomes for infants’ born following a spontaneous preterm birth.

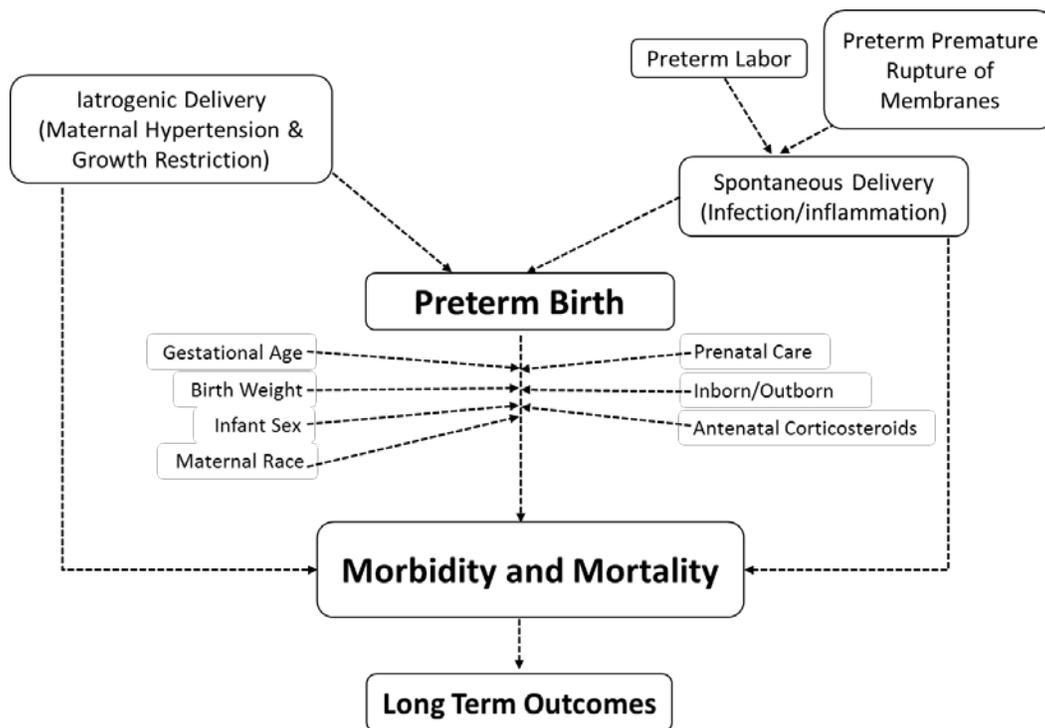


Figure 2.2: Contributors to Preterm Birth, Infant Morbidity and Mortality.

Part of this discrepancy also comes from defining maternal hypertension. Some studies only compare preeclampsia to normotensive mothers while some combine multiple diagnoses. Another reason for the variation is due to statistical approach and selection of covariates. A 2011 Italian study of infants reported differences in preterm delivery rates by hypertension diagnosis, with 21.2% of women with preeclampsia delivering very preterm, 37.2% born to mothers with chronic hypertension with superimposed hypertension, and lower rates to women with chronic hypertension (7.8%) and gestational hypertension (5.9%), and only 1.2% of normotensive women delivering very preterm.⁶⁶ Regional differences in ability and willingness to treat extremely preterm infants also play a role in risk of mortality.^{51,67}

1.4. Morbidity

Similar to the debate regarding the risk of mortality, there have been varying reports of the importance of maternal hypertension on the risk of morbidity in preterm infants born to mothers with hypertension. As preterm birth rates have risen, survival has increased due to technological advances and collaborative medical efforts to improve care—such as through the Vermont Oxford Network. Prior to assisted ventilation in the 1970s, very few infants born prior to 28 weeks gestation survived. Assisted ventilation, postnatal surfactant, administration of antenatal corticosteroids, and increased use of neonatal intensive care have resulted in improvement of survival rates.^{50,69} In recent years, improvements in neonatal care have reduced the rate of severe morbidity in survivors from 46.4% to 41.4% between 2000 and 2009, however the impact of extremely early births remain high, both for individual outcomes and societal costs incurred.^{37,43} Extremely preterm infants are at high risk of injury to their undeveloped organs. Serious morbidity occurs to the neonatal brain, through intraventricular hemorrhage (IVH) and periventricular leukomalacia (PVL); eyes, in the form of retinopathy of prematurity (ROP); and lungs, due to acute respiratory distress syndrome or chronic lung injury (CLD). Maternal infections, resulting in pPROM and preterm labor as etiologies for preterm birth, have been associated with early onset sepsis, IVH, respiratory dysfunction, and development of NEC in preterm infants.^{70,71}

Intraventricular hemorrhage (IVH) is a hemorrhage into the germinal matrix tissues. It is associated with neonatal seizures, periventricular leukomalacia, increased intracranial pressure, and post-hemorrhagic hydrocephalus.⁷² IVH is classified into

stages, with grade 1 composing blood in the germinal matrix, grade 2 being blood in the lateral ventricle without ventricular distention, grade 3 including ventricular distention, and grade 4 involving the parenchymal space. Grade is inversely associated with gestational age.⁷³ PVL often occurs with IVH, and is a white matter injury, characterized by infarction and necrosis, often occurring after a decrease in cerebral blood flow.⁷² Diagnosis for both are made following cranial ultrasound or computed tomography, and the highest risk for IVH occurs in the first week of life.

Many morbidities, including PVL, have been linked to fetal exposure to infection and/or inflammation. One study suggested that vaginal delivery was associated with increased risk of IVH and PVL, but that vaginal deliveries may be a proxy for maternal infection/inflammation due to a higher rate of cesarean sections in iatrogenic deliveries, and vaginal deliveries following pPROM and spontaneous preterm labor.⁷⁴ Similar results were reported by Vergani et al., who noted that in non-iatrogenic births of less than 32 weeks, a higher risk of IVH was noted in infants showing signs of placental infection on pathology.⁷⁵ Verma et al. also reported an increase in IVH and PVL in 500 to 1750 gram infants born following pPROM and preterm labor in comparison to medically indicated deliveries. They reported that 33% of infants born following pPROM, 38.9% of those born following preterm labor, and 17.7% of infants born after physician indicated births developed IVH.⁷⁶ More severe IVH, grades 3 and 4, have been found to be associated with early sepsis and a lack of antenatal steroids in comparison to matched controls in infants less than 1500 grams.⁷⁷ Gagliardi specifically looked at the association with maternal hypertension, IVH and PVL in infants born prior to 31 weeks gestation and reported a decreased risk of severe IVH and PVL in mothers with

hypertension compared to those without and mothers with chorioamnionitis.^{62,78} A similar population based study of 22 to 29 week infants in France also demonstrated decreased risk of IVH and PVL in infants born to hypertensive mothers when compared to those born after pPROM.⁷⁹

Retinopathy of prematurity (ROP) is a significant cause of blindness due to reduced angiogenesis in the eyes of preterm infants. ROP is a disease with 2 phases, the first being a period of hyperoxia with reduction of vascular endothelial growth factor (VEGF) and followed by a period of relative hypoxia with an upregulation of VEGF and increased angiogenesis. It is attributed to exposure of the immature retina to high oxygen levels. ROP is diagnosed in stages, with stage I having mildly abnormal blood vessel growth, stage II having moderate abnormal growth, stage III with severe abnormal growth, and stage IV presenting with a partially detached retina.⁸⁰ The main risk factors include low gestational age at birth, low birth weight, receiving supplemental oxygen therapy.^{81,82} Postnatal weight gain also serves as a reliable predictive aid in determining risk in infants born prior to 30 weeks gestation or at less than 1500 grams birth weight.⁸³ Interestingly, both maternal aspirin therapy during pregnancy—which is used for prevention of preeclampsia, and exposure to in utero infection/inflammation are also considered risk factors. Studies comparing extremely preterm infants report increased risk of ROP in infants born to mothers with disorders of placentation (including preeclampsia and growth restriction) compared to those born following chorioamnionitis.⁹ Restricting analyses to infants born to mothers with hypertension also demonstrates increased risk of severe ROP when compared to infants born after presumed infection/inflammation.^{62,78}

Necrotizing enterocolitis (NEC) is inflammatory disease of the small intestine, leading to necrosis of the bowel. It occurs in between 1 and 8% of patients in the neonatal intensive care unit.⁸⁴ The specific pathogenesis is not understood, though the biggest risk factors are prematurity and low birth weight. It has been proposed that increased rates of cesarean sections may contribute by preventing exposure to vaginal flora.⁸⁵ Symptoms include abdominal distention, gastrointestinal bleeding, and pneumatosis intestinalis. Severe NEC also includes air in the portal vein or pneumoperitoneum following intestinal perforation. While NEC usually occurs in the first two weeks of life, it has a high mortality rate, with 18% of infants with mild NEC, 21% of those with moderate NEC, and 62% of those with severe NEC, dying from the condition.⁸⁴ Rates of NEC have been increasing, but this is primarily due to improved neonatal care improving survival and allowing for subsequent morbidities to develop. Up to 90% of infants that develop NEC would have died prior to development if not for advanced neonatal practices.⁸⁴ NEC rates decrease with increasing gestational age, however the proportion of deaths due to NEC rises as gestational age increases.⁸⁶

Bronchopulmonary dysplasia (BPD) is a form of chronic lung disease (CLD) resulting from lung damage caused by mechanical ventilation, including high oxygen exposure, positive pressure ventilation, or poor bronchial drainage following intubation.⁸⁷ In severe cases, it requires long term use of oxygen and lifelong breathing problems. Infants receiving oxygen supplementation at 36 weeks postmenstrual age or 34 weeks postmenstrual age if discharged with oxygen are considered to have CLD.⁸⁸ There is some evidence that the inciting factors that cause CLD may begin prior to birth as a result of systemic inflammatory response in utero.⁸⁹ BPD is most common in infants born at the

lowest gestational ages and those with birth weights less than 1000 grams—the infants with the most immature lungs who rely exclusively on assisted ventilation, with as many as 77% of these infants being diagnosed.⁸⁷ BPD was reported to occur more frequently in infants born prior to 28 weeks gestation to mothers with intrauterine vascular disorders (including preeclampsia), with 29% of these infants, compared to 11% of those born following spontaneous preterm labor.⁹⁰ Gagliardi also reported increased risk for BPD in extremely preterm infants born to mothers with hypertension and other disorders of placentation compared to those with infection/inflammation or clinical chorioamnionitis.^{62,78}

Infections are another major cause of morbidity in extremely preterm infants. These are classified as early and late, depending on whether the infection occurred prior to or after 72 hours of life. Early sepsis is rare due to prenatal identification of Group B Streptococcus and chemophylaxis at delivery, with less than 2% of very low birth weight infants being diagnosed. Identification of specific bacterial infections identify group B-streptococcal infections and *Escherichia coli*. Late sepsis is more common, affecting as many as 25% of extremely preterm infants, in large part due to extended NICU stays resulting in more time for exposure.⁹¹ These infections are mostly due to gram positive coagulase-negative staphylococci. Infections are inversely linked to BW and GA with high morbidity and mortality, with a higher percentage of deaths occurring with increased gestational age.⁹¹ Risk of early sepsis is lower in infants born to mothers with hypertension compared to those born to mothers with chorioamnionitis.⁶²

The development of each individual, as well as a combination of multiple morbidities are associated with poor prognosis, particularly in infants who are born the

smallest and earliest. Half of surviving extremely preterm birth suffered severe neonatal morbidities.⁹² The development of major morbidity in very low birth weight infants who survive to hospital discharge ranges from 83% of 501 to 750 gram infants to 18.7% of 1251 to 1500 gram infants.⁴³ Combined assessment scores for predicting outcome of infants who develop one or more morbidities have shown promise in prognosis. Schmidt scores have been validated in extremely low birth weight infants of 500 to 999 grams, using a simple count of BPD, brain injury, and severe ROP. While each morbidity individually correlated an odds ratio of 2.4 to 3.7 for poor outcome at 18 months corrected age, a simple count revealed a predictive values of poor outcome at 18%, 42%, 62%, and 88% with 0 to 3 of these morbidities occurring.⁹³ The inclusion of NEC and infection within this model slightly increased the ability to predict poor outcomes at 18 months.⁹⁴ Being able to confidently predict future prognosis is important for both clinical practice and counseling of families facing difficult decisions regarding infants born extremely preterm. The NICHD maintains an online calculator for predicting outcome using variables available at time of birth.⁹⁵ However clinical course clearly plays a role in determining survival and future health. Predictive methods for calculating how morbidities impact long term outcomes are inexact in extremely preterm infants, and yet it is imperative that prognoses be reevaluated as clinical course progresses.⁹⁶ Each morbidity carries its own risks, both for survival and long term outcome.

