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Making Breathing Easier:

Does Surfactant Reduce the Association of Neonatal Respiratory Distress Syndrome with Maternal Hypertension?

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Making Breathing Easier:

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By

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Bachelor of Arts

Vanderbilt University

2007

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A thesis submitted to the Faculty of the
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ABSTRACT

Making Breathing Easier:

Does Surfactant Reduce the Association of Neonatal Respiratory Distress Syndrome with Maternal Hypertension?

By Erin Meade Duncan

CONTEXT: There is conflicting information regarding the association between maternal hypertension (mHTN, any diagnosis of hypertension while pregnant) and neonatal respiratory distress syndrome (RDS). Additionally, few studies have investigated mHTN and surfactant administration, which is a common treatment of neonatal RDS.

OBJECTIVE: To assess the direct effects of mHTN on neonatal RDS, and to see what total effect remains after consideration of surfactant administration (indirect effect).

DESIGN, SETTING, AND PARTICIPANTS: A retrospective cohort was comprised of U.S. birth certificate information from 2005-2009. Eligibility included live, singleton hospital births from 24-36 completed weeks' gestation, with exclusion of births including antenatal steroids and meconium staining (n=1,049,473). Directed acyclic graphs were constructed to incorporate information from literature review and expert opinion and select risk factors. Associative models for direct and indirect effects were constructed via multivariable logistic regression ~~and~~ using chunk method followed by backwards elimination.

MAIN OUTCOME MEASURES: Adjusted OR (aOR) of mHTN with and without adjustment for surfactant administration, percent difference in aORs between direct effect (mHTN on RDS) and indirect effect (mHTN on RDS via surfactant administration), and prevalence of neonatal RDS (given proxy of ventilation over 6 hours).

RESULTS: There is a significant association with mHTN and neonatal RDS by all gestational age categories, (aOR 1.77 for all eligible births, 1.47-1.81 after stratification by gestational age, $P<0.0001$). The association with mHTN and RDS continues after adjustment for surfactant administration (aOR 1.69 for all eligible births, 1.42-1.70 after stratification by gestational age, $P<0.0001$).

CONCLUSION: Given the extensive literature affirming the ability of exogenous surfactant to diminish the morbidity associated with neonatal RDS, this analysis suggests that healthcare providers are not appropriately targeting neonates in need of surfactant in cases of mHTN.

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TABLE OF CONTENTS

LIST OF ABBREVIATIONS

HTN=hypertension; cHTN=chronic hypertension; PIH=pregnancy induced hypertension; HELLP= hemolysis, elevated liver enzymes, low platelets; mHTN=maternal hypertension; SGA=small for gestational age; NICU=neonatal intensive care unit; RDS=respiratory distress syndrome; PTB=preterm birth; MAS=meconium aspiration syndrome; CNM=certified nurse midwife; DAG=directed acyclic graph; OR=odds ratio; VIF=variable inflation factor; RR=risk ratio; β1=beta coefficient

CHAPTER 1:

Background

MATERNAL HYPERTENSION

Methods of Classification Clinically there are at least four different classifications of hypertension (HTN) during pregnancy. These are: a) chronic hypertension (cHTN): blood pressures greater than 140/90 prior to 20 weeks' gestation; b) pregnancy induced hypertension (PIH): blood pressures greater than 140/90 first diagnosed after 20 weeks' gestation; c) pre-eclampsia: elevated blood pressures with protein in maternal urine, regardless of gestational age at diagnosis; and d) HELLP syndrome: hemolysis, elevated liver enzymes, and low platelets, often associated with pre-eclampsia, although the mechanism is unknown. The literature defines maternal HTN (mHTN) inconsistently. Studies investigating mHTN as the primary exposure tend to utilize separate definitions of cHTN and PIH to show causation, while studies investigating other maternal characteristics such as chronic disease or social determinants lump together all HTN diagnoses into one large "maternal hypertension" class (1-14). Still others exclude women with cHTN as a pre-existing condition (15). The argument is that cHTN can act synergistically with PIH, thus complicating the causal relationship between mHTN and poor neonatal outcomes. For the purposes of this study, mHTN is defined as any diagnosis of hypertension while pregnant.

Relationship to gestational age and birth weight Several studies have examined the impact of mHTN on gestational age and birth weight, both of which are extensively associated with poor neonatal outcomes (1, 8, 12, 16, 17). Habli et al. (2007) stratified by gestational age when examining the effect of different statuses of mHTN (pre-eclampsia, PIH, and normotensive pregnancies) on neonatal outcomes (2). They found that in pregnancies that delivered between 35 and 36 weeks' gestation, PIH was associated with both small for gestational age infants (SGA, defined as birth weight less than the 10^{th} percentile for the given gestational age) (18) and neonatal intensive care unit (NICU) admissions ($P<0.05$ for both associations) (2). In a secondary

analysis limited to infants delivered at 36 weeks, the presence of PIH, regardless of severity, showed increased rates of respiratory distress syndrome (RDS, defined as increased work of breathing due to a deficiency of surfactant, suspected in infants with increased respiratory rate, nasal flaring and grunting, often confirmed by a chest x-ray showing "ground glass opacities") (19) when compared to normotensive pregnancies at that gestational age (P <0.05) (2). This finding led the authors to conclude that it was early gestational age, caused by mHTN, which increased the odds of poor neonatal outcomes (2).

In contrast to Habli et al. (2007), Piper and Langer (1993) explored birth weight and chronic disease on lung maturity, specifically macrosomic infants of diabetic mothers and infants that developed intrauterine growth restriction (defined as intrauterine weight estimated below the 10^{th} percentile for the given gestational age) (18) secondary to mHTN (14). They found no significant difference in prevalence of either diabetes or mHTN by gestational age (no odds ratio (OR) given) and no association between maternal chronic disease and fetal lung maturity, as defined by the lecithin/sphingomyelin ratio (L/S, a value less than two results in an increased risk of RDS) (18, 19), when adjusted by gestational age. Thus, while many studies have shown that associations between mHTN and low birth weight exist, the causal pathway of mHTN leading to low birth weight, further leading to RDS, cannot be assumed (1, 6, 7, 15).

SURFACTANT

In the past decade, most studies conducted examining surfactant administration in the neonate focus on preterm deliveries only, although some also consider birth weight in the analysis (16, 17, 20, 21).

Synergism with Antenatal Steroids Many studies have looked at the combined effect of surfactant with antenatal steroids, which will be discussed later in this review (16, 17, 20, 21). Of note, Dani et al. (2009) note that while additive interaction (synergism) between surfactant and antenatal

steroids is documented, many neonatologists are hesitant to give surfactant to infants whose mother received antenatal steroids because of a high number needed to treat (16, 20). A 2008 clinical report by Engle and the Committee on Fetus and Newborn substantiates this claim, stating that up to 55% of infants born between 29-30 weeks' gestation whose mother received antenatal steroids did not receive surfactant after delivery; further, the discrepancy between antenatal steroids and surfactant administration decreased at earlier gestational ages (20).

Timing of Administration There are three different classifications of surfactant administration, all dependent on the timing of the dose: 1) prophylactic, defined as a dose given either prior to the onset of symptoms consistent with RDS or within the first 30 minutes of life; 2) early rescue, defined as a dose given after the onset of symptoms or between 1 to 2 hours postpartum; and 3) late rescue, defined as a dose given after the onset of symptoms after 2 hours postpartum. While the literature prior to the mid-2000's emphasized the superior efficacy of prophylactic surfactant doses to rescue doses in preventing neonatal morbidity, the advent of nasal continuous positive airway pressure has made the administration of surfactant easier in neonates demonstrating signs of RDS, thus minimizing the benefit of prophylaxis to rescue (16, 17, 20). Since both types of dosing occur soon after delivery, it is unclear which method is documented in the birth certificate (22).

RESPIRATORY DISTRESS SYNDROME

Identified by a 2006 Cochrane review as the "single-most important cause of morbidity and mortality in the preterm infant," reduction of RDS in the U.S. has been the focus of much research in neonatology and maternal fetal medicine (3, 17, 20, 21, 23-24). In addition to changes in surfactant administration, two factors have dominated the discussion for prevention of RDS: 1) the administration and proper timing of antenatal steroids; and 2) the presence of meconium

aspiration syndrome (MAS, defined as inhalation of first stool (meconium) either before or during delivery, causing airway obstruction, inflammation and surfactant inactivation) (18).