1.5. Growth Restriction and Small for Gestational Age

Small for gestational age (SGA) infants are defined as those being within the lowest 10th percentile for birth weight corrected for gestational age. These infants may be

small due to a variety of factors, including genetic, however many SGA infants are small due to growth restriction in utero. Maternal, fetal, and placental factors all play an important role in optimizing—or compromising—growth potential. Infants who fail to meet their potential have the highest risk of increased mortality and morbidities when compared to appropriately grown infants.^{97,98} Intrauterine growth restriction (IUGR), the fetal identification of delayed growth maturation, is a phenotype resulting from many underlying factors, but is commonly cited as the single largest contributing factor to perinatal mortality in otherwise healthy fetuses.⁹⁹ Growth restriction has an attributable cause in only about 40% of cases. Most identifiable causes include abnormalities in uteroplacental perfusion, fetoplacental perfusion, and abnormal villous structure at the fetal maternal interface.¹⁰⁰ IUGR infants are classified by symmetry. Symmetrically growth restricted infants make up 20 to 30% of growth restriction, while asymmetric growth restriction is observed in the remaining 70 to 80%.¹⁰¹ Symmetrical growth restriction is believed to occur early in development, and includes reduced measures of all biometrical measures of fetal growth. This type of growth restriction is more commonly associated with fetal malformations and early exposure to infections such as cytomegalovirus.¹⁰² As many as 20% of fetuses with recognized intrauterine growth restriction have chromosomal abnormalities or malformations.^{102,103} Asymmetric growth restriction typically has later onset with head sparing and decreased abdominal circumference, indicating a reduction in adipose tissue deposit but more normal brain development. Asymmetric growth restriction is associated with utero-placental insufficiency seen in cases of preeclampsia and maternal hypertension, as well as maternal malnutrition.^{101,102}

Due to the high incidence of mortality in the presence of malformations or chromosomal abnormalities, these infants are frequently excluded from studies examining morbidity and mortality in IUGR and SGA infants. Within otherwise healthy low birth weight infants, perinatal mortality in SGA infants is approximately 3-fold higher than that of appropriately grown infants.¹⁰⁴⁻¹⁰⁶ SGA infants born at the lowest gestational ages and who have the lowest birth weights have the highest risk of poor prognosis when compared to appropriately grown infants.^{104,107,108} The greater the degree of growth restriction, as evidenced by birth weights of less than the 3rd percentile, the higher morbidity and mortality.¹⁰⁹ These infants have an 8-fold increased risk of mortality when compared to infants within the 25-75th percentiles.⁵² Growth restriction is considered to be the largest independent predictor of mortality. Multiple studies of stillbirth demonstrate stillborn infants have higher degrees of growth restriction, as evidenced by smaller weight for gestational age, compared to live born SGA infants.¹¹⁰⁻¹¹³ Surviving SGA infants have repeatedly been shown to have poorer outcomes, demonstrated by higher rates of assisted ventilation, BPD, and CLD when compared to appropriately grown infants.^{98,104,114}

SGA and IUGR frequently occur in the presence of maternal hypertension. Preeclampsia and chronic hypertension are recognized risk factors for IUGR and SGA.^{74,108,113,115,116} Compared to normotensive mothers, risk of SGA is dependent on diagnosis, with an increase of 1.5-fold for mild preeclampsia, 3.2-fold in the presence of severe preeclampsia, and a 2.5-fold increase with chronic hypertension.¹¹³ It has been suggested that IUGR is a symptom of preeclampsia, linking growth restriction to disease severity.¹¹⁷

Observed rates of SGA in the presence of hypertension differ with gestational age. The SCOPE study, studying SGA infants born at all gestational ages between 2004 and 2008, reported 10.7% occurred in the presence of maternal hypertension.¹¹² This association changes in the preterm population, with more SGA seen in hypertensive mothers at lower gestational ages. Within a population of 24 to 31 week infants, 75% of SGA infants were born to hypertensive mothers, and half of those in the 10th to 25th percentile.¹¹⁸ Similarly, Chen et al. reported 21.5% of infants born to mothers with hypertension prior to 32 weeks were identified as SGA, while only 5.9% of infants born to mothers without hypertension were SGA.⁶⁴ Preterm, infants born after PE are 10-25% smaller than their peers of similar GA.¹¹⁹

Mortality rates for these infants varied greatly, with 10% for SGA infants born to mothers with hypertension, and 23% for those without hypertension.⁶⁴ Mortality rates of 46% lower have been reported for preterm singleton SGA infants born to mothers with hypertension compared to other SGA infants.⁵² Other studies have not found this association, and report no difference in mortality or morbidity rates in the presence and absence of maternal hypertension.¹²⁰

Multiple explanations for why it appears SGA infants have lower mortality when born to mothers with hypertension when compared to other SGA infants have been suggested. One explanation is that growth restriction in the presence of maternal hypertension encourages fetal lung maturation, resulting in better survival after delivery.¹²¹ More likely, improved accuracy in dating pregnancies, and thus determining gestational age at time of birth, has improved knowledge of appropriate maturity level.

Historically, larger infants were presumed to be older, and thus expected to be at a higher developmental maturity.¹²² However, in the presence of growth restriction, infants who are identical in terms of birth weight can have differing gestational ages. In this situation, the infant who is more developmentally mature would be expected to have a better outcome, despite being growth restricted.

1.6. Long Term Outcomes

It is well established that severe neonatal morbidity is associated with an increased risk of neurodevelopmental and physical delay.¹²³⁻¹²⁹ Most neonatal predictors associated with improved survival are also associated with an increased chance of survival free of major sensorineural disability.¹²³ Morbidities most often linked to long term delay are bronchopulmonary dysplasia (or chronic lung disease), major brain injury, necrotizing enterocolitis, nosocomial infections, and retinopathy of prematurity¹²⁴⁻¹²⁷. Necrotizing enterocolitis (NEC) affects 1 to 8% of NICU patients and is also linked with poor neurodevelopmental outcome.^{128,129}

Disability rates as high as 65% were reported in infants born <29 weeks gestation in the mid-1980s. Mortality prior to discharge and severe morbidity in VLBW infants decreased substantially from 2000 to 2009; a high proportion of extremely preterm infants still develop 1 or more severe morbidities, which are associated with long term neurodevelopmental or physical delay.⁴³ Despite a decrease in the most severe disabilities in infants born <28 week GA in 2005^{43,124}, 59.1% of extremely preterm infants are diagnosed with some level of disability at 2 years of age.¹³⁰ Severe disability is defined as a major neurologic abnormality, such as cerebral palsy, unilateral or bilateral blindness,

deafness requiring hearing aids, or cognitive functioning less than 2 standard deviations below the mean on cognitive assessments. The majority of infants who develop delay have mild impairment without cerebral palsy or neurosensory impairments.¹²⁵ More importantly, special outpatient services are utilized by 54.7% of infants born <28 weeks GA by 18 to 22 months.¹³¹

The relationship between maternal HTN and long term outcome is also complex, with several studies reporting a negative association in infant outcome at follow-up, and an equal number reporting a positive association. For instance, Grether *et al.* and Murphy *et al.* both report a reduced rate of cerebral palsy seen in children who were born extremely preterm.^{132,133} Alternatively, increased rates of cerebral palsy were reported by Hagberg and Jonas in infants born to mothers with pregnancies complicated by HTN.^{134,135} A case-control study by Gray *et al.* reports infants born 24 to 32 weeks GA have lower risk of cerebral palsy and no increased risk of cognitive impairment.¹³⁶ Randolph *et al.* examined the National Institute of Child Health and Development very low birth weight (VLBW) database, and reported 32% decreased risk of death or neurodevelopmental impairment in infants born to hypertensive mothers.¹³⁷ For cognitive delay, there are similarly conflicting reports, with some studies citing a higher incidence of neurodevelopmental problems in extremely preterm infants born to mothers with preeclampsia or HTN, and some studies reporting lower risk of neonatal and NICU mortality as well as less cognitive impairment at 2-year follow-up in extremely preterm infants born in the Netherlands.¹³⁸⁻¹⁴² While the majority of studies focus on early follow-up at 18 to 24 months corrected age, some studies have also evaluated longer term follow-up. Evaluation of movement and cognitive performance at 1 year predicts follow-

up at 4 years in infants born <1000g.¹⁴³ 2-year neurodevelopmental assessment has been reported to be a good predictor of school-age ability; abnormal 2-year disability and delay accurately predict the need for special education services at age 5 to 6.¹⁴⁴ In addition, preterm birth is associated with lower cognitive scores and increased risk of attention deficit hyperactivity disorder compared to term controls at age 5.¹⁴⁵

1.7. Clinical Decision Making and Ethics

With delivery being the only “cure” for preeclampsia, families can find themselves facing a heartbreaking decision—do they wait to see if the disease state progresses, risking maternal life, or do they terminate or induce to save the mother, but risk the fetus? When preeclampsia occurs before twenty-two weeks or after thirty-seven weeks of gestation, the answers are straightforward. Before twenty-two weeks, and the fetus’ chance of survival is nil, while after thirty-seven weeks, the fetus, barring other complications, will adapt well to extrauterine life. However, infants born between twenty-three weeks and thirty-seven weeks face many obstacles and survival is often dictated by the availability of a high-level neonatal intensive care unit and quality care.

Often when a pregnant woman initially presents with hypertension, she can be managed with anti-hypertensives and inpatient monitoring for worsening symptoms. This often buys additional time for the fetus to develop, antenatal steroids to be administered, and for patients to be transferred to tertiary care facilities with high-level neonatal intensive care units prior to delivery. Randomization to expectant management in early onset preeclampsia cases has been shown to delay delivery by an average of 15 to 24 days for mothers diagnosed prior to 25 weeks gestational age, and by 9.5 days for those

diagnosed between 25 and 34 weeks gestational age.¹⁴⁶ Expectant management does result in increased maternal morbidity, including development of HELLP and eclampsia.¹⁴⁶ Barring severe maternal disease, delaying delivery can greatly improve neonatal outcome. Maternal anti-hypertensives can frequently control blood pressure well beyond the needed 12-24 hours to administer corticosteroids. Alternatively, other causes of delivery, such as clinical chorioamnionitis, pPROM, or premature labor do not always allow obstetricians the time to weigh multiple options prior to delivering.

Regional differences also exist in attitudes about offering aggressive treatment at the lowest gestational ages—the periviable at 22 and 23 weeks gestational age. A study comparing proactive management and selective management in regions of Sweden found proactive management to be associated with improved survival without increased neonatal morbidity.¹⁴⁷ There are large variations in infant mortality rates between countries, across regions within countries, and also between different racial and ethnic groups.⁶⁷ The MOSAIC cohort study of European births occurring prior to 32 weeks gestation demonstrated mortality rates as high as 18-20% in the Netherlands and Poland, compared to rates of 7-9% in Germany and the United Kingdom, where aggressive treatment is common.^{148,149}

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CHAPTER 2: THE EFFECT OF MATERNAL HYPERTENSION ON MORTALITY IN INFANTS 22 TO 29 WEEKS GESTATION

2.1. 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 (GA).

Methods: 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 GA were evaluated in 2-week GA 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 NICU discharge compared to 20% of the 66,379 infants not associated with hypertension. Infants associated with maternal hypertension had significantly lower mortality, after adjusting for other characteristics, than preterm infants not born to hypertensive mothers, at all GAs examined as follows: 22/23: OR 0.65 [95% CI 0.55 to 0.77]; 24/25: OR 0.77 [95% CI 0.71 to 0.84]; 26/27: OR 0.66 [95% CI 0.59 to 0.74]; 28/29: OR 0.58 [95% CI 0.51 to 0.67]. Additionally, births associated with maternal hypertension increase dramatically by GA, resulting in a larger proportion of births associated with maternal hypertension at later GAs.

Conclusions: Preterm birth due to any cause carries significant risk of mortality, especially at the earliest of viable GAs. 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 prior to counseling parents.

2.2. Introduction

Neonatal mortality in the very low birth weight (VLBW) population, defined as those with birth weights of less than 1500 grams, has declined considerably in the early 1990s, but has since leveled off, while birth rates within this population have increased from 9% in 1981 to 12.5% in 2004.¹⁻⁵ Declines in neonatal mortality rates have been attributed to improvements in perinatal care and prenatal monitoring, including widespread use of surfactant and antenatal steroid therapies.^{6,7} However, infants born at the lowest gestational ages (GA) still face high rates of mortality and serious morbidities, often with life-long health problems stemming from preterm birth.⁸⁻¹⁰ Between 2000 and 2009, 49.2% of infants recorded in the Vermont Oxford Network (VON) who were born at birth weight (BW) of 501 to 1500 grams, died or suffered a severe neonatal morbidity.¹¹ In the United States, the preterm delivery rate is 12-13%; the vast majority of these occur at the latest of preterm GAs. Approximately 20% of preterm births occur prior to 31 weeks gestation.⁴ Both lower GA and lower BW are associated with higher mortality rates with survival occurring in 2-35% of newborns at 23 weeks, 17-62% at 24 weeks, and 35-72% at 25 weeks.^{12,13}

Hypertension, including diagnoses of chronic hypertension, gestational hypertension, preeclampsia, eclampsia, and HELLP syndrome (**h**emolysis, **e**levated **l**iver enzymes, and **l**ow **p**latelets), complicates 6-8% of pregnancies in the United States.¹⁴ Chronic hypertension, defined as hypertension existing prior to 20 weeks gestation, is 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.¹⁵ Women with chronic hypertension are at an 8-fold higher risk of developing superimposed preeclampsia compared to the general population, and were at least twice as likely to experience adverse neonatal outcomes.¹⁶ 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 5-8% of pregnancies.¹⁷ 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.¹⁸⁻²⁴

We examined the hypothesis that infants born to mothers with hypertension will have a lower mortality rate, after adjusting for maternal and perinatal covariates, than infants who are not delivered in association with maternal hypertension. Preterm births are attributed to a short list of 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.²⁵ pPROM and many preterm labors are associated with maternal infection. Infection causes a pro-inflammatory cytokine cascade that is implicated as a major contributor to toxic uterine environments, with implications on both short-term survival and long term impairment.²⁶⁻³⁰ 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.³¹ 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. Alternatively, maternal hypertension results in a different form of proinflammatory environment, one we hypothesize to be less detrimental to infant survival.

2.3. 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 grams, or between 22+0 and 29+6 weeks GA.³² Beginning in 2008, the first obstetric factors, including dichotomous variables for maternal hypertension and diagnosis of chorioamnionitis were collected.³³ For this reason, births occurring during calendar years 2008 through 2011 were examined. Inclusion was limited to infants born in the 667 North American centers. Infants from multiple gestations were excluded as multiple gestation is both a risk factor for preterm birth, and are specifically associated with increased risk of 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 as their inclusion (n=4288) would have artificially inflated our mortality rates.³⁴ 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. Chronic hypertension is not differentiated from hypertensive disorders specific to pregnancy. Mortality is defined as death prior to discharge. Infants who were 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 discharge. Antenatal steroid administration is coded when dosing was administered at any time prior to delivery, with no differentiation in the database between a single dose and full course of treatment. Prenatal care refers to documentation of any prenatal visits.

Initial demographic characteristics examined differences between infants born to hypertensive mothers versus infants born to non-hypertensive mothers 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 birth weight. These covariates were chosen due to their association with outcomes and prior inclusion in VON models. 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.³⁵ 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 $\alpha=0.05$.

2.4. 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. Across GA however, 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 a similar trend seen within the rates increasing with increasing GA (Figure 2.1).

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 , -HTN = 558.4 ± 98.7 grams; 24/25: HTN = 605.4 ± 163.0 , -HTN = 732.8 ± 134.4 ; 26/27: 785.8 ± 186.1 , -HTN = 967.5 ± 181.4 ; 28/29: HTN = 1040.3 ± 226.3 , 1244.8 ± 232.2 grams (all

p 's < .001). They were more likely to be inborn, born by cesarean section, be small for gestational age, and have received antenatal steroids (Table 2.1).

Univariate analyses indicated odds of mortality for HTN relative to other causes as being GA dependent, with a reduced rate of mortality at 22/23 weeks (OR 0.82, 95% CI: 0.71 to 0.97), increased risk of mortality at 24/25 weeks (OR 1.26, 95% CI: 1.17 to 1.36), increased risk at 26/27 (OR 1.10, 95% CI: 1.00 to 0.20), and reduced odds at 28/29 weeks (OR 0.88, 95% CI 0.77 to 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 birth weight alone resulted in a reduced odds estimate of mortality at all GAs (Table 2.2).

Multivariate analysis allowed for a more complete risk assessment adjusting for the many factors known to contribute to neonatal mortality: birth weight, infant sex, maternal race, inborn/outborn, antenatal steroids, and prenatal care. Significantly reduced standardized rates of mortality were observed at all GAs in association with maternal hypertension as an independent variable; within the 22/23 cohort, mortality was 64.4% of infants born to hypertensive mothers, while 71.8% of those in the comparison group died (OR 0.64, 95% CI 0.53 to 0.76). In the 24/25 week cohort, mortality rates were lower; 23.3% of infants exposed to hypertension and 27.8% of other infants (OR 0.75, 95% CI 0.69 to 0.82]. Mortality at 26/27 weeks was 7.7% in infants exposed to hypertension and 11.0% in the remaining infants (OR 0.65, 95% CI 0.59 to 0.75). The most mature group, 28/29 weeks, had the lowest mortality rates, at 2.8% for the group of interest and 4.6% of comparison infants (OR 0.60, 95% CI 0.52 to 0.70).

2.5. Discussion

There are conflicting reports on the effect of maternal hypertension on the outcome of preterm infants. We report here that infant mortality is decreased at all gestational ages for those born to mothers with hypertension when compared to other infants. Several studies have reported hypertension in pregnancy is associated with increased fetal, perinatal, and neonatal death.^{18,20-23} Others report no association or decreased risk of mortality.¹⁹ Chen *et al.* examined early neonatal, late neonatal, and postneonatal death in infants born to hypertensive mothers, compared to infants from non-hypertension associated pregnancies. Mortality was lower in infants born between 24 and 31 weeks GA, who were exposed to maternal hypertension than similar infants who were not born from hypertension-associated pregnancies, (OR 0.38, 95% CI 0.34 to 0.42).³⁶ Randolph *et al.* examined the National Institute of Child Health and Development VLBW database, and reported a 32% decreased risk of death/neurodevelopmental impairment in infants born to hypertensive mothers.³⁷ Population based Australian and New Zealand Neonatal Network, reported infants born prior to 29 weeks gestation to have odds ratio of 0.68 (95% CI: 0.52 to 0.90) in the presence of maternal hypertension when compared to other infants.¹⁸ Similarly, Gagliardi *et al.* reported a lower GA at birth, and higher risk of mortality in infants, 23-31 weeks gestation, who were born to mothers with infection and/or inflammation than those born to hypertensive mothers.³⁸ Conflicting results appear to be attributable to differences in statistical approach as the choice of covariates can result in differing conclusions. Our univariate analyses demonstrated a gestational-age dependent effect of maternal hypertension on mortality, but correcting for maternal race, infant sex, BW, antenatal

steroids, prenatal care, and inborn/outborn status, revealed a decreased risk of mortality at all GAs examined. BW had the strongest influence on mortality rates. Following adjustment, all GA cohorts had lower odds of mortality in infants born to hypertensive mothers.

Despite improvements in perinatal-neonatal medicine, mortality rates in extremely preterm infants remain high. Extremely preterm births are most commonly attributed to spontaneous preterm labor, pPROM, or delivery for maternal or fetal indicators. In each of these situations, obstetric factors have greatly influenced postnatal outcome through intrauterine environment and maternal health. In considering maternal hypertension, two arguments have been presented to explain the mechanism through which hypertension influences fetal development. The first suggests hypertension in pregnancy encourages improved fetal maturation in the presence of reduced uteroplacental blood flow and increased intrauterine stress.³⁹ The second argument suggests that many other causes of preterm birth, not related to hypertension, are linked to infection and inflammation, where the proinflammatory cytokine cascade associated with these infections increases risk of serious morbidities, including periventricular leukomalacia (PVL) and intraventricular hemorrhage (IVH). Von Dadelszen *et al.* attributed higher observable SNAP-II scores, lower rates of PVL and IVH, and increased survival in SGA infants born to hypertensive mothers, to a combination lack of exposure to infection and a higher developmental maturity at birth.³⁹ While the VON VLBW database attempts to capture data pertaining to the presence of infection and/or inflammation by including a variable for chorioamnionitis, initial evaluation of this variable led us to determine the data captured is a poor representation as diagnosis often

is determined from pathologic review or culture, and is unlikely to be reported in infant charts due to time elapsed between birth and the return of results. Additionally, many cases are likely subclinical, and therefore not recorded as such in the maternal record.

Given our findings and previous supporting literature, one potential interpretation of the data presented is that infants born to hypertensive mothers have lower rates of mortality when compared to other infants due to the lack of underlying maternal disorders that worsen the outcomes of infants who are exposed to a pro-inflammatory uterine environment.

One limitation of the current study lies in VON's definition of hypertension. By including all cases in which mothers had the identification of a singular blood pressure reading of 140 mmHg systolic or 90 mmHg diastolic in the maternal record, the incidence of maternal disease could be overestimated. The VON definition also does not discriminate between chronic and pregnancy associated hypertensive diagnoses. In a comparison of births between women with gestational hypertension and those with preeclampsia, both were associated with increased perinatal morbidity and mortality compared to pregnancies not complicated by hypertension.⁴⁰ However, Buchbinder *et al.* reported higher rates of preterm delivery and more SGA infants born to women with severe gestational hypertension than to those with mild preeclampsia, demonstrating that particular diagnoses are not indicative of disease severity and fetal effect.⁴¹ Also, as chronic hypertension is also associated with increased risk of developing superimposed preeclampsia, intrauterine growth syndrome, and stillbirth, the inability to differentiate specific diagnoses may not be crucial.⁴²

We see a higher rate of inborn infants born to hypertensive mothers compared to those outborn. This is understandable, as one factor that differentiates maternal hypertension from other causes of birth is the issue of expectant care. Often when a pregnant woman initially presents with hypertension, she can be managed with anti-hypertensive agents and both maternal and fetal monitoring for worsening symptoms. Alternatively, other causes of delivery, such as clinical chorioamnionitis, pPROM, or premature labor may not allow adequate time for appropriate transfer of care. A review of studies utilizing randomization of expectant management in early onset preeclampsia cases reports mean delays in delivery of an average of 15.4-24 days (<25 weeks GA at diagnosis) and 9.5 days (25-34 weeks GA). This likely increases the likelihood of mothers receiving, and clinical effect seen, with a full course of antenatal steroids, though the VON VLBW database does not differentiate between a single dose and full course.

Mortality in extremely preterm infants also reflects variations in practice management, parental decision-making, and clinical ethics. The majority of deaths are due to immaturity, there are also clinical policies on aggressive resuscitation that are ill defined for the lowest GAs. Though the MOSAIC study focuses on European-born infants, it is highly likely their results are transferrable to regional variations within the United States. These include a high level of variability in center-specific willingness to aggressively treat infants born on the cusp of viability (<25 weeks), and likely factor into the high mortality rates seen at the lowest GAs.^{43,44}

Most studies evaluate infants by birth weight, allowing for comparisons between infants of similar size; this may misclassify infants by GA. Birth weight traditionally was used because it is an available and accurate measure, yet is a proxy for both maturity and

growth.⁴⁵ As we report, infants born 22+0 to 29+6 weeks GA to hypertensive mothers are, on average, born at increased GA, but with smaller birth weight than their counterparts. Omission of birth weight from our logistic models resulted in projected ORs of 1.51 (1.39 to 1.63) and 1.29 (1.16 to 1.44) at GAs of 24/25 and 26/27, respectively. There were no significant differences in outcome according to maternal hypertension within 22/23 or 28/29 week cohorts. While birth weight and GA are typically closely correlated, both GA and birth weight are clinically significant independent measures of variability, accounting for the majority of mortality. Similar findings have been previously reported.^{18,46} Preterm infants born from pregnancies complicated by preeclampsia measure 10-25% smaller than similar gestational aged infants born from pregnancies without hypertension, and are 3-4 times more likely to be SGA.²⁰ Given the distribution of hypertension within the population, it is likely that even within our 2-week GA cohorts, infants born to hypertensive mothers are slightly older, and therefore more mature, than comparable infants.