OTHER CONSIDERATIONS

Antenatal Steroids In 2000, the National Institute of Child Health and Human Development and the Office of Medical Applications of Research of the National Institutes of Health reaffirmed their 1994 consensus recommendations that all pregnant women between 24 and 34 weeks' gestation be given a single course of corticosteroids if delivery was imminent (within seven days), with the primary goal of promoting fetal lung maturity and the secondary goals of decreasing preterm birth (PTB, < 37 completed weeks' gestation) and other morbidities of prematurity (26). Since then, multiple studies have demonstrated that the administration of antenatal steroids improves neonatal pulmonary outcomes. A 2008 clinical guideline by Engle consolidated data from previous studies demonstrating that antenatal steroid administration not only significantly reduces RDS (Risk Ratio (RR) 0.65), but also significantly reduces surfactant administration (RR 0.45) and infant mortality (RR 0.62) (20). This guideline confirmed the findings of a Cochrane review in 2006, which reported a significant reduction in RDS among infants receiving antenatal steroids (RR 0.66) as well as recommending antenatal steroid use in women with mHTN (11). Unfortunately, Lee et al. (2011) found that, from 2005-2007, less than 80% of Californian mothers who should have received antenatal steroids by the guideline recommendations actually did so (27). Furthermore, Elimian et al. (1999) concluded that while antenatal steroid administration is associated with a significant reduction in RDS in all obstetric groups (P=0.05), antenatal steroid administration itself did not show reductions in either surfactant administration or RDS in infants of hypertensive moms (P=0.14 and P=0.38, respectively) (25).

Meconium Aspiration Syndrome The 2008 Engle report also explored past literature reviewing surfactant use in infants with MAS. Engle found a decrease in severity of respiratory difficulties secondary to MAS in infants that received surfactant compared to controls who did not receive surfactant (RR 0.64) (20). Results were reaffirmed by Wirbelauer and Speer in 2009 that, while certain chronic conditions such as gestational diabetes inhibit neonatal lung maturity by preventing endogenous surfactant production, MAS can actually inactivate already produced surfactant, leading to a post-natal lung immaturity and increased risk of RDS (odds not reported) (24).

Maternal Race and Ethnicity

Association with Maternal Hypertension Miranda, et al. (2010), and Baraban, McCoy, and Simon (2008) identified a correlation between mHTN and maternal race in North Carolina and California, respectively. Miranda concluded that Hispanic mothers were significantly less likely to experience mHTN and that non-Hispanic black mothers were significantly more likely to experience mHTN when each group was compared non-Hispanic white mothers (Hispanic OR 0.65-0.76 without trend when measured by increasing maternal age; non-Hispanic black OR 1.13-1.60 with increasing trend when measured by increasing maternal age) (1). Baraban, McCoy and Simon (2008) found similar conclusions to Miranda et al. (2010) and also noted that rates of mHTN have increased in Los Angeles county from 1991-2003, with the largest increase among non-Hispanic Black mothers and similar increases between white mothers and Hispanic mothers (4.8%, 2.6% and 2.3%, respectively) (4).

Latina Paradox Most discussion of maternal race and ethnicity has focused on neonatal outcomes, specifically low birth weight and PTB, rather than on maternal chronic disease (8, 28-31). Data have consistently shown that foreign-born and, more specifically, Mexican-born mothers, often have better birth outcomes than expected given socio-economic status, age and education: the so-called “Latina Paradox” (1, 29, 32). However, this protection typically

disappears after one generation in the U.S., suggesting that factors that may cause women to move to the U.S. (good health, ability to work, etc.) are negated by actual life in the U.S. (urban life, poor diet, etc.) (1, 29, 32).

Limitations of Birth Certificates

Maternal Chronic Disease In a 2000 study of 2,699 births in Washington state, Bradford, et al. (2007) examined the true positive rate (TPR) of selected birth certificate information in Certified Nurse-Midwife (CNM)-attended deliveries versus physician-attended deliveries. They found that CNM-attended deliveries were significantly more likely to have accurate reporting of PIH and premature rupture of membranes (PROM) ($P<0.001$ and $P=0.002$, respectively) (33). Furthermore, a second Washington-based study by Lyndon-Rochelle et al. (2005) found that correct diagnoses were more likely to be reported in hospital discharge data than on birth certificates; moreover, birth certificates underreported many maternal conditions, including cHTN, PIH and diabetic disorders (odds not reported) (34). Several other papers reach the same conclusion: while the 2003 revision to birth certificate data is easily accessible and a vast improvement on the 1998 revision, it is not always reliable and is grossly user dependent (22, 33-36).

Race and Ethnicity In examining the impact of recording maternal race and ethnicity on birth certificates, Kirmeyer and Martin (2007) found that birth weight by gestational age shows a bimodal trend (with birth weights centering around 1300g and 3200g, respectively) in births occurring between 28 and 31 weeks' gestational age. This trend suggests that documentation by last menstrual period may cause misclassification by gestational age. Fortunately, this trend has declined from 1990 to 2000, although the change has been less apparent in Hispanic mothers (a -9.36% change in the second curve, compared to -25.12% in non-Hispanic blacks and -13.13% in non-Hispanic whites, no *P*-value reported). Additionally, Hispanic mothers were the only ethnic group to see an overall increase in births between 28-31 weeks' gestation in the same time period

(+32.38%). These results taken together, the authors called for further studies to investigate how documentation of gestational age can be impacted by maternal ethnicity (37).

Leslie, Diehl, and Galvin (2006) found little correlation between maternal country of origin and birth outcome in Hispanic births in North Carolina from 1993-1997 (PTB rate 8.2% in U.S. born Hispanic mothers, compared to 8.0% in Mexican born mothers), contradicting national data. Nonetheless, the authors suggest that the large Hispanic community in North Carolina continues to contribute to the protective qualities of the paradox (38).

CHAPTER II:

Making Breathing Easier: Does Surfactant Reduce the Association of Neonatal Respiratory Distress Syndrome with Maternal Hypertension?

INTRODUCTION

With the 2003 update of the U.S. Birth Certificate, researchers have an increasingly easy, concise, and accessible source of information regarding maternal conditions and perinatal outcomes (22, 33-36). Research has examined the increasing incidence in gestational diabetes and its association with micro- and macrosomia (defined as birth weight less than 2500g and greater than 4000g, respectively) (34, 35), poor fetal lung maturity, and PTB. However, unlike diabetes, there is no unified statement on whether mHTN also increases the risk of RDS in the neonate (defined as within the first 28 days post-partum) (2, 8, 12, 14, 16, 17, 40).

To counteract fetal lung immaturity, exogenous surfactant has been identified since the 1980's (and readily available since 1990) (19) as a method to improve neonatal lung function in the viable premature infant (born between 24 and 37 weeks' gestation). However, most of the recent literature has focused on how the advent of antenatal steroids has decreased the rate of neonatal RDS (11, 16, 17, 20, 25-27) without examining if surfactant alone can decrease the risk of RDS in infants of mothers with chronic disease.

Problem Definition

Maternal Hypertension and Neonatal Respiratory Distress Syndrome Torrance et al. (2008) examined lung maturity in infants born to mothers with PIH and HELLP syndrome, respectively (3). They found that, when compared to infants born to normotensive mothers,

infants born to mothers with PIH were less likely to demonstrate lung immaturity, while infants born to mothers with HELLP were more likely to demonstrate lung immaturity (P=0.02 and P=0.04, respectively) (3). The discussion hypothesized that these variations could be attributed to chronic placental insufficiency from PIH leading to an acceleration of fetal lung maturity, while HELLP syndrome increases oxidative stress, thus compromising lung maturity (3). Langenveld et al. (2011) also found that, compared to infants born to normotensive mothers, the risk of RDS was decreased in infants born to hypertensive mothers (OR 0.81 in PIH, OR 0.69 in pre-eclampsia) (12).