Maternal well-being greatly impacts infant health; the importance of maternal factors have recently received a great deal of attention. Within our population, we see a skew toward more births at later preterm GAs, leading us to believe reasons for early delivery vary across GA, and as such, our findings are somewhat attributable to a heterogeneous maternal comparison group. As we demonstrated, the composition of our population changes as GA increases, and a greater number of later-gestation aged infants are born to mothers with hypertension. This reflects a “control” population that is likely also changing, either to reflect subclinical infection, or other idiopathic etiologies. We unfortunately lack the ability to examine other maternal factors, such as socioeconomic

status, alcohol use, smoking status, and the initiation of prenatal care; all variables that have implications in terms of understanding how maternal factors influence preterm infant outcome.

Factors at birth, including infant sex, exposure to antenatal steroids, GA and birth weight are the strongest indicators of survival at the time of birth, however many postnatal measures also predict survival. Ambalavanan *et al.* reports the importance of using adaptable models to reevaluate outcome prediction as clinical information becomes available.⁴⁷ While our model predicts mortality rates, it utilizes covariates that are available at the time of birth, and thus does not factor the effect of subsequent morbidity on mortality rates. In clinical practice, it is important to recognize how clinical course, particularly the development of severe morbidities, can drastically change infants' projected outcome.

2.6. Conclusion

Understanding the contribution of maternal hypertension on mortality in VLBW infants will aid obstetricians and neonatologists in counseling parents, and could influence clinical decision making in provision of early intervention for infants on the cusp of viability. For deliveries prior to 30 weeks, risk of morbidity and mortality are high, with a strong association between GA at birth and rate of survival. However, if an infant is born between 22+0 and 29+6 weeks gestation, to a mother with hypertension, that infant faces decreased odds of mortality than similar infants born to mothers without hypertension. We believe this association is likely due to differences in intrauterine environment.

Table 2.1: Demographic information by maternal hypertension status.

	No Hypertension (66,379)	Hypertension (21,896)
Inborn Location*	81 %	90 %
Cesarean Delivery*	52 %	89 %
Prenatal Care*	94 %	97 %
Male Sex*	55 %	48 %
Race*		
Black	31.7 %	36.3 %
White	40.8 %	41.2 %
Hispanic	21.2 %	17.3 %
Other	6.4 %	5.1 %
Birth weight (grams)*	949 (308)	863 (271)
Small for Gestational Age*	4 %	20 %
Gestational Age (weeks)*	26.2 (2.1)	27.0 (1.8)
Antenatal Steroids*	72 %	85 %
1 minute Apgar*	4.6 (2.5)	4.7 (2.5)

Data are presented as percentage or population mean \pm SD. An * identifies a significant difference between groups, $p < .05$.

Table 2.2: Unadjusted and adjusted ratios for mortality in infants born to hypertensive mothers.

	Unadjusted	Adjusted for Birth Weight	Adjusted for all Covariates
22/23 Weeks	0.83 (0.70 to 0.96)	0.55 (0.46 to 0.65)	0.65 (0.55 to 0.77)
24/25 Weeks	1.26 (1.17 to 1.36)	0.73 (0.67 to 0.79)	0.77 (0.71 to 0.84)
26/27 Weeks	1.10 (1.00 to 1.20)	0.59 (0.53 to 0.66)	0.66 (0.59 to 0.74)
28/29 Weeks	0.88 (0.77 to 0.99)	0.52 (0.46 to 0.59)	0.58 (0.51 to 0.67)

Data are presented as odds ratios with corresponding 95% Confidence Intervals.

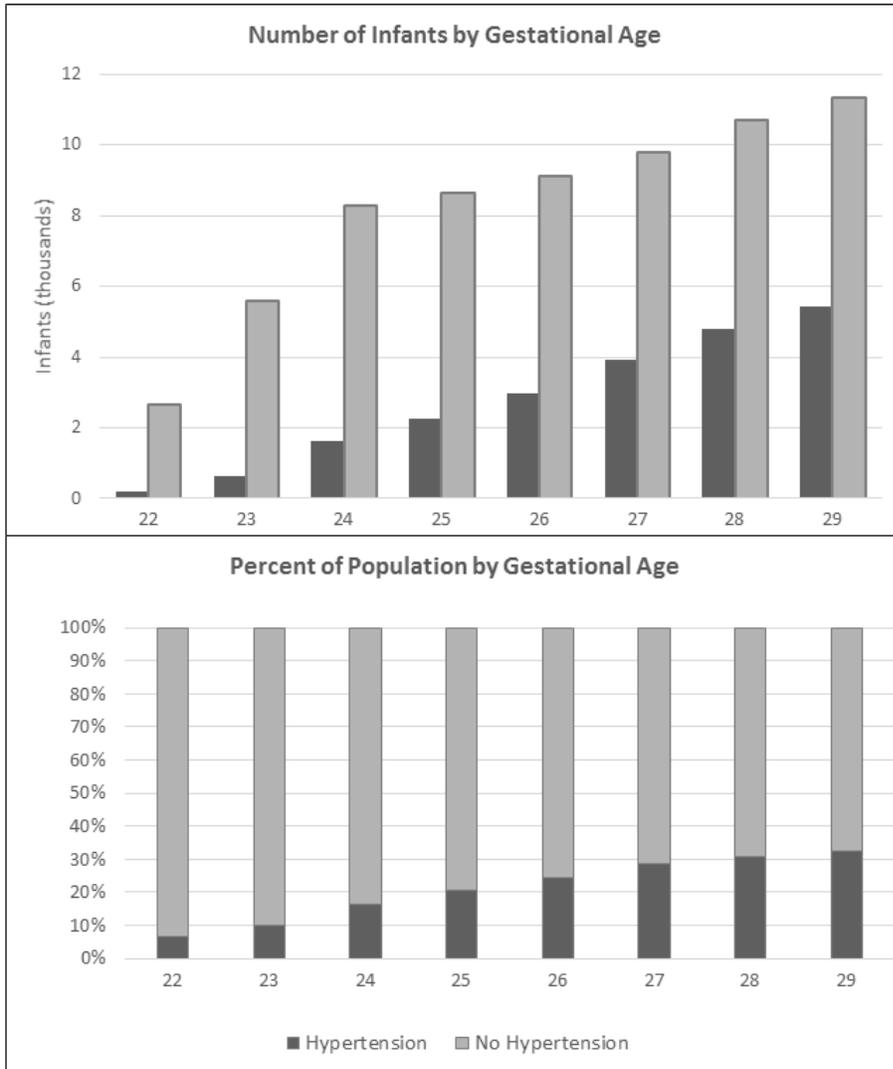


Figure 2.1: Distribution of infants born by gestational age and hypertension status, in raw numbers and as a percentage of each gestational age population.

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**CHAPTER 3: SURVIVING INFANTS BORN BETWEEN 22+0 AND 29+6
WEEKS GESTATION HAVE DECREASED MAJOR MORBIDITY WHEN
BORN OF HYPERTENSIVE MOTHERS**

3.1. Abstract

Extremely preterm infants have high rates of morbidity; complications that are linked with long term disability and neurodevelopmental delay. The association between maternal hypertension and early morbidity is unclear.

We evaluated 72,016 infants born 22+0 to 29+6 weeks GA, in North American Vermont Oxford Network centers, 2008-2011 for the effect of maternal hypertension (HTN) on risk of morbidity prior to discharge in infants 22+0 to 29+6 weeks gestational age (GA). All survived to NICU discharge and were analyzed for development of severe morbidity during their NICU stay. Morbidities included chronic lung disease (CLD), intraventricular hemorrhage grades 3-4 (IVH), cystic periventricular leukomalacia (PVL), retinopathy of prematurity grades 3-5 (ROP), necrotizing enterocolitis grades >2 (NEC), infection, and a combined risk scores. Rates were compared between HTN and -HTN within 2-week GA cohorts. Logistic regression was used to adjust, within cohorts, for birth weight, antenatal steroid exposure, infant sex, maternal race, location, prenatal care and birth year. Odds ratios are reported with 95% confidence intervals.

Infants born at lower GAs had higher rates of all morbidities. Rates of HTN increased with GA. HTN infants were smaller (mean 863±271 vs. 949±308 grams; $p<.01$), yet older (mean 27.0±1.8 vs. 26.2±2.1 wks GA; $p<.01$). After adjustment, surviving HTN infants exhibited fewer serious morbidities and were less likely to have ≥ 2 serious morbidities than -HTN infants across all GAs.

Surviving preterm infants born prior to 30 weeks gestation have high rates of severe morbidity. Infants born to mothers with hypertension have decreased risk of developing severe morbidity than comparison infants. This may translate to a reduced risk of long term developmental delay. Understanding how maternal hypertension influences outcome can aid in counseling families of extremely preterm infants.

3.2. Introduction

Infants born at extremely low gestational ages, below 30 weeks gestation, have high rates of mortality and morbidity. Although survival has improved, the smallest of these infants still have very high rates of morbidity and subsequent severe developmental delay.¹ These births and follow-up care prove costly. In 2005 alone, \$26.2 billion were spent on costs associated with preterm births occurring prior to 36 weeks gestation in the United States.² In addition burdens due to emotional strain and lost wages associated with high demands for ongoing care weigh heavily on caregivers and families of children with disabilities.³

The majority of preterm births have been attributed to two categories of causation, disorders of placentation, including preeclampsia and intrauterine growth restriction, or inflammation, including preterm labor, preterm premature rupture of membranes (pPROM), placental abruption, and cervical insufficiency.^{4,5}

Maternal hypertension complicates approximately 10% of pregnancies, and is associated with adverse pregnancy outcomes including maternal and fetal death, intrauterine growth restriction, and preterm birth.⁶ For preterm infants born to hypertensive mothers, there are conflicting reports on the outcome status of these infants. Several studies have reported that infants born to hypertensive mothers suffer from higher rates of morbidity and developmental disability, while other studies report the opposite effect.^{7,8} Over the past 2 decades, rates of preeclampsia have increased by 25%, as such, understanding the effect of hypertension on fetal development and infant outcome is essential.⁹

It is well established that some neonatal morbidities are associated with an increased risk of neurodevelopmental and physical delay. The specific morbidities most often linked to long term delay include bronchopulmonary dysplasia or chronic lung disease (CLD), major brain injury, nosocomial infections, necrotizing enterocolitis (NEC), and retinopathy of prematurity (ROP).¹⁰⁻¹⁵ The greater the number of individual morbidities suffered, and the more severe their presentation, the higher the risk of long term developmental impact. Combined risk assessment scores have been used to demonstrate that the additive effect of key morbidities including bronchopulmonary dysplasia, major brain injury, and severe retinopathy of maturity, yield a predictive 18%, 42%, 62%, and 88% rate, respectively, of presence of neurodevelopmental disability at 18 months corrected age in infants born under 1000 grams.¹⁶

Extremely preterm birth rates have increased in the past decade. While improvements in neonatal care over the past decade have reduced the rate of severe morbidity in survivors from 46.4% to 41.4%, the impact of extremely early births remain high, both for individual outcomes and the societal costs incurred.^{1,17} Maternal hypertension is one maternal complication contributing to extremely preterm birth. Extremely preterm infants born to hypertensive mothers have lower rates of mortality than infants not born to hypertensive mothers.¹⁸ Understanding maternal contributions to infant susceptibility is important, and the association between maternal hypertension and subsequent development of severe morbidities is not well understood. While maternal hypertension is unmistakably a serious maternal condition, we hypothesize that it has a less detrimental effect on fetal development and subsequent neonatal outcome than other

etiologies contributing to extreme prematurity, and will result in fewer serious morbidities during neonatal intensive care unit (NICU) stay.

3.3. Methods

Infants were identified from the Vermont Oxford Network (VON) Very Low Birth Weight (VLBW) database. The VON VLBW database collects de-identified data using predetermined definitions and uniform reporting forms across all participating member centers.¹⁹ The University of Vermont Institutional Review Board approved the VON VLBW database for research purposes. Infants included in the VLBW database must have a birth weight 401 and 1500 grams or born at gestational ages 22+0 to 29+6 and either inborn or transferred to a VON member center. The inclusion of maternal hypertension in the database limited our analysis to 2008 to 2011. In this analysis, infants were included if they were born between 22+0 and 29+6 weeks gestation, from singleton gestation, inborn or transferred within 28 days of birth to one of the 667 North American VON member centers, between 2008 to 2011, and survived until discharge from the NICU. Infants with life threatening birth defects (n=2099) were excluded from analysis.²⁰

Maternal hypertension is defined as a single reading above 140 systolic or 90 diastolic, prior to or during the pregnancy and identified in the maternal medical record at the time of delivery presentation. Infants born in VON centers are classified as inborn while those born elsewhere and transferred within the first 28 days of life are classified as outborn. All transferred infants are tracked for survival status until final discharge. Antenatal steroid administration is coded as yes if dosing was administered at any time prior to delivery. Prenatal care refers to documentation of any prenatal visits.

Infants were identified as having a morbidity if they were diagnosed with severe intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), severe ROP, NEC, CLD, or infection. Severe IVH was defined as grades 3 and 4, and cases were identified using cranial ultrasound, MRI, or computed tomography scan within 28 days of birth.²¹ PVL diagnosis required the presence of periventricular cysts on similar imaging techniques. Severe ROP was classified as stages ≥ 3 .²² The absence of retinal examination was recorded as an absence of ROP. NEC was identified by one or more clinical characteristics and one or more radiographic finding. CLD classified as receiving oxygen supplementation at 36 weeks postmenstrual age or if discharged with oxygen prior to 34 weeks postmenstrual age.²³ For infants discharged prior, presence of oxygen use at discharge confirmed a diagnosis. Infections, including early bacterial sepsis within 3 days of birth, late bacterial infections identified as coagulase-negative *Staphylococcus*, fungal, nosocomial, or other bacterial infections diagnosed more than 3 days after birth were evaluated individually and are reported as an overall risk of infection.

Morbidity was also evaluated using combined risk assessments modified from Schmidt *et al*, as an indicator of projected long term disability and neurodevelopmental delay.¹⁶ These combined risk assessment scores using a simple count of brain injury, including both IVH and PVL, bronchopulmonary dysplasia, and severe ROP as markers of injury which have a high predictive level on outcomes at 18 months corrected age.¹⁶ Combined risk assessment scores based on Schmidt were dichotomized ≤ 1 vs ≥ 2 in order to identify risk for long term disability of greater than 50%.

Comparisons were made between surviving infants born to hypertensive mothers versus those born to non-hypertensive mothers using chi-square tests and t-tests, with

statistical significance accepted at $\alpha=.05$ (Table 3.1). Infants were analyzed in 2-week gestational age increments: 22/23, 24/25, 26/27, and 28/29, to account for differences in developmental maturity and obstetric management practices with advancing gestation. Comparisons within GA cohorts were also performed. Each morbidity was analyzed separately, using logistic regression modeling to estimate the independent effect of hypertension. A variable combining risk of any severe morbidity was similarly evaluated. Combined risk assessments of less than or equal to 1 or greater than or equal to 2 were also evaluated. For all models, infant sex, maternal race, inborn/outborn, antenatal steroid exposure, prenatal care, and birth weight were included as covariates. These covariates were selected due to their association with outcomes and prior inclusion in VON models.^{1,24} Odds ratios are reported with 95% confidence intervals (CI). Standardized rates of morbidity 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. Regression analyses were based on generalized estimating equations (GEE) that accounted for the clustering of infants within hospital.²⁵ All analyses were performed using SAS Statistical Software Version 9.3 (SAS Institute, Cary, NC).

3.4. Results

The VON VLWB database contains records from 92,472 singleton infants born between 2008 and 2011. Chromosomal abnormalities and birth defects occurred in 4288 infants who were excluded from analysis. Death occurred in 15,853 infants. An

additional 315 infants were excluded due to missing survival data. Of the 72,016 infants identified as surviving to hospital discharge, 26% were born to mothers with hypertension. Births as a percentage of the population increased with increasing GA, with 3.6% of all infants born at 22/23 weeks, 21.1% at 24/25, 32.2% at 26/24, and 43.1% at 28/29 weeks gestation. We also observed increasing rates of maternal hypertension with increased GA, composing 10.2% of the overall population at 22/23 weeks, 17.6% at 24/25, 26.5% at 26/27, and 31.8% of the population at 28/29 weeks.

The study population was racially diverse, with 41% Caucasian, 32% Black, 20% Hispanic, and 6% classified as Other. There were more male infants, composing 53% of the study population, but the majority of infants, 53%, born to hypertensive mothers were female. While the majority of infants were inborn, received antenatal steroids, and prenatal care, rates for each were higher for those born to hypertensive mothers (Table 3.1).

At all GAs, infants born to hypertensive mothers were smaller than comparison infants. Within the 23/24 GA week cohort, there was an 8% discrepancy in size, 15% at 24/25 weeks, 18% at 26/27, and 16% within the 28/29 week cohort. Alternatively, the infants of hypertensive mothers were also older in terms of GA, with the mean GA of infants born to hypertensive mothers being 27.3 weeks while comparison infants were born at mean 26.7 weeks.

One or more severe morbidities were seen in 52.8% of surviving infants. Infants born within the lower week GA cohorts, 22/23 and 24/25, had higher rates of all morbidities, with 93% of 22/23 week, 82% of 24/25, 57% of 26/27, and 32% of 28/29 week infants developing at least one morbidity. Unadjusted risk for any morbidity was

higher in infants born at greater than 24 weeks gestation when born to hypertensive mothers (Table 3.2). After adjustment for birthweight (Table 3.3), infants born after 24 weeks gestation had decreased risk of developing any severe morbidity when born to hypertensive mothers. Fully adjusted odds ratios, with corresponding 95% confidence intervals (95% CI), and standardized rates are presented for each morbidity in Table 3.4.

CLD was observed most frequently, in 36.0% of surviving infants. Prior to adjustment, infants born to hypertensive mothers had higher rates of CLD when born at GAs above 24 weeks. There were no differences in the 22/23 week cohort, with more than 75% of each group developing CLD. After adjustment, infants born between 22 and 27 weeks did not differ between groups, however those in the 28/29 week cohort had lower odds (OR: 0.88 95% CI: 0.82 to 0.95) of developing CLD when born to hypertensive mothers.

Infections were second most frequently occurring, in 19.7% of survivors. Prior to adjustment, infants born to mothers with hypertension had no difference in risk of developing infection when born at 22 to 25 weeks. For those born between 26 and 29 weeks, risk was increased in infants born to hypertensive mothers. After adjustment, there was no difference in risk for 22/23 or 28/29 week infants and risk was decreased in 24/25 and 26/27 week infants born to hypertensive mothers.

ROP (9.4%), severe IVH (8.2%), NEC (7.0%), and PVL (3.5%) were observed in fewer infants. Infants born to hypertensive mothers had a lower risk of developing severe IVH at all GA in both univariate and multivariable models, the other morbidities were more complex. For each, ROP, NEC, and PVL, results were GA dependent, with a

reductions in risk seen within the higher GA infants born to hypertensive mothers (Table 3.4).

Combined risk assessment, assessing risk of developing ≥ 2 severe morbidities, resulted in no univariate differences risk to infants born to hypertensive mothers at GAs at less than 28 weeks. Within the 28/29 week cohort, only 1% of infants attained a combined risk assessment score of ≥ 2 , however there was a statistically significant decrease in risk for infants born to hypertensive mothers (OR: 0.82 95% CI: 0.70 to 0.97). After adjustment, there was no difference in risk between groups for 22/23 week infants, however all other infants had reduced risk of developing ≥ 2 severe morbidities when born to hypertensive mothers.

3.5. Discussion

Maternal health plays an important role in determining infant outcomes. In our study, after adjustment, infants born to hypertensive mothers had significantly lower odds of developing IVH within any gestational age cohort, PVL or ROP after 24 weeks gestation, NEC at 24/25 and 28/29, any infection at 24 to 27 weeks GA, CLD at 28/29, and an overall decreased risk of developing any severe morbidity when born after 24 weeks gestation. For no morbidity evaluated was maternal hypertension independently associated with an increased risk of morbidity. Similarly to some other reports, we report infants born to hypertensive mothers had a higher GA and better outcomes than comparison infants.⁴ These findings conflict with some studies which suggest infants born to hypertensive mothers have decreased risk of IVH and PVL, but increased risk of

other morbidities. In a recent population based study by Gagliardi *et al*, 23-31 week Italian infants born to mothers with disorders of placentation surviving NICU discharge had lower risk of IVH and PVL but higher risk of BPD and ROP than infants born following chorioamnionitis.⁴ A similar population based study of 22 to 29 week infants in France also demonstrated decreased risk of IVH and PVL in infants born to hypertensive mothers when compared to those born after pPROM.²⁶ Maternal infections, most typically linked to pPROM and preterm labor as etiologies for preterm birth, have been associated with IVH, respiratory dysfunction, and development of NEC in preterm infants.^{27,28}

The driving predictor of morbidity was birth weight, with adjustment for birth weight alone leading to a “flip” in odds ratio, from increased risk associated with maternal hypertension to a decreased risk in CLD, ROP, and infection after 24 weeks. By including other known predictors of morbidity in a fully adjusted model, including infant sex, maternal race/ethnicity, inborn/outborn status, prenatal care, and antenatal steroids, odds ratios continued to predict lower risk of all serious morbidities. The inclusion of other predictors caused odds ratios to be slightly higher than when adjusting for birth weight alone. This supports prior studies reporting increased risk of morbidity and mortality in small for gestational age infants.²⁹⁻³¹ Bernstein *et al*. reported increased risk of NEC and respiratory distress syndrome in growth restricted very-low-birth-weight infants.³⁰ These findings mimic our results in that prior to adjustment, CLD and NEC rates were higher in our infants born to mothers with hypertension (who were smaller), but adjustment for birth weight resulted in decreased risk for both morbidities.

The occurrence of morbidities stems from immaturity of infants' developing organ systems. IVH and PVL often occur together, with combined injury associated with high rates of cerebral palsy and low developmental scores.³² Our results highlight reduced risks across all GAs and of similar magnitudes in severe ROP, severe IVH, and PVL, which may be indicative of a related pathway between these morbidities. CLD, brain injury, and severe ROP are independently associated with poor developmental outcome during childhood, including low Bayley II scores, cerebral palsy, and neurodevelopmental disabilities.

Predictive methods for calculating how morbidities impact long term outcomes are inexact in extremely preterm infants. Schmidt's combined risk assessment scores have been validated in extremely low birth weight infants of 500 to 999 grams, using a simple count of BPD, brain injury, and severe ROP. While each morbidity individually yielded an odds ratio of 2.4 to 3.7 for poor outcome at 18 months corrected age, a simple count revealed predictive values of poor outcome at 18%, 42%, 62%, and 88% with 0 to 3 of these morbidities occurring.¹⁶ Adding additional unique morbidities, including NEC and infection within this model slightly increased the ability to predict poor outcomes at 18 months.³³ While this system is validated only in infants 500 to 999 grams, we elected to include infants outside of this BW window as the majority of infants beyond this range were within the 28/29 week GA cohort, and thus at a lower risk of developing severe morbidity. The benefit of combined risk assessment scores is the potential for revised later life projections of disability based on clinical progress of individual infants. This allows for more comprehensive clinical counseling to parents in regards to outcome.

We report higher rates of 0 and 1 and lower rates of 2 or more morbidities in infants born to hypertensive mothers when using combined risk assessments in our overall population. Within cohorts, rates of ≤ 1 or ≥ 2 morbidities are similar with and without maternal hypertension, and prior to adjusting for other covariates. After adjustment, all GA cohorts have significantly lower risk of developing ≥ 2 serious morbidities. Combined risk assessments suggest the development of severe morbidity is an effective measure of long term outcome. Using this logic, it is likely that extremely low gestational age infants born to hypertensive mothers have better long term outcomes than comparison infants due to their reduced risk of developing CLD, IVH, PVL, ROP, and NEC.