However, others have suggested the opposite, i.e., that mHTN actually increases the risk of RDS. In a 2007 study, Gilbert, Young and Danielsen found that infants born to hypertensive mothers had a significant increase in their odds of RDS (OR 4.0, compared to infants born to normotensive mothers) (13). Since 2000, similar, although not as strong, results have been found by Habli et al. (2007); Baraban, McCoy, and Simon (2008); and Hauth et al. (2000) (2, 4, 15).

Maternal Hypertension, Surfactant, and Respiratory Distress Syndrome There has been little published information to establish an association between mHTN and surfactant administration (16, 17, 21, 23-24). A small retrospective study by Torrance et al. (2008) examined respiratory outcomes in preterm SGA babies with and without signs of placental insufficiency in utero (3). They found that infants born to mothers with HELLP syndrome were significantly more likely to receive surfactant compared to infants born to normotensive mothers (OR 5.3). While they found decreased odds of surfactant administration to infants of mothers with PIH and pre-eclampsia, neither trend was statistically significant (3).

Research Objective In response to these observations, this retrospective cohort study aims to build on another study examining the total effect of mHTN on neonatal RDS by investigating whether exogenous surfactant mediates this association.

Hypotheses

Primary hypothesis ("Direct Effect," previously documented): infants delivered to mothers with mHTN will have increased odds of RDS.

Secondary hypothesis ("Indirect Effect," explored here): exogenous surfactant administration to the neonate mediates the association between mHTN and RDS; the extent of this effect is unknown.

METHODS

Subjects and Sample Data on patient characteristics and outcomes came retrospectively from the Centers for Disease Control and Prevention's National Center for Health Statistics public access Research Data Center. All U.S. births from 2005-2009 were examined when they met the following characteristics: live, singleton, hospital births between 24 and 36 completed weeks' gestation utilizing the 2003 Revision.

A Priori Analysis Using a review of the literature and verbal discussion with experts in neonatology and maternal epidemiology, a series of a priori directed acyclic graphs (DAGs) were constructed to evaluate the primary and secondary hypotheses as well as the covariates.

Measurement All measurements and analyses were conducted using SAS 9.3 (Cary, NC). Given the large sample size and to distinguish the difference between etiologic and statistical significance, this study utilized an alpha of 0.001. Unless otherwise stated, all assumptions for logistic regression (linearity on the log scale) were met. According to information available on the birth certificate, neonatal ventilation over 6 hours was used as a proxy for RDS.

Descriptive Overview Relationships between mHTN, maternal and neonatal risk factors, and neonatal RDS were explored. Possible covariates were divided into three subcategories: *1) maternal characteristics*, which was further subdivided into *a) obstetric history* (primiparous, multiparous, and multiparous with a history of PTB), and *b) medical history* (chronic diabetes, gestational diabetes, and chorioamnionitis)*; 2) delivery conditions* (cesarean delivery, fetal intolerance, and PROM); and *3) neonatal characteristics* (male infant, and surfactant given) (see **APPENDIX 1: VARIABLES** for more information).

Analysis A descriptive analysis gave frequency and percentage for dichotomous variables by all eligible births and after stratification by gestational age. To reflect breakdowns found in the

literature and via expert opinion, these were defined as extremely preterm (24-27 weeks), very preterm (28-31 weeks), preterm (32-34 weeks) and late preterm (35-37 weeks) (2, 5, 12, 37). All other analyses continue to investigate by these divisions.

Confounding In building an associative model for mHTN on neonatal RDS, a table of possible confounders was constructed using simple logistic regression. Covariates found to be significant for both mHTN and RDS were considered confounders for the given division of gestational age. Unless otherwise stated, confounders were included in the construction of associative models.

Interaction Crude logistic regression using interaction terms between gestational age and mHTN and between gestational age and surfactant assessed potential interaction between gestational age and the direct and indirect exposures. In the same manner, interaction was also investigated between mHTN and the previously identified risk factors, as well as between surfactant and the same risk factors. A significant *P*-value of the interaction term for surfactant and the risk factor in question was used as an indication of interaction.

Associative Models Associative models not including surfactant were built to explore the direct effect, and then again using surfactant to explore the indirect effect. Variable inflation factor (VIF) assessed collinearity. Confounders and interaction terms found previously with mHTN and surfactant were added into the associative models unless otherwise stated. C-index assessed goodness of fit for all candidate models. If multiple candidates demonstrated c-indices with less than 10% variation, the more parsimonious model was selected. Non- significant terms were removed via backwards selection.

Surfactant Administration Final models examining the impact of mHTN on RDS both with and without surfactant (indirect and direct effects) were stratified by gestational age. The resulting percent differences calculated the degree of variance between the total effect of mHTN on RDS both with and without surfactant to determine the effect of mHTN that remains after surfactant administration.

RESULTS

A Priori Analysis The DAG for the direct and indirect effects, in conjunction with the literature review, helped to establish the process for approaching data analysis (**FIGURE II.1**). DAGs for covariates (**FIGURE II.2**) revealed that many typical covariates, including maternal factors (origin, race, age, socio-economic status, prenatal care, and induction of labor) and neonatal factors (low birth weight, NICU admission, and ventilation for at least one hour but less than six hours) were already controlled for by controlling for descendants. Thus, these variables were not included in analysis (**FIGURE II.3**).

According to trends in the literature, the dataset was restricted to pregnancies not complicated by antenatal steroids or MAS (11, 20, 24, 26) (**FIGURE II.3**). Given that a woman with a history of PTB is by definition multiparous, parity and history of PTB were combined to make one variable "multiparous with a history of PTB" (**FIGURES II.2-II.4**).

Measurement

Descriptive Overview Frequencies and percentages for all risk factors were summarized for the 1,049,473 births eligible for the study (**TABLE II.1**). Analysis of variance (ANOVA) showed that all risk factors varied significantly across gestational ages, with the exception of chronic diabetes (P=0.006). With increasing gestational age, nearly all risk factors trended either up (multiparity, gestational diabetes) or down (RDS, primiparity, multiparity with a previous PTB, chorioamnionitis, cesarean delivery, fetal intolerance, PROM, surfactant administration). The exceptions included chronic diabetes (no trend) and mHTN (peak at 13.7% of births in the very premature cohort) (**TABLE II.1**).

Most risk factors were comparatively rare in the "all eligible births" set, with both the primary exposure (mHTN) and outcome (RDS) impacting 10.6% and 3.6% of eligible pregnancies, respectively. Other rare risk factors included multiparity with a history of PTB,

chronic diabetes, gestational diabetes, chorioamnionitis, fetal intolerance, PROM, and surfactant (4.4%, 1.4%, 5.1%, 1.0%, 5.1%, 7.9%, and 1.4% of all eligible births, respectively). However, once viewed by gestational age, the "rareness" of these risk factors was no longer maintained, as some trended down as gestational age increased (RDS, max 20.1%; PROM, max 17.4%; and surfactant administration, max 11.2%, all for extremely preterm births) (**TABLE II.1**). When viewing the extremes of gestational age, these trends remained, with all variance among all risk factors showing significance with the exception of chronic diabetes (P=0.59) (**TABLE II.2**).

Despite literature linking maternal smoking to RDS, maternal smoking was not included in the analysis because over 20% of births did not report smoking status. It is acknowledged that this omission could cause some exposure misclassification. Other variables dropped due to excessive numbers of missing data, as well as a dearth of information in the literature regarding any association with mHTN, included weight gain during pregnancy, with more than 10% missing, and 5 minute APGAR, with over 5% missing (**FIGURE II.4**).

Analysis

Confounding As the alpha was set at 0.001, a two table approach was used to find potential confounders between mHTN and RDS for given gestational ages rather than the typical 10% difference between crude and adjusted ORs (aORs). Without stratification by gestational age, the only risk factor that was not found to be a confounder was multiparity with a history of PTB (P =0.010 for association to mHTN) (**TABLE II.3**). This lack of confounding continued after stratification by gestational age (P=0.039, P=0.29, P=0.09, and P=0.016 for association to mHTN for extremely preterm, very preterm, preterm, and late preterm births, respectively) (**TABLES II.3A-II.3D**).