While this study has many strengths, the foremost being the size of this large multi-center database, it also suffers from limitations associated with definitions within the database. The VON database uses a very pragmatic definition of maternal hypertension, accepting either a singular systolic reading over 140 mmHg or a singular diastolic reading over 90 mmHg as maternal hypertension. This prevents us from exploring differences between hypertension diagnoses, so our results likely reflect some degree of obstetric management in cases where pregnancies can be prolonged. However, risk factors for and outcomes of infants born to each category are similar, so we believe it is unlikely that further parsing definitions would change our results.³⁴ Additionally, chronic hypertension, while a recognized contributor to fetal growth restriction, is only observed in approximately 2% of pregnant women, and thus is unlikely to compose much of our hypertension population.

It is important to address the selection of covariates as prior to adjustment, infants born to hypertensive mothers appeared to have increased risk of developing CLD, severe ROP, infections, and a combined 1 or more morbidity. Our covariates—BW, infant sex, maternal race/ethnicity, antenatal steroids, prenatal care, and location of birth are all well accepted by other models and reported in NICHD and prior VON publications.^{1,35} GA and BW are the two greatest predictors of outcomes at time of birth, and as BWs were significantly lower in infants born to hypertensive mothers as opposed to comparison infants, we viewed the decision to include BW within GA cohorts as crucial to understanding the independent contributions of hypertension to established models. In addition, by stratifying our population by gestational age, we have a better predictor of development than studies which use birth weight to define their population. Historically, birth weight was easily available and presumed to be the best predictor of fetal development. However the common use of ultrasound for pregnancy dating has resulting in gestational age being a much more accurate representative measure of fetal development—especially with the extremely preterm population, where fetal growth restriction is commonly reflected in low birth weights. We attribute the disagreement in results from prior publications to statistical approach.

The birth weight paradox has been addressed in prior publications.³⁶⁻³⁸ In this paradox, the association between prenatal variables and postnatal outcomes may result in collider bias when the adjusted variable may have been affected by a causal relationship between the two variables. That raises the question of whether birth weight is a proxy for fetal development. In order to determine if our findings were the result of collider bias,

we also modeled BW corrected for GA in order to minimize this potential bias, and conclusions were the same as correcting for BW within GA windows.

Maternal hypertension can lead to preterm birth, as well as fetal growth restriction, which both impact morbidity. These interactions could potentially result in collider bias. However, other factors also result in preterm birth and growth restriction.

Our understanding of intrauterine exposure to infection and inflammation is evolving. We project inflammation associated with infection, even when subclinical, has a more detrimental effect on fetal development than that associated with hypertension. Recent studies outline ways in which infants born after exposure to different uterine environments have different outcome projections.³⁹⁻⁴¹ Hypertension in pregnancy, while a serious condition that threatens both mother and fetus, seems to have a less detrimental effect on fetal/neonatal development than that associated with alternate processes leading to preterm birth. After adjustment, infants born to hypertensive mothers have decreased risk of developing IVH, PVL, or ROP, as well as lower rates of CLD, NEC, and infections. In addition, they have lower combined risk assessments, which have been validated as a method of evaluating risk of long term delay. These findings are important for clinical management, long term projections of development risk and health care needs, as well as counseling of parents of NICU infants.⁴²⁻⁴⁸

Table 3.1: Infant demographics and maternal characteristics for infants born to mothers with and without hypertension.

	No Hypertension (53,053)	Hypertension (18,963)
Inborn*	80.5	90.4
Cesarean Delivery*	54.6	89.8
Prenatal Care*	94.1	96.6
Male Sex*	54.3	47.4
Race*		
Black	31.3	35.5
White	41.3	41.9
Hispanic	20.9	17.4
Other	6.5	5.2
Birth weight, Grams (mean \pm SD)*	1016 \pm 285	901 \pm 257
22/23 weeks*	605 \pm 89	558 \pm 101
24/25 weeks*	749 \pm 131	635 \pm 163
26/27 weeks*	977 \pm 175	800 \pm 180
28/29 weeks*	1250 \pm 226	1046 \pm 222
Gestational Age, Weeks (mean \pm SD)*	27.1 \pm 1.8	27.7 \pm 1.6
Antenatal Steroids*	77.8	87.1

Individual characteristics marked with an asterisk are significantly different between groups ($p < .05$).
 Tabled values represent percent unless otherwise indicated.

Table 3.2: The independent predictive value of maternal hypertension on severe morbidity, unadjusted.

Gestational Age, Unadjusted	22/23 Odds Ratio (95% CI) Observed rates (-HTN%, HTN%)	24/25 Odds Ratio (95% CI) Observed rates (-HTN%, HTN%)	26/27 Odds Ratio (95% CI) Observed rates (-HTN%, HTN%)	28/29 Odds Ratio (95% CI) Observed rates (-HTN%, HTN%)
Any Morbidity	0.75 (0.50 to 1.13) (93%, 91%)	1.16 (1.03 to 1.30) (81%, 84%)	1.26 (1.19 to 1.35) 56%, 61%	1.11 (1.06 to 1.17) (31%, 34%)
Chronic Lung Disease	0.99 (0.75 to 1.31) (77%, 76%)	1.30 (1.18 to 1.44) (62%, 68%)	1.53 (1.43 to 1.63) (37%, 47%)	1.35 (1.27 to 1.44) (16%, 21%)
Severe ROP	0.80 (0.59 to 1.08) (42%, 36%)	1.23 (1.11 to 1.36) (23%, 27%)	1.35 (1.19 to 1.52) (6%, 8%)	1.07 (0.86 to 1.32) (1.3%, 1.4%)
Periventricular Leukomalacia	0.92 (0.59 to 1.42) (9.0%, 8%)	0.71 (0.57 to 0.89) (6%, 4.0%)	0.72 (0.60 to 0.86) (4%, 3%)	0.60 (0.50 to 0.72) (3%, 2%)
Severe Intraventricular Hemorrhage	0.59 (0.42 to 0.82) (25%, 16%)	0.62 (0.54 to 0.71) (16%, 11%)	0.48 (0.42 to 0.55) (9%, 5%)	0.56 (0.48 to 0.64) (4%, 2%)
Necrotizing Enterocolitis	0.78 (0.53 to 1.14) (13%, 11%)	0.86 (0.75 to 0.99) (11%, 9%)	1.01 (0.91 to 1.13) (8%, 8%)	0.95 (0.85 to 1.06) (5%, 4%)
Any Infection	1.10 (0.86 to 1.40) (46%, 49%)	1.07 (0.98 to 1.17) (33%, 35%)	1.15 (1.08 to 1.23) (19%, 22%)	1.20 (1.12 to 1.29) (10%, 12%)
Morbidity Count ≥ 2	0.80 (0.61 to 1.06) (46%, 41%)	1.08 (0.98 to 1.19) (27%, 28%)	1.09 (0.97 to 1.22) (8%, 9%)	0.82 (0.70 to 0.97) (2%, 1%)

Odds ratios (with associated 95% confidence intervals) and observed rates are presented

Table 3.3: The independent predictive value of maternal hypertension on severe morbidity, adjusted for birth weight.

Gestational Age, Adjusted for BW:	22/23	24/25	26/27	28/29
	Odds Ratio (95% CI) Observed rates (-HTIN%, HTIN%)	Odds Ratio (95% CI) Observed rates (-HTIN%, HTIN%)	Odds Ratio (95% CI) Observed rates (-HTIN%, HTIN%)	Odds Ratio (95% CI) Observed rates (-HTIN%, HTIN%)
Any Morbidity	0.63 (0.42 to 0.95) (94%, 90%)	0.79 (0.70 to 0.90) (82%, 79%)	0.83 (0.78 to 0.89) (58%, 54%)	0.80 (0.75 to 0.84) (34%, 29%)
Chronic Lung Disease	0.87 (0.66 to 1.15) (77%, 74%)	0.95 (0.85 to 1.05) (63%, 62%)	0.94 (0.87 to 1.00) (40%, 38%)	0.85 (0.79 to 0.91) (19%, 16%)
Severe ROP	0.73 (0.54 to 0.99) (42%, 35%)	0.83 (0.75 to 0.92) (25%, 21%)	0.62 (0.54 to 0.71) (8%, 5%)	0.56 (0.44 to 0.70) (1.6%, .9%)
Periventricular Leukomalacia	0.95 (0.61 to 1.47) (9%, 9%)	0.66 (0.53 to 0.83) (6%, 4%)	0.71 (0.58 to 0.87) (4%, 3%)	0.63 (0.52 to 0.77) (3%, 2%)
Severe Intraventricular Hemorrhage	0.59 (0.42 to 0.84) (25%, 16%)	0.62 (0.54 to 0.72) (16%, 11%)	0.49 (0.42 to 0.56) (9%, 5%)	0.57 (0.48 to 0.66) (4%, 2%)
Necrotizing Enterocolitis	0.77 (0.52 to 1.13) (13%, 10%)	0.77 (0.66 to 0.91) (11%, 8.5%)	0.88 (0.78 to 1.00) (8%, 7%)	0.77 (0.68 to 0.86) (5%, 4%)
Any Infection	1.00 (0.78 to 1.29) (47%, 47%)	0.89 (0.81 to 0.98) (34%, 31%)	0.85 (0.79 to 0.92) (21%, 18%)	0.93 (0.86 to 1.00) (11%, 10%)
Morbidity Count ≥ 2	0.73 (0.55 to 0.97) (46%, 39%)	0.77 (0.70 to 0.85) (28%, 23%)	0.61 (0.54 to 0.68) (10%, 6%)	0.53 (0.44 to 0.64) (3%, 1%)

Odds ratios (with associated 95% confidence intervals) and calculated standardized rates are presented.

Table 3.4: The independent predictive value of maternal hypertension on severe morbidity, fully adjusted model.

Gestational Age Adjusted:	22/23		24/25		26/27		28/29	
	Odds Ratio (95% CI) Standardized rates (-HTN%, HTN%)	Odds Ratio (95% CI) Standardized rates (-HTN%, HTN%)	Odds Ratio (95% CI) Standardized rates (-HTN%, HTN%)	Odds Ratio (95% CI) Standardized rates (-HTN%, HTN%)	Odds Ratio (95% CI) Standardized rates (-HTN%, HTN%)	Odds Ratio (95% CI) Standardized rates (-HTN%, HTN%)	Odds Ratio (95% CI) Standardized rates (-HTN%, HTN%)	
Any Morbidity	0.69 (0.46 to 1.04) (94%, 91%)	0.82 (0.73 to 0.93) (82%, 79%)	0.86 (0.80 to 0.92) (58%, 55%)	0.83 (0.79 to 0.88) (33%, 30%)				
Chronic Lung Disease	0.89 (0.67 to 1.18) (77%, 75%)	0.95 (0.86 to 1.05) (63%, 62%)	0.96 (0.89 to 1.03) (40%, 39%)	0.88 (0.82 to 0.95) (18%, 17%)				
Severe ROP	0.75 (0.55 to 1.02) 42%, 35%	0.85 (0.77 to 0.95) (24%, 22%)	0.68 (0.59 to 0.78) (8%, 5%)	0.60 (0.47 to 0.76) (2%, 1%)				
Periventricular Leukomalacia	0.95 (0.61 to 1.47) (9%, 9%)	0.71 (0.57 to 0.90) (6%, 4%)	0.77 (0.63 to 0.95) (4%, 3%)	0.68 (0.55 to 0.83) (3%, 2%)				
Severe Intraventricular Hemorrhage	0.62 (0.44 to 0.87) (25%, 17%)	0.68 (0.59 to 0.79) (16%, 12%)	0.55 (0.48 to 0.64) (9%, 5%)	0.65 (0.55 to 0.76) (4%, 3%)				
Necrotizing Enterocolitis	0.81 (0.54 to 1.20) (13%, 11%)	0.82 (0.70 to 0.96) (11%, 9%)	0.92 (0.81 to 1.06) (8%, 7%)	0.81 (0.72 to 0.92) (5%, 4%)				
Any Infection	1.03 (0.81 to 1.31) (47%, 47%)	0.90 (0.82 to 0.99) (34%, 31%)	0.88 (0.81 to 0.95) (21%, 19%)	0.96 (0.89 to 1.04) (11%, 10%)				
Morbidity Count ≥ 2	0.77 (0.58 to 1.02) (46%, 40%)	0.81 (0.73 to 0.89) (28%, 24%)	0.68 (0.61 to 0.77) (9%, 7%)	0.61 (0.50 to 0.74) (2%, 1.5%)				

Odds ratios (with associated 95% confidence intervals) and calculated standardized rates are presented.

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CHAPTER 4: MATERNAL HYPERTENSION AND MORTALITY IN SMALL FOR GESTATIONAL AGE 22+0 TO 29+6 WEEK INFANTS

4.1. Abstract

Infants born prior to 30 weeks gestational age (GA) to mothers with hypertension (HTN) have lower rates of mortality and serious morbidities when corrected for maternal and infant characteristics, including birth weight. Given the association between growth restriction and maternal HTN, we sought to determine if small for gestational age (SGA) infants, (birth weight <10th percentile for GA), have a similar decreased risk of mortality when born to mothers with HTN.

We identified 6,897 singleton SGA, 22+0 to 29+6 week GA infants born between 2008 and 2011 and cared for at 578 North American centers in the Vermont Oxford Network. Singleton infants with chromosomal abnormalities and birth defects were excluded. SGA was defined by 2001 & 2002 US national statistics, accounting for sex and race/ethnicity. Mortality rates were compared between the 4,317 born to mothers with HTN and 2,580 comparison infants. Logistic regression was used to adjust for BW, infant sex, maternal race, inborn/outborn, antenatal steroid exposure, prenatal care and GA. Data are presented as mean±SD. Odds ratios (OR) are reported with associated 95% confidence intervals (CI).

SGA HTN infants were older (mean 26.9±1.9 vs. 26.6±2.2 weeks; p<.001) than comparison SGA infants. There were no significant differences in BW (HTN: 584±159 vs -HTN: 562±156 grams; p=.27). Death occurred in 29% of SGA HTN infants and 43% of comparison infants. Univariate analyses revealed lower mortality for SGA HTN infants (OR 0.54, 95% CI: 0.48 to 0.60). After adjustment, mortality remained lower in the SGA HTN group when compared to other SGA infants (OR=0.60, CI: 0.52 to 0.69).

Extremely preterm SGA infants face exceedingly high rates of mortality. Although maternal HTN is associated with SGA, SGA infants born to mothers with HTN have decreased risk of mortality compared to SGA infants born to mothers without HTN, after adjustment for antenatal and maternal characteristics. This finding is important for parental counseling and, we speculate, the result of detrimental physiologic effects associated with alternative mechanisms for fetal growth restriction.

4.2. Introduction

Small for gestational age (SGA) infants have increased mortality when compared to appropriately grown infants (AGA).¹ SGA infants are most commonly defined as those being within the lowest 10th percentile birth weight for a given gestational age. A variety of factors, including genetic, maternal, fetal, and placental health play a role in determining growth potential; infants who fail to meet their potential have the highest risk of increased mortality and morbidities. Intrauterine growth restriction (IUGR), the fetal identification of delayed growth maturation, is commonly cited as the single largest contributing factor to perinatal mortality in otherwise healthy fetuses.² Infants born preterm are more frequently identified as growth restricted in comparison to term infants.³ The cause of IUGR is identifiable in approximately 40% of pregnancies, but remains idiopathic in the majority of cases. Most identifiable causes include abnormalities in uteroplacental perfusion and, fetoplacental perfusion.⁴

Within the United States, 12-13% of infants are born preterm, before 37 weeks gestation.⁵ Infants categorized as extremely preterm, under 32 weeks gestation, compose 52.7% of overall infant mortality, yet include only 1.9% of 2013 United States live births.⁶ While only 10% of infants are regularly identified as being SGA, the incidence of delayed growth is significantly higher in preterm infants, with up as many as 30% of low birth weight preterm babies with birth weights which would meet criteria for IUGR if they had remained in utero.⁷ These infants face an increased risk of perinatal mortality of 4 to 10 times that of AGA infants and preterm infants identified as SGA have a reported 13.8 times increased risk of death within the first year of life.⁸

Maternal hypertension has been consistently associated with the identification of IUGR, with as many as 59% of infants born to women with severe early onset preeclampsia being classified as growth restricted.⁹ In terms of SGA, there is a 3-4 fold increase in risk in women with preeclampsia compared to those without.¹⁰ Chronic hypertension is associated with the greatest incidence of low birth weight when compared to normotensive women or to those with hypertension developing during pregnancy.^{10,11} In the preterm population, infants born to a mother with preeclampsia, a subset of those developing hypertension during pregnancy, are on average 10-25% smaller than comparison infants of a similar gestational age.¹²

We have previously reported that infants born prior to 30 weeks gestation have a decreased risk of mortality when born to hypertensive mothers, as compared to similar weight infants born to normotensive mothers.¹³ Given the clear associations between maternal hypertension and growth restriction, and increased mortality in the preterm SGA population, we sought to determine if this association holds in an SGA population, with SGA infants born to hypertensive mothers having a decreased risk of mortality when compared to SGA infants born to normotensive mothers.

4.3. Materials and Methods

Small for gestational age infants born between 22+0 and 29+6 weeks gestational age were identified as a part of the VON VLBW database. To be included in the VLBW database, infants must have been born either between 401 and 1500 grams, or between 22+0 and 29+6 weeks GA.¹⁴ We examined mortality in infants born in the years 2008 to 2011 due to the availability of obstetric data, including maternal hypertension status.

Inclusion was limited to infants born in the 667 North American centers. Infants from multiple gestations and those with chromosomal abnormalities and birth defects associated high rates of mortality were excluded. The VLBW database exists in de-identified form, and as such, the University of Vermont Institutional Review Board has deemed it exempt from review.

Small for gestational age infants were identified using the 2001 & 2002 US national statistics, accounting for gestational age, infant sex and maternal race/ethnicity.¹⁵ Maternal HTN was categorized dichotomously from maternal medical records at the time of delivery presentation, with the presence of a single reading above 140 systolic or 90 diastolic, prior to or during pregnancy defining hypertensive status. Infants born in VON reporting 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. Antenatal steroid administration is defined as dosing administered at any time prior to delivery, with no differentiation in the database between a single dose, full course or multiple courses of treatment. Prenatal care refers to documentation of any prenatal visits. Mortality was defined as death prior to discharge. All transferred infants are tracked for survival status until final discharge.

Mortality rates were compared between the 4,317 SGA infants born to mothers with HTN and the 2,580 comparison SGA infants. Initial demographic characteristics evaluated differences between infants born to hypertensive mothers versus infants born to non-hypertensive mothers using chi² square and t-tests. Observed mortality rates between infants born to mothers with and without hypertension were compared within the total population and within 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. Logistic regression was used to estimate the independent effect of hypertension on infant mortality. Additional covariates in the model were birth weight, infant sex, maternal race, inborn/outborn status, antenatal steroid exposure, prenatal care, and gestational age. These covariates were chosen due to their association with outcomes and prior inclusion in VON models.^{1,16} 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.¹⁷ 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 $\alpha=.05$.

4.4. Results

Small for gestational age infants accounted for 6897 (7.9%) births recorded within the VON VLBW database between 2008 and 2011. Fewer infants were classified as SGA at 22 weeks gestation, however rates were fairly consistent from 23 to 29 weeks gestation (Figure 4.1). SGA infants born to hypertensive mothers were more likely to be inborn, and delivered by cesarean (Table 4.1). There was an overrepresentation of African American/Black male infants in the hypertension group, however the rate of male births was markedly lower (52.8%) in HTN SGA than comparison SGA infants (60.4%).

The hypertension group received higher rates of prenatal care and were more likely to have received antenatal steroids than comparison infants. They were also born at a slightly higher gestational age (mean 26.9 ± 1.9 vs. 26.6 ± 2.2 weeks; $p < .001$). The infants born to mothers with hypertension had slightly higher birth weights than comparison infants (HTN: 584 ± 159 vs -HTN: 562 ± 156 grams; $p < .001$).

Mortality was high within our SGA population, with death occurring prior to NICU discharge in 29% of SGA infants born to hypertensive mothers and 43% of comparison infants. Mortality rates decreased with increasing gestational age in both groups, however remained higher in infants born to mothers without hypertension within all gestational age windows (Figure 4.2). Univariate analyses demonstrated markedly lower mortality for SGA HTN infants with an odds ratio of 0.54 (95% CI: 0.48 to 0.60). After adjustment for clinically relevant variables, mortality remained lower in the SGA HTN group when compared to other SGA infants (OR=0.60, CI: 0.52 to 0.69). Other variables contributing to the mortality model included birth weight (OR=0.45 per 100 grams, CI: 0.41 to 0.49), male sex (OR= 1.91, CI: 1.68 to 2.17), antenatal steroids (OR= 0.45, CI: 0.38 to 0.54), gestational age (OR=0.82 per week, CI: 0.78 to 0.87), and race other than black (Hispanic OR=0.86, CI: 0.68 to 1.09; Caucasian OR=0.78, CI:0.68 to 0.91; Other OR=0.75, CI: 0.57 to 0.99). These results are presented in Table 4.2.

Within 2-week gestational age cohorts, the greatest reductions in mortality relating to maternal hypertension were seen at the lowest gestational ages. Infants born to mothers with HTN had significantly lower mortality than comparison infants in all cohorts born prior to 28 weeks GA (Table 4.3; 22/23: OR 0.23, CI: 0.12 to 0.45; 24/25: OR 0.68, CI: 0.53 to 0.88; 26/27: OR 0.57, CI: 0.46 to 0.70). For infants born at 28/29

weeks gestation, there was no significant relationship between maternal hypertension and mortality (OR 0.78, CI: 0.59 to 1.03).

4.5. Discussion

As expected, we report SGA infants in both groups have high rates of mortality, with decreases seen with increasing gestational age. Preterm infants born on the lower end of the growth curve face much higher odds of mortality compared to AGA infants, regardless of pregnancy complications.^{18,19} Multiple studies have reported preterm SGA infants face a 3-fold increase in mortality compared to non-SGA infants of similar gestational age.^{1,20} Our results demonstrate that while infants classified as SGA face high rates of mortality, there are population subsets, including those born to mothers with hypertension, who have decreased risk when compared to other SGA infants. This effect is seen in all infants born prior to 30 weeks gestation with the greatest effect at the lowest gestational ages at time of birth.

Several studies have suggested that maternal hypertension is associated with decreased survival in SGA infants, however many of these studies do not restrict to the preterm population. By restricting population to preterm infants, mortality in SGA infants born to hypertensive mothers is decreased when compared to normotensive mothers. Chen reported that preterm SGA infants born to mothers with hypertension have lower risk of mortality but term SGA infants have increased mortality when born to mothers with pregnancy-induced hypertension.²¹ The greatest reduction in risk associated with maternal hypertension was seen in the early preterm birth group, with moderate reduction in mortality risk for late preterm infants, and an increase in risk or mortality for term

infants born to mothers with hypertension.²¹ These results are similar to our findings, where the greatest reduction in mortality is seen at the lowest gestational ages when infants are born to mothers with hypertension.

There is a clear link between growth restriction and maternal hypertension, however that relationship varies with gestational age. Among SGA infants born at all gestational ages, at participating New Zealand and Australian centers, 25.3% were born to mothers with hypertension while 74.7% were born to normotensive mothers.²² Restricting to the preterm population yields very different results, as we report that 62.5% of North American preterm SGA infants were born to hypertensive mothers.

A large meta-analysis demonstrated women with chronic hypertension have increased risk of low birth weight, preterm birth, and SGA; antihypertensive treatment was shown to exacerbate these risks, and for every 10 mmHg reduction in blood pressure due to treatment, an average reduction of 145 gram reduction in fetal growth was observed.²³ Similarly, a population based Taiwanese study demonstrated an association between women receiving vasodilators and risk of delivering low birth weight infants.²⁴

One explanation for the observed improved survival of infants born to mothers with hypertension is likely that comparatively, maternal hypertension is less damaging for fetal development than other causes of growth restriction. These teratogenic exposures include infections such as cytomegalovirus, rubella, syphilis, and toxoplasmosis, malnutrition, chronic maternal diseases including kidney disease, clotting disorders, heart disease, and sickle cell anemia, or maternal exposures to known teratogens such as alcohol, drug abuse, or smoking. In effect, that would result in

observed decreased mortality in infants born to mothers with hypertension that is not related to hypertension, but is due to increased risk resulting from other causes of growth restriction and preterm birth.