Other risk factors found not to be confounders after stratification for gestational age include gestational diabetes (P=0.200 for association to RDS for extremely preterm births), male sex (P=0.017 for association to RDS for extremely preterm births) (**TABLE II.3A**), multiparity

without a history of PTB (P=0.79 for association to RDS for late preterm births), and chorioamnionitis (P=0.33 for association to mHTN for late preterm births). (**TABLE II.3D**).

With respect to surfactant, it remained a confounder for all gestational age stratifications, with moderate and consistent correlation to mHTN (OR 2.22 for all eligible births; OR 1.49, OR 2.21, OR 2.12, OR 2.00 for extremely preterm, very preterm, preterm, and late preterm births, respectively, all P values <0.0001) and strong, increasing correlation to RDS (OR 74.70 for all eligible births; OR 21.23, OR 30.28, OR 44.87, OR 103.70 for extremely preterm, very preterm, preterm, and late preterm births, respectively, all P values <0.0001) (**TABLES II.3A-II.3D**).

Interaction Interaction was not present between mHTN and gestational age (P =0.06) but was present between surfactant and gestational age (P <0.0001) when viewing all eligible births (P-values for interaction term, data not shown). Risk factors that showed interaction with surfactant included obstetric risk factors (multiparity and multiparity with a history of PTB), medical factors (chorioamnionitis), and delivery factors (cesarean delivery, fetal intolerance, and PROM) (all P <0.0001) (**TABLE II.4**).

After stratification by gestational age, most potential interactions remained constant, with few exceptions. While chorioamnionitis showed interaction in all eligible births, it did not show interaction after stratification (P=0.56, P=0.13, P=0.03, and P=0.29 in extremely preterm, very preterm and late preterm births, respectively). Multiparity was the only risk factor that trended away from significant interaction with increasing gestational age (P=0.002 in late preterm births). No risk factors went from non-significant to significant interaction with increasing gestational age (**TABLE II.4**).

Building Models Candidates for the associative models included the 1) crude, 2) saturated, 3) interactive, 4) confounded, and 5) combined (interactive and confounded) models (**TABLE II.5**). All candidate models, with the exception of the crude model, included surfactant as a risk factor. There were no concerns for collinearity, as the VIF for all risk factors in all scenarios was less than 2 (data not shown). A second set of associative models were built in the

same manner as the direct effect (described previously), this time using surfactant as a confounder and considering interaction terms with surfactant and the risk factors in order to assess the indirect effect.

For all gestational age divisions, the saturated candidate had either better discrimination (c-index=0.778 for very preterm births) or the same discrimination (c-index=0.776, 0.761, 0.718 for all eligible, extremely preterm, and late preterm births, respectively) compared to the combined candidates. Additionally, discrimination in the preterm birth cohort varied less than 10% between the saturated (c-index=0.733) and the combined candidates (c-index=0.734). As a result, all final models were constructed using backward selection from the saturated models. Non-significant terms dropped from candidate models included primiparity (late preterm births), multiparity (all models), chronic diabetes (extremely preterm births), gestational diabetes (all eligible, extremely preterm and very preterm births), chorioamnionitis (extremely preterm births), and male infant (extremely preterm births). All final models showed less than 1% variation in discrimination from their respective saturated candidate (**TABLE II.5**).

All final models showed confounding with the crude, with changes in the beta co-efficient (β1) between the crude and adjusted for mHTN of 35%, 28%, 37%, 33%, and 36% for all eligible, extremely preterm, very preterm, preterm, and late preterm births, respectively (crude OR 2.24, 1.62, 2.31, 2.20, 2.00, compared to aOR 1.69, 1.42, 1.70, 1.69, 1.55 for all eligible births and by increasing gestational age, respectively; all $P<0.0001$) (**TABLE II.6, TABLE II.5)**. Additionally, all final models had aORs for surfactant that were much greater than the aORs for mHTN (surfactant aOR 59.52, 19.70, 25.81, 37.80, and 85.61for all eligible births all eligible births and by increasing gestational age, respectively) (**TABLE II.7**). For the final models, see **TABLE II.6**.

Evaluating Indirect Effect of Maternal Hypertension through Surfactant Once the models were made, aORs for mHTN were compared to answer the secondary hypothesis. Percent differences between aORs for mHTN without the inclusion of surfactant (direct effect) compared

to the aORs for mHTN with the inclusion of surfactant (indirect effect) were all less than 10% and without trend (5%, 3%, 7%, 3%, 4% in all eligible births, extremely preterm, very preterm, preterm and late preterm births, respectively) (**TABLE II.8).**

DISCUSSION

This large, retrospective cohort quantifies the total effect of mHTN on neonatal RDS, as well as mitigation (if any) of that effect by exogenous surfactant. While the literature has been inconsistent on the association of mHTN and RDS (2-4, 12, 14, 15, 19), the results of this study show a clear association (aOR mHTN for direct effect 1.77 for all eligible births, ranging 1.47-1.81 after gestational age stratification) (**TABLE II.8**) that is minimally diminished by surfactant administration (aOR mHTN for indirect effect 1.69 for all eligible births, ranging 1.42-1.70 after gestational age stratification) (**TABLE II.8**). Assuming the validity of the birth certificate data, the results point to a harmful association of mHTN on neonatal RDS.

In fact, the percent differences between aORs of mHTN for the direct and indirect effects are less than 10% both before and after stratification of gestational age. This suggests one of the following: 1) healthcare providers are not appropriately targeting neonates in need of surfactant in cases of mHTN; or 2) surfactant does not help prevent RDS in cases of mHTN as previously thought. Given the extent of literature affirming the ability of exogenous surfactant to diminish the morbidity associated with neonatal RDS (16, 17, 20, 22), the former is the more likely possibility.

In an attempt to focus purely on the impact of exogenous surfactant, this analysis was limited to neonates whose mothers were not given antenatal steroids. Since the effect of exogenous surfactant did not appear to be highly effective in reducing RDS risk among these infants and the literature has shown a synergism between surfactant and antenatal steroids, appropriate treatment for all women with mHTN may be to administer antenatal steroids prophylactically, although the timing of this administration needs further elucidation.

Trends While the frequency of most risk factors trends either up or down with increasing gestational age, mHTN (the primary exposure) does not. This is because mothers delivering at

earlier gestational ages are removed from the later gestational age pool, a form of preterm delivery bias. Additionally, obstetricians are more likely to induce labor prior to 34 weeks' gestation if mHTN is severe, as suggested by Sibai (2000). In contrast, the percentage of births affected by chronic diabetes remains statistically constant with increasing gestational age (ANOVA P=0.006), suggesting that some chronic conditions are more easily managed while pregnant than mHTN.

Strengths One of the greatest strengths of this study is its size. With over 1,000,000 births, this captures one quarter of U.S. births fitting the eligibility criteria (n=3,867,748) (44). As such, and given the rareness of mHTN, the sample population easily approximates the target population. Additionally, setting the alpha to 0.001 allows a maximization of power. Finally, given the large dataset, gestational age could be further subdivided, allowing for applicability in the clinical setting.

By focusing this study on births delivered between 24 and 36 completed weeks' gestation, those most at risk for neonatal RDS (20, 21) can be examined, as well as targeting neonates more likely to receive surfactant (16, 17, 20, 21). Additionally, using these restrictions in gestational age increases the rate of surfactant administration to 14 per 1,000 (**TABLE II.1**), compared to 3.7 per 1,000 in the general population (35).

Limitations The major limitation of this study was that it employed only publicly available data. A proxy for RDS (ventilation over 6 hours) was utilized, and the varying degrees of mHTN had to be combined rather than viewed separately (there is no allotment on the 2003 revision for pre-eclampsia or HELLP syndrome) (3, 12, 14). The timing of surfactant administration was not defined. Given that a "rescue" dose could happen within 2 hours of life, and making a second assumption that the NICU and the obstetrics floors are communicating well, researchers assumed that most administration was captured (16, 17, 20, 22). That said, there is likely some degree of

exposure and outcome misclassification. Since the timing of administration cannot be determined, discussion of surfactant and RDS must be limited to correlation and not causation.

While the birth certificate should ideally be an accurate source of information, literature reviews have shown that it struggles to identify maternal chronic conditions (22, 33-36) and lacks universality in dealing with mothers from different cultures (37, 38). Combination with discharge documentation would aid in overcoming this potential selection bias (33).

Lastly, while many of the risk factors examined should intuitively demonstrate interaction, the impact of such interaction was not statistically strong enough to account in building models. Nonetheless, finding interaction among so many risk factors does complicate the picture, and future studies should continue to take possible interaction into account.

TABLES FOR CHAPTER II

TABLE II.1: Descriptive Analysis of Eligible Births, by frequency (%)

Relationships between mHTN, maternal and neonatal risk factors, and neonatal RDS explored, with a descriptive analysis giving frequency and percentage for dichotomous variables by all eligible births and after stratification by gestational age (as reflected by literature review and expert opinion). Bold p-value shows non-significant association (alpha=0.001). Ventilation over 6 hours used as proxy for RDS. Bolded p-values show non-significant association. (alpha=0.001). Data from U.S. Birth Certificates with the given inclusion criteria: live, singleton, hospital birth between 24-27 weeks' gestation; Delivery between 2005-2009 and utilized 2003 Revision of Birth certificate; delivery not complicated by antenatal steroids or meconium aspiration syndrome.

RISK FACTOR		All Eligible Births n= 1,049,473	Extremely Preterm Births n= 34,164	Very Preterm Births n= 90,514	Preterm Births n= 252,824	Late Preterm Births n= 671,971	p value (F- value)[a]
PRIMARY INTEREST	Maternal Hypertension	110,781 (10.6)	4,221 (12.4)	12,293 (13.7)	28,580 (11.4)	65,687 (9.8)	<.0001 (534.17)
	Neonatal Respiratory Distress Syndrome	37,636 (3.6)	6,818 (20.1)	9,431 (10.5)	10,915 (4.3)	10,472 (1.6)	<.0001 (16,448.3)
SECONDARY INTEREST	Surfactant Given	15,071 (1.4)	3,793 (11.2)	4,622 (5.1)	3,674 (1.5)	2,982 (0.5)	<.0001 (12,379.7)
MATERNAL CONDITIONS	Obstetric History						
	Primiparous	408,523 (39.4)	16,193 (48.6)	38,175 (42.9)	99,823 (40.0)	254,332 (38.3)	
	Multiparous	582,196 (56.1)	15,218 (45.7)	46,517 (52.3)	138,016 (55.3)	382,445 (57.5)	<.0001 (375.4)
	Multiparous + previous PTB	46,291 (4.4)	1,900 (5.7)	4,338 (4.9)	11,828 (4.7)	28,225 (4.2)	
	Medical History						
	Chronic Diabetes	14,254 (1.4)	461 (1.4)	1,263 (1.4)	3,590 (1.4)	8,940 (1.3)	**0.006 (4.12)**
	Gestational Diabetes	52,835 (5.1)	822 (2.4)	3,697 (4.1)	12,804 (5.1)	35,512 (5.3)	<.0001 (248.46)
	Chorioamnionitis	10,604 (1.0)	1,206 (3.5)	1,540 (1.7)	2,614 (1.0)	5,244 (0.8)	<.0001 (988.58)
DELIVERY CONDITIONS	Cesarean Delivery	403,404 (38.4)	19,255 (56.4)	43,881 (48.5)	103,097 (40.8)	237,171 (35.3)	<.0001 (4,007.12)
	Fetal Intolerance	53,463 (5.1)	2,414 (7.1)	5,919 (6.5)	13,938 (5.5)	31,192 (4.6)	<.0001 (347.59)
	PROM	82,838 (7.9)	5,901 (17.4)	10,121 (11.3)	25,221 (10.0)	41,140 (6.2)	<.0001 (3,365.89)
NEONATAL CONDITIONS	Male	564,762 (53.7)	18,036 (52.8)	48,091 (53.1)	137,040 (54.2)	361,595 (53.8)	<.0001 (15.6)

Extremely Preterm=24-27 weeks' gestation; Very Preterm=28-31 weeks' gestation; Preterm=32-34 weeks' gestation; Late Preterm=35-37 weeks' gestation; PTB=preterm birth; PROM=premature rupture of membranes

[a] Analysis of Variance

Table II.2: Descriptive Analysis for Eligible Births, by frequency (%) for Extremes of Age (Extremely Preterm Births vs. Late Preterm Births)

Relationships between mHTN, maternal and neonatal risk factors, and neonatal RDS explored, with a descriptive analysis giving frequency and percentage for dichotomous variables by extremely preterm and late preterm births (as reflected by literature review and expert opinion). Bold p-value shows non-significant association (alpha=0.001). Data from U.S. Birth Certificates with the given inclusion criteria: live, singleton, hospital birth between 24-27 weeks' gestation; Delivery between 2005-2009 and utilized 2003 Revision of Birth certificate; delivery not complicated by antenatal steroids or meconium aspiration syndrome.

PREDICTOR		Extremely Preterm Births n= 34,164 (%)	Late Preterm Births n= 671,971 (%)	F Value[a]	p-value[a]
PRIMARY INTEREST	Maternal Hypertension	4,221 (12.4)	65,687 (9.8)	280.89	<.0001
	Neonatal Respiratory Distress Syndrome	6,818 (20.1)	10,472 (1.6)	50159.2	<.0001
SECONDARY INTEREST	Surfactant Given	3,793 (11.2)	2,982 (0.5)	42040	<.0001
MATERNAL CONDITIONS	Obstetric History				
	Primiparous	16,193 (48.6)	254,332 (38.3)	1254.34	<.0001
	Multiparous	15,218 (45.7)	382,445 (57.5)	2036.99	<.0001
	Multiparous + previous PTB	1,900 (5.7)	28,225 (4.2)	159.27	<.0001
	Medical History				
	Chronic Diabetes	461 (1.4)	8,940 (1.3)	**0.29**	**0.59**
	Gestational Diabetes	822 (2.4)	35,512 (5.3)	551.37	<.0001
	Chorioamnionitis	1,206 (3.5)	5,244 (0.8)	2756.27	<.0001
DELIVERY CONDITIONS	Cesarean	19,255 (56.4)	237,171 (35.3)	6459.71	<.0001
	Fetal Intolerance	2,414 (7.1)	31,192 (4.6)	415.42	<.0001
	PROM	5,901 (17.4)	41,140 (6.2)	6837.17	<.0001
NEONATAL CONDITIONS	Male	18,036 (52.8)	361,595 (53.8)	13.11	<0.001

Extremely Preterm=24-27 weeks' gestation; Late Preterm=35-37 weeks' gestation; PTB=preterm birth; PROM=premature rupture of membranes

[a]Analysis of Variance

TABLE II.3 Potential Confounders between Maternal Hypertension and Neonatal Respiratory Distress Syndrome (All eligible births, no stratifcation by gestational age)

Tables of possible confounders constructed using simple logistic regression. Ventilation over 6 hours used as proxy for RDS. Covariates found to be significant for both mHTN and RDS considered confounders for the given division of gestational age. Bolded p-values show non-significant association. (alpha=0.001). Data from U.S. Birth Certificates with the given inclusion criteria: live, singleton, hospital birth between 24-27 weeks' gestation; Delivery between 2005-2009 and utilized 2003 Revision of Birth certificate; delivery not complicated by antenatal steroids or meconium aspiration syndrome.

		MATERNAL HYPERTENSION (%)						RESPIRATORY DISTRESS SYNDROME (%)					
	RISK FACTOR	YES n=110,781 (10.6)	NO n= 935,007 (89.4)	OR [a]	(95% CI)		p-value[c]	YES n=37,636 (3.6)	NO n=1,006,911 (96.4)	OR [b]	(95% CI)		p-value[c]
MATERNAL CONDITIONS	Obstetric History												
	Primiparous	55,405 (13.6)	353,118 (86.4)	---	---	---		16,079 (4.0)	390,888 (96.1)	---	---	---	
	Multiparous	48,453 (8.3)	588743 (91.7)	0.58	0.57	0.59	<0.0001	17,709 (3.1)	562,441 (97.0)	0.77	0.75	0.78	<0.0001
	Multiparous + previous PTB	6,079 (13.1)	40,212 (86.9)	0.96	0.94	0.99	**0.010**	3,401 (7.4)	42,605 (92.6)	1.94	1.87	2.02	<0.0001
	Medical History												
	Chronic Diabetes	5,157 (36.2)	9,097 (63.8)	4.97	4.80	5.15	<0.0001	1,006 (7.1)	13,171 (92.9)	2.08	1.95	2.22	<0.0001
	Gestational Diabetes	12,001 (22.7)	40,834 (77.3)	2.66	2.61	2.72	<0.0001	2,235 (4.3)	50,357 (95.8)	1.20	1.15	1.26	<0.0001
	Chorioamnionitis	924 (8.8)	9,619 (91.2)	0.81	0.76	0.87	<0.0001	1,065 (10.1)	9,461 (89.9)	3.07	2.88	3.27	<0.0001
DELIVERY CONDITIONS													
	Cesarean	67,156 (16.7)	335,083 (83.3)	2.76	2.72	2.79	<0.0001	23,242 (5.8)	378,289 (94.2)	2.68	2.63	2.74	<0.0001
	Fetal Intolerance	10,869 (20.4)	42,450 (79.6)	2.29	2.24	2.34	<0.0001	4,830 (9.1)	48,334 (90.9)	2.92	2.83	3.01	<0.0001
	PROM	5,984 (7.3)	75,998 (92.7)	0.65	0.63	0.67	<0.0001	6,563 (8.0)	75,323 (92.0)	2.62	2.55	2.69	<0.0001
NEONATAL CONDITIONS													
	Surfactant Given	3,075 (20.5)	11,913 (79.5)	2.22	2.13	2.31	<0.0001	10,131 (67.2)	4,940 (32.8)	74.70	72.06	77.44	<0.0001
	Male	57,746 (10.3)	505,072 (89.7)	0.93	0.92	0.94	<0.0001	21,677 (3.9)	540,422 (96.1)	1.17	1.15	1.20	<0.0001

PTB=preterm birth; PROM=premature rupture of membranes

[a]Odds Ratio of given risk factor increasing the likelihood of maternal hypertension

[b]Odds Ratio of given risk factor increasing the likelihood of respiratory distress syndrome

[c]p-value of Maximum Likelihood Estimate

TABLE III.3A Potential Confounders between Maternal Hypertension and Neonatal Respiratory Distress Syndrome (Extremely preterm births, dataset limited to births between 24-27 weeks' gestation)

Tables of possible confounders constructed using simple logistic regression. Ventilation over 6 hours used as proxy for RDS. Covariates found to be significant for both mHTN and RDS considered confounders for the given division of gestational age. Bolded p-values show non-significant association. (alpha=0.001). Data from U.S. Birth Certificates with the given inclusion criteria: live, singleton, hospital birth between 24-27 weeks' gestation; Delivery between 2005-2009 and utilized 2003 Revision of Birth certificate; delivery not complicated by antenatal steroids or meconium aspiration syndrome.

		MATERNAL HYPERTENSION (%)						RESPIRATORY DISTRESS SYNDROME (%)					
	RISK FACTOR	YES n= 4,221 (12.4)	NO n= 29,716 (87.6)	OR[a]	(95% CI)		p-value[c]	YES n= 6,818 (20.1)	NO n= 27,162 (79.9)	OR [b]	(95% CI)		p-value[c]
MATERNAL CONDITIONS	Obstetric History												
	Primiparous	2,172 (13.4)	14,021 (86.6)	---	---	---		3,333 (20.7)	12,786 (79.3)	---	---	---	
	Multiparous	1,698 (11.2)	13,520 (88.8)	0.81	0.76	0.87	<0.0001	2,752 (18.2)	12,408 (81.9)	0.85	0.80	0.90	<0.0001
	Multiparous + previous PTB	288 (15.2)	1,612 (84.8)	1.15	1.01	1.32	**0.039**	601 (31.9)	1,286 (68.2)	1.79	1.62	1.99	<0.0001
	Medical History												
	Chronic Diabetes	183 (39.7)	278 (60.3)	4.80	3.97	5.80	<0.0001	121 (26.4)	337 (73.6)	1.44	1.17	1.77	<0.001
	Gestational Diabetes	220 (26.8)	602 (73.2)	2.66	2.27	3.12	<0.0001	178 (21.8)	637 (78.2)	1.12	0.94	1.32	**0.200**
	Chorioamnionitis	73 (6.1)	1,116 (93.9)	0.45	0.36	0.57	<0.0001	380 (31.6)	821 (68.4)	1.89	1.67	2.15	<0.0001
DELIVERY CONDITIONS													
	Cesarean	3,582 (18.7)	15,560 (81.3)	5.10	4.67	5.56	<0.0001	4,450 (23.2)	14,725 (76.8)	1.59	1.50	1.68	<0.0001
	Fetal Intolerance	491 (20.5)	1,907 (79.5)	1.92	1.73	2.13	<0.0001	898 (37.4)	1,504 (62.6)	2.59	2.37	2.82	<0.0001
	PROM	451 (7.7)	5,416 (92.3)	0.54	0.49	0.60	<0.0001	1,647 (28.0)	4,228 (72.0)	1.73	1.63	1.85	<0.0001
NEONATAL CONDITIONS													
	Surfactant Given	630 (16.8)	3,130 (83.2)	1.49	1.36	1.63	<0.0001	2,883 (76.0)	910 (24.0)	21.13	19.47	22.93	<0.0001
	Male	1,995 (11.1)	15,918 (88.9)	0.78	0.73	0.83	<0.0001	3,689 (20.6)	14,257 (79.4)	1.07	1.01	1.13	**0.017**

PTB=preterm birth; PROM=premature rupture of membranes

[a]Odds Ratio of given risk factor increasing the likelihood of maternal hypertension

[b]Odds Ratio of given risk factor increasing the likelihood of respiratory distress syndrome

[c]p-value of Maximum Likelihood Estimate

TABLE II.3B Potential Confounders between Maternal Hypertension and Neonatal Respiratory Distress Syndrome (Very preterm births, dataset limited to births between 28-31 weeks' gestation)

Tables of possible confounders constructed using simple logistic regression. Ventilation over 6 hours used as proxy for RDS. Covariates found to be significant for both mHTN and RDS considered confounders for the given division of gestational age. Bolded p-values show non-significant association. (alpha=0.001). Data from U.S. Birth Certificates with the given inclusion criteria: live, singleton, hospital birth between 24-27 weeks' gestation; Delivery between 2005-2009 and utilized 2003 Revision of Birth certificate; delivery not complicated by antenatal steroids or meconium aspiration syndrome.

		MATERNAL HYPERTENSION (%)						RESPIRATORY DISTRESS SYNDROME (%)					
	RISK FACTOR	YES n= 12,293 (13.7)	NO n= 77,770 (86.4)	OR [a]	(95% CI)		p-value [c]	YES n= 9,431 (10.5)	NO n= 80,668 (89.6)	OR [b]	(95% CI)		p-value [c]
MATERNAL CONDITIONS	Obstetric History												
	Primiparous	6,364 (16.7)	31,811 (83.3)	---	---	---		4,345 (11.4)	33,705 (88.6)	---	---	---	
	Multiparous	5,096 (11.0)	41,421 (89.0)	0.62	0.59	0.64	<0.0001	4,071 (8.8)	42,270 (91.2)	0.75	0.71	0.78	<0.0001
	Multiparous + previous PTB	696 (16.0)	3,642 (84.0)	0.96	0.88	1.04	**0.29**	888 (20.6)	3,426 (79.4)	2.01	1.86	2.18	<0.0001
	Medical History												
	Chronic Diabetes	535 (42.4)	728 (57.6)	4.82	4.30	5.39	<0.0001	246 (19.6)	1,007 (80.4)	2.12	1.84	2.44	<0.0001
	Gestational Diabetes	963 (26.1)	2,734 (74.0)	2.33	2.16	2.52	<0.0001	469 (12.7)	3,217 (87.3)	1.26	1.14	1.39	<0.0001
	Chorioamnionitis	100 (6.6)	1,426 (93.5)	0.44	0.36	0.54	<0.0001	330 (21.6)	1,195 (78.4)	2.41	2.13	2.73	<0.0001
DELIVERY CONDITIONS													
	Cesarean	9,878 (22.6)	33,804 (77.4)	5.32	5.08	5.57	<0.0001	6,309 (14.4)	37,368 (85.6)	2.34	2.24	2.45	<0.0001
	Fetal Intolerance	1,491 (25.3)	4,404 (74.7)	2.30	2.16	2.45	<0.0001	1,328 (22.6)	4,553 (77.4)	2.74	2.57	2.93	<0.0001
	PROM	851 (8.5)	9,199 (91.5)	0.56	0.52	0.60	<0.0001	1,802 (17.9)	8,271 (82.1)	2.07	1.96	2.19	<0.0001
NEONATAL CONDITIONS													
	Surfactant Given	1,144 (24.9)	3,446 (75.1)	2.21	2.06	2.37	<0.0001	3,247 (70.3)	1,375 (29.8)	30.28	28.28	32.42	<0.0001
	Male	6,154 (12.9)	41,691 (87.1)	0.87	0.84	0.90	<0.0001	5,217 (10.9)	42,647 (89.1)	1.10	1.06	1.15	<0.0001

PTB=preterm birth; PROM=premature rupture of membranes

[a]Odds Ratio of given risk factor increasing the likelihood of maternal hypertension

[b]Odds Ratio of given risk factor increasing the likelihood of respiratory distress syndrome

[c]p-value of Maximum Likelihood Estimate

TABLE II.3C Potential Confounders between Maternal Hypertension and Neonatal Respiratory Distress Syndrome (Preterm birth, dataset limited to births between 32 and 34 weeks' gestation)

Tables of possible confounders constructed using simple logistic regression. Ventilation over 6 hours used as proxy for RDS. Covariates found to be significant for both mHTN and RDS considered confounders for the given division of gestational age. Bolded p-values show non-significant association. (alpha=0.001). Data from U.S. Birth Certificates with the given inclusion criteria: live, singleton, hospital birth between 24-27 weeks' gestation; Delivery between 2005-2009 and utilized 2003 Revision of Birth certificate; delivery not complicated by antenatal steroids or meconium aspiration syndrome.

		MATERNAL HYPERTENSION (%)						RESPIRATORY DISTRESS SYNDROME (%)					
	RISK FACTOR	YES n= 28,520 (11.4)	NO n= 223,301 (88.7)	OR[a]	(95% CI)		p-value [c]	YES n= 10,915 (4.3)	NO n= 240,702 (95.7)	OR [b]	(95% CI)		p-value [c]
MATERNAL CONDITIONS	Obstetric History												
	Primiparous	14,303 (14.3)	85,520 (85.7)	---	---	---		4,632 (4.7)	94,774 (95.3)	---	---	---	
	Multiparous	12,430 (9.0)	125,586 (91.0)	0.81	0.76	0.87	<0.0001	5,185 (3.77)	132,349 (96.2)	0.80	0.77	0.84	<0.0001
	Multiparous + previous PTB	1,623 (13.7)	10,205 (86.3)	0.95	0.90	1.01	**0.09**	991 (8.4)	10,759 (91.6)	1.89	1.76	2.03	<0.0001
	Medical History												
	Chronic Diabetes	1,358 (37.8)	2,232 (62.2)	4.94	4.62	5.30	<0.0001	299 (8.4)	3,274 (91.6)	2.04	1.81	2.31	<0.0001
	Gestational Diabetes	3,071 (24.0)	9,733 (76.0)	2.64	2.53	2.76	<0.0001	766 (6.0)	11,968 (94.0)	1.44	1.34	1.56	<0.0001
	Chorioamnionitis	218 (8.4)	2,383 (91.6)	0.71	0.62	0.82	<0.0001	206 (8.0)	2,384 (92.1)	1.92	1.67	2.22	<0.0001
DELIVERY CONDITIONS													
	Cesarean	18,805 (18.3)	83,965 (81.7)	3.19	3.11	3.28	<0.0001	6,598 (6.4)	96,026 (93.6)	2.30	2.21	2.40	<0.0001
	Fetal Intolerance	2,987 (21.5)	10,913 (78.5)	2.27	2.18	2.37	<0.0001	1,442 (10.4)	12,416 (5.2)	2.80	2.64	2.97	<0.0001
	PROM	1,853 (7.4)	23,257 (92.6)	0.60	0.57	0.63	<0.0001	1,873 (7.5)	23,190 (92.5)	1.95	1.85	2.05	<0.0001
NEONATAL CONDITIONS													
	Surfactant Given	772 (21.1)	2,892 (78.9)	2.12	1.95	2.30	<0.0001	2,272 (61.8)	1,402 (38.2)	44.87	41.84	48.12	<0.0001
	Male	14,811 (10.9)	121,714 (89.2)	0.90	0.88	0.92	<0.0001	6,355 (4.7)	129,999 (95.3)	1.19	1.14	1.23	<0.0001

PTB=preterm birth; PROM=premature rupture of membranes

[a]Odds Ratio of given risk factor increasing the likelihood of maternal hypertension

[b]Odds Ratio of given risk factor increasing the likelihood of respiratory distress syndrome

[c]p-value of Maximum Likelihood Estimate

TABLE II.3D Potential Confounders between Maternal Hypertension and Neonatal Respiratory Distress Syndrome (Late preterm births, dataset limited to births between 35-37 weeks' gestation)

Tables of possible confounders constructed using simple logistic regression. Ventilation over 6 hours used as proxy for RDS. Covariates found to be significant for both mHTN and RDS considered confounders for the given division of gestational age. Bolded p-values show non-significant association. (alpha=0.001). Data from U.S. Birth Certificates with the given inclusion criteria: live, singleton, hospital birth between 24-27 weeks' gestation; Delivery between 2005-2009 and utilized 2003 Revision of Birth certificate; delivery not complicated by antenatal steroids or meconium aspiration syndrome.

		MATERNAL HYPERTENSION (%)						RESPIRATORY DISTRESS SYNDROME (%)					
	RISK FACTOR	YES n= 65,687 (9.8)	NO n= 604,220 (90.2)	OR[a]	(95% CI)		p-value[c]	YES n= 10,472 (1.6)	NO n= 658,379 (98.4)	OR [b]	(95% CI)		p-value[c]
MATERNAL CONDITIONS	Obstetric History												
	Primiparous	32,566 (12.8)	221,766 (87.2)	---	---	---		3,769 (1.5)	249,623 (98.5)	---	---	---	
	Multiparous	29,229 (7.6)	353,216 (92.4)	0.56	0.55	0.57	<0.0001	5,701 (1.5)	375,414 (98.5)	1.01	0.97	1.05	**0.79**
	Multiparous + previous PTB	3,472 (12.3)	24,753 (87.7)	0.96	0.92	0.99	**0.016**	921 (3.3)	27,134 (96.7)	2.25	2.09	2.42	<0.0001
	Medical History												
	Chronic Diabetes	3,081 (34.5)	5,859 (65.5)	5.03	4.81	5.26	<0.0001	340 (3.8)	8,553 (96.2)	2.55	2.28	2.85	<0.0001
	Gestational Diabetes	7,747 (21.8)	27,765 (78.2)	2.78	2.70	2.85	<0.0001	822 (2.3)	34,535 (97.7)	1.54	1.43	1.65	<0.0001
	Chorioamnionitis	533 (10.2)	4,694 (89.8)	1.05	0.96	1.14	**0.33**	149 (2.9)	5,061 (97.1)	1.86	1.58	2.20	<0.0001
DELIVERY CONDITIONS	Cesarean	34,891 (14.7)	201,754 (85.3)	2.26	2.22	2.30	<0.0001	5,885 (2.5)	230,170 (97.5)	2.39	2.30	2.48	<0.0001
	Fetal Intolerance	5,900 (19.0)	25,226 (81.0)	2.27	2.20	2.33	<0.0001	1,162 (3.8)	29,861 (96.3)	2.63	2.47	2.80	<0.0001
	PROM	2,829 (6.9)	38,126 (93.1)	0.67	0.64	0.70	<0.0001	1,241 (3.0)	39,634 (97.0)	2.10	1.98	2.23	<0.0001
NEONATAL CONDITIONS	Surfactant Given	529 (17.8)	2,445 (82.2)	2.00	1.82	2.20	<0.0001	1,729 (58.0)	1,253 (42.0)	103.70	96.14	111.86	<0.0001
	Male	34,786 (9.7)	325,749 (90.4)	0.96	0.95	0.98	<0.0001	6,416 (1.8)	353,519 (98.2)	1.36	1.31	1.42	<0.0001

PTB=preterm birth; PROM=premature rupture of membranes

[a]Odds Ratio of given risk factor increasing the likelihood of maternal hypertension

[b]Odds Ratio of given risk factor increasing the likelihood of respiratory distress syndrome

[c]p-value of Maximum Likelihood Estimate

TABLE II.4 Interactions between Risk factors and Surfactant

Crude logistic regression using interaction terms between risk factors and surfactant assessed potential interaction. A significant P-value of the interaction term for surfactant and the risk factor in question was used as an indication of interaction. Bolded p-values show non-significant association (alpha=0.001). Models constructed as follows: Neonatal respiratory distress syndrome = maternal hypertension + Surfactant + risk factor + maternal hypertension AND risk factor + Surfactant AND risk factor; When considering all eligible births, p-value for "Surfactant AND gestational age" interaction term <0.0001; Data from U.S. Birth Certificates with the given inclusion criteria: live, singleton, hospital birth between 24-27 weeks' gestation; Delivery between 2005-2009 and utilized 2003 Revision of Birth certificate; delivery not complicated by antenatal steroids or meconium aspiration syndrome.

	MATERNAL CONDITIONS						DELIVERY CONDITIONS			NEONATAL CONDITIONS	
	Obstetric History			Medical History							
Model by Gestational Age	Primi-parous	Multi-parous	Multiparous + previous PTB	Chronic Diabetes	Gestational Diabetes	Chorio-amnionitis	Cesarean	Fetal Intolerance	PROM	Male	Surfactant Given
All Eligible Births[a] (n=1,049,473)	**0.0056** N	<0.0001 Y	<0.0001 Y	**0.0016** N	**0.0437** N	<0.0001 Y	<0.0001 Y	<0.0001 Y	<0.0001 Y	**0.0084** N	
Extremely Preterm Births (n=34,164)	**0.0183** N	<0.0001 Y*	<0.0001 Y*	**0.7564** N	**0.5763** N	**0.568** N	<.0001 Y*	<.0001 Y*	**0.0295** N	**0.09** N	
Very Preterm Births (n=90,514)	**0.2617** N	0.001 Y*	<0.0001 Y*	**0.2981** N	**0.1877** N	**0.1345** N	<0.0001 Y*	<0.0001 Y	<0.0001 Y*	**0.5126** N**	
Preterm Births (n=252,824)	**0.0565** N	0.001 Y	<0.0001 Y	**0.0238** N**	**0.3504** N**	**0.0332** N**	<0.0001 Y	<0.0001 Y	<0.0001 Y	**0.5101** N	
Late Preterm Births (n= 671,971)	**0.2496** N	**0.0024** N	<0.0001 Y*	**0.1642** N	**0.1684** N**	**0.294** N	<.0001 Y*	<.0001 Y	<.0001 Y*	**0.013** N	

Extremely Preterm=24-27 weeks' gestation; Very Preterm=28-31 weeks' gestation; Preterm=32-34 weeks' gestation; Late Preterm=35-37 weeks' gestation; Y=Interaction Present; N=No interaction present; PTB= Preterm Birth; PROM=Premature Rupture of Membranes

[a]Using p value of "Surfactant AND Risk Factor" interaction term for given gestational age

*"Maternal Hypertension AND Risk Factor" interaction term unsignificant

**"Maternal Hypertension AND Risk Factor" interaction term significant

TABLE II.5: Variables used in Model Construction, by gestational age

Associative models using surfactant were built to explore the the indirect effect (shown below). Confounders and interaction terms found previously with mHTN and surfactant were added into candidates unless otherwise stated. C-index assessed goodness of fit. If multiple candidates demonstrated c-indices with less than 10% variation, the more parsimonious model was selected. Non-significant terms were removed via backwards selection. All models test the formula Neonatal Respiratory Distress Syndrome=Maternal Hypertension + Surfactant + (risk factors marked "Y"); Exception: crude models for each gestational age were as follows: Neonatal Respiratory Distress Syndrome=Maternal Hypertension). Bold p-value shows non-significant association (alpha=0.001). Data from U.S. Birth Certificates with the given inclusion criteria: live, singleton, hospital birth between 24-27 weeks' gestation; Delivery between 2005-2009 and utilized 2003 Revision of Birth certificate; delivery not complicated by antenatal steroids or meconium aspiration syndrome.

	MATERNAL CONDITIONS						DELIVERY CONDITIONS			NEONATAL CONDITIONS	OUTCOMES				
	Obstetric History			Medical History											
Model by Gestational Age	Primi-parous	Multi-parous	Multiparous + previous PTB	Chronic Diabetes	Gestational Diabetes	Chorio-amnionitis	Cesar-ean	Fetal Intoler-ance	PROM	Male	OR	(95% CI)		p-value[b]	c-index
All Eligible Births (n=1,049,473)															
Crude[a]	--	--	--	--	--	--	--	--	--	--	2.24	2.19	2.30	<.0001	0.550
Saturated	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	1.69	1.64	1.74	<.0001	0.766
Interaction	N	Y	Y	N	N	Y	Y	Y	Y	N	1.56	1.46	1.67	<.0001	0.764
Confounding	N	Y	N	Y	Y	Y	Y	Y	Y	Y	1.68	1.63	1.73	<.0001	0.764
Combined[c]	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	1.56	1.45	1.67	<.0001	0.766
FINAL MODEL[a]	Y	N	Y	Y	N	Y	Y	Y	Y	Y	1.69	1.64	1.74	<.0001	0.766
Extremely Preterm Births (n=34,164)															
Crude[a]	--	--	--	--	--	--	--	--	--	--	1.62	1.51	1.74	<.0001	0.529
Saturated	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	1.42	1.30	1.55	<.0001	0.761
Interaction	N	Y	Y	N	N	N	Y	Y	N	N	1.44	1.34	1.54	<.0001	0.746
Confounding	N	Y	Y	Y	N	Y	N	Y	Y	Y	1.55	1.42	1.69	<.0001	0.754
Combined[c]	N	Y	Y	Y	N	Y	Y	Y	Y	Y	0.98	0.76	1.27	**0.892**	0.761
FINAL MODEL[a]	Y	N	Y	N	N	N	Y	Y	Y	N	1.42	1.30	1.55	<.0001	0.759
Very Preterm Births (n=90,514)															
Crude[a]	--	--	--	--	--	--	--	--	--	--	2.31	2.20	2.43	<.0001	0.561
Saturated	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	1.69	1.59	1.80	<.0001	0.778
Interaction	N	Y	Y	N	N	N	N	N	Y	Y	1.76	1.47	2.10	<.0001	0.776
Confounding	N	Y	N	Y	N	Y	Y	Y	Y	Y	1.69	1.59	1.79	<.0001	0.775
Combined[c]	N	Y	Y	Y	N	Y	Y	Y	Y	Y	1.75	1.46	2.09	<.0001	0.777
FINAL MODEL[a]	Y	N	Y	Y	N	Y	Y	Y	Y	Y	1.70	1.59	1.80	<.0001	0.778
Preterm Births (n=252,824)															
Crude[a]	--	--	--	--	--	--	--	--	--	--	2.20	2.10	2.30	<.0001	0.551
Saturated	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	1.69	1.60	1.78	<.0001	0.733
Interaction	N	Y	Y	Y	Y	Y	Y	Y	Y	N	2.08	1.85	2.33	<.0001	0.732
Confounding	N	Y	N	Y	Y	Y	Y	Y	Y