A notable limitation of our study comes from the inability to differentiate between the differing maternal hypertensive diagnoses. As preeclampsia, chronic hypertension, and pregnancy associated (gestational) hypertension have all been linked with SGA infants and poor outcomes, our results are likely an underestimation of reduced risk of mortality. By classifying births following a single high blood pressure reading as maternal hypertension, the number of cases is likely an overestimation, resulting in some SGA infants who are growth restricted due to other factors, and who may therefore face an increased risk of mortality due to those factors.

Several studies have reported a large discrepancy between birth weight curves and those using fetal growth parameters, particularly among extremely preterm infants. Bernstein et al. noted significant differences in multiple cross-sectional studies comparing birth weight growth curves and those derived from fetal ultrasound. The first utilized regression lines comparing 350 birth weights at various gestational ages to 350 ongoing pregnancies, finding larger variability in the low gestational ages.²⁵ A second, larger study, reported more than 26% of preterm fetal weights were greater than the 90th percentile, with less than 2% below the 10th percentile when compared to birth weight.²⁶ These findings underscore that healthy fetuses with normal growth remain in utero, while those who are growth restricted have high rates of preterm birth.

When birth weight is used as the determination for appropriate growth, Zeitlin et al. suggested a cut-off at the twenty-fifth percentile would be more appropriate for identification of preterm infants at increased risk of mortality due to growth restriction.¹⁸ She reported increased odds of mortality of 3.98 (95% CI 2.79-5367) for infants with a birth weight of less than the 10th percentile born between 24 at 31 weeks gestation, and 2.15 (95% CI 1.54-3.00) for infants in the 10-25th birth weight percentiles when compared to those in the 50-75th percentile.¹⁸ The difference seen in growth curves becomes less important with increasing gestational age, as infants born closer to term have more comparison infants, and therefore have a more normal distribution of birth weight, highlighting the potential value of a hybrid growth curve which combines fetal and birth weight standards.²⁷ As many as 65-73% of SGA infants born between 25 and 30 weeks gestation may be misclassified as AGA, while infants born at term are highly unlikely to be misclassified due to the large number of comparison infants.²⁸ This is predominantly due to the health of infants born at particular gestational ages; term infants are healthier and are more likely to have been able to reach their growth potential, while preterm infants are faced with adverse intrauterine environments that impact growth potential and contribute to preterm birth.

Misclassification of growth restricted infants' results in only the most growth restricted infants being classified as SGA. Infants born prior to 34 weeks gestation were identified as SGA in 11.6% of the population using neonatal growth standards, but the use of fetal growth standards resulted in 23.3% of the same infant pool who were growth restricted.²⁹ This discrepancy results in a population of growth-restricted infants who are identified as being at increased risk of mortality according to birth weight standards, but

using fetal standards results in SGA being associated with increased risk of morbidity, including respiratory distress syndrome, bronchopulmonary dysplasia, interventricular hemorrhage, retinopathy of prematurity.²⁹ This population bias results in infants identified as SGA who are the smallest of growth restricted infants, and who therefore face the highest risk of mortality. Lackman et al. suggests the misidentification of at-risk fetuses may play a role in high stillbirth rates for growth restricted infants because they do not receive the increased prenatal monitoring given to pregnancies with known growth restriction.³⁰ This population bias clearly restricts the identification of infants included in this analysis, however as our primary objective was to identify mortality risk in SGA infants, we believe our use of birth weight curves for SGA identification is appropriate. We expect that if we were to repeat the study using fetal or hybrid growth curves, SGA infants born to hypertensive mothers would ultimately have lower rates of mortality and likely, also of major morbidity.

Factors affecting mortality risk in preterm infants are numerous, and the choice of variables included in multivariable models greatly impact results. Multivariable models are better at predicting diagnostic and prognostic outcomes than simple assessment of birth weight and gestational age.³¹ The NICHD recognizes gestational age, birth weight, sex, singleton status, and the reception of antenatal steroids in their Extremely Preterm Birth Weight Outcome calculator.³² Multivariable modeling allows for better inclusion of the overall perinatal period, multiple factors affecting outcome, and changes in status. Similarly, inclusion of covariates, such as prenatal care and inborn status at birth, which vary between groups, can be argued as being clinically relevant, with regard to outcome as one group is biased towards receiving better clinical care than

the other. As our results demonstrate, despite a significant univariate difference in which the hypertension group was both more likely to be inborn and to receive prenatal care, neither of these covariates affected the odds of mortality.

Preterm SGA infants have high mortality, but subsets of SGA infants appear to have unique clinical outcomes. In this report we identify SGA infants born prior to 30 weeks gestation to hypertensive mothers have less mortality than other similar gestational age SGA infants, particularly at the earliest gestational ages, and that maternal hypertension is an independent predictor of outcome and should be considered in neonatal prognosis.

Table 4.1: Small for gestational age infant demographics and maternal characteristics for infants born to mothers with and without hypertension.

	No Hypertension (2,580)	Hypertension (4,317)
Location*		
Inborn	88.5	90.7
Cesarean Delivery*	76.1	95.5
Prenatal Care*	95.8	98.3
Male Sex*	60.4	52.8
Race*		
(Black)	28.0	32.6
(White)	44.1	40.5
(Hispanic)	20.4	20.3
(Other)	7.5	6.7
Birth weight, grams (mean ± SD)	562 ± 156	584 ± 159
Gestational Age, Weeks*	26.6 ± 2.2	26.9 ± 1.9
Antenatal Steroids*	72.4	85.6
1 minute Apgar*	3.8 ± 2.5	4.1 ± 2.4
Mortality Rate*	43.1	28.9

Individual characteristics marked with an asterisk are significantly different between groups (p<.05). Values represent percent unless otherwise indicated.

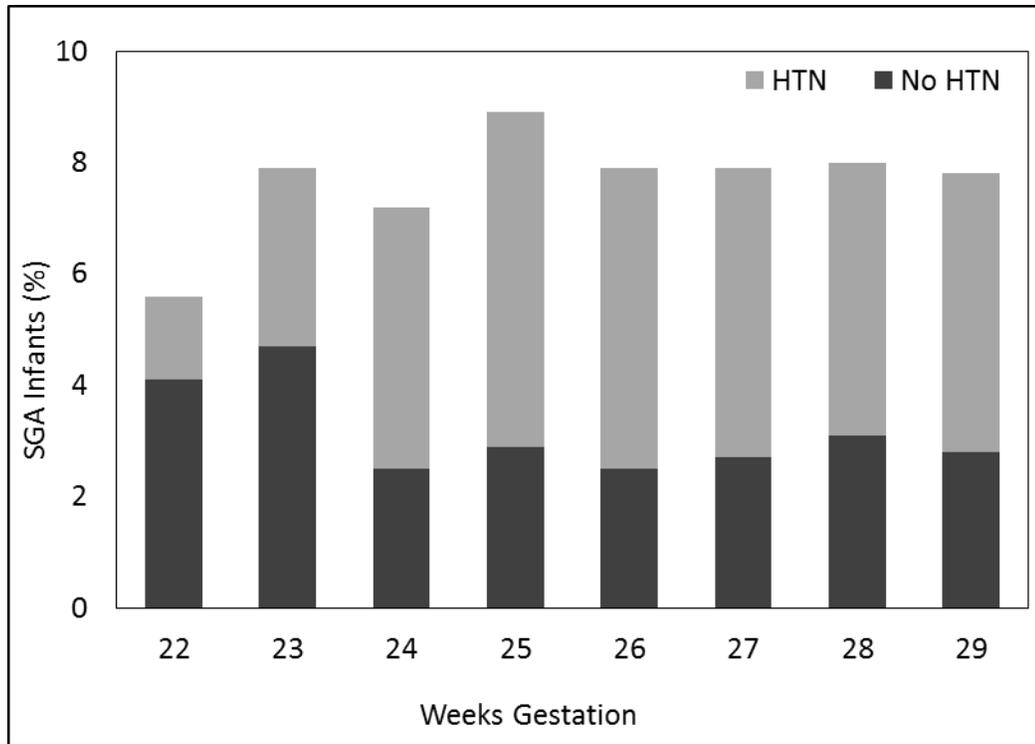


Figure 4.1: Incidence of small for gestational age infant birth at each gestational age by maternal hypertension status.

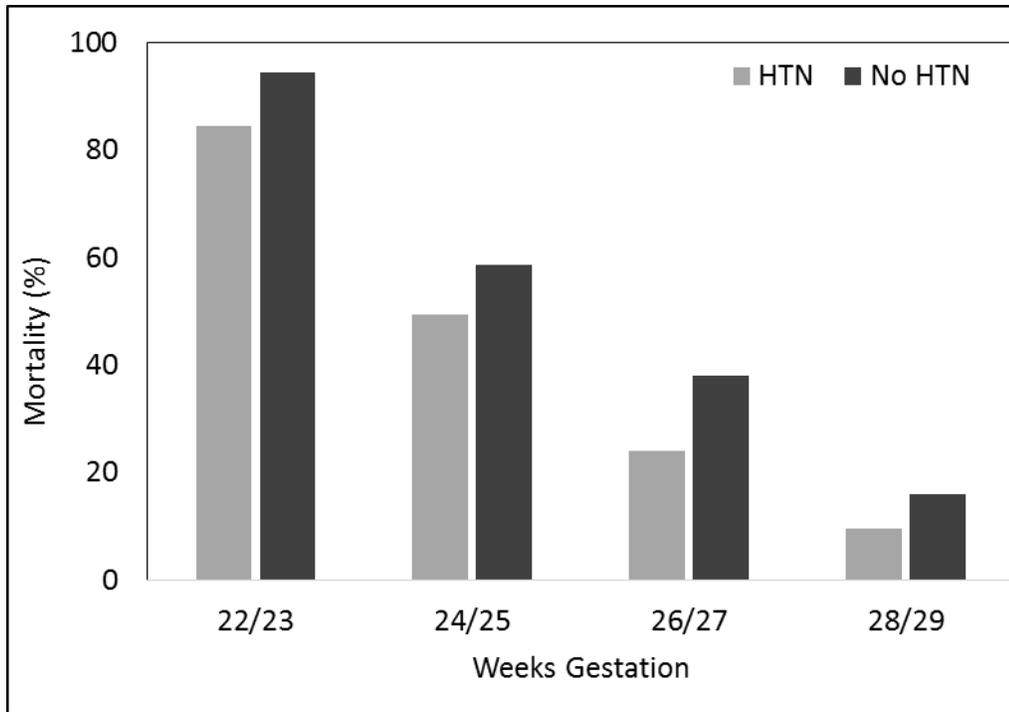


Figure 4.2: Infant mortality of SGA infant birth at each gestational age by maternal HTN status.

Table 4.2: The independent predictive value of maternal hypertension on mortality in small for gestational age infants.

	Odds Ratio	95% Confidence Interval
Hypertension	0.60	0.52 to 0.69
Birth Weight	0.45	0.41 to 0.49
Male Sex	1.91	1.68 to 2.17
(Ethnicity) Hispanic	0.86	0.68 to 1.09
(Race) Caucasian	0.78	0.68 to 0.91
(Race) Other	0.75	0.57 to 0.99
Location	1.09	0.76 to 1.58
Antenatal Steroids	0.45	0.38 to 0.54
Prenatal Care	0.70	0.47 to 1.03
Gestational Age	0.82	0.78 to 0.87

Odds ratios of relationship of mortality with all covariates in all SGA infants born 22+0 to 29+6 weeks GA. Reference race is African American/Black.

Table 4.3: Odds ratios of relationship of maternal hypertension and mortality in small for gestational age infants within 2-week gestational age cohorts.

	Odds Ratio, Unadjusted	95% Confidence Interval	Odds Ratio, Adjusted for Birth Weight	95% Confidence Interval	Odds Ratio, Adjusted for all Covariates	95% Confidence Interval
22/23 Weeks	0.33	0.19 to 0.55	0.18	0.10 to 0.33	0.23	0.12 to 0.45
24/25 Weeks	0.69	0.56 to 0.86	0.61	0.48 to 0.77	0.68	0.53 to 0.87
26/27 Weeks	0.53	0.44 to 0.64	0.56	0.46 to 0.68	0.57	0.46 to 0.70
28/29 Weeks	0.56	0.43 to 0.72	0.71	0.54 to 0.93	0.78	0.59 to 1.03

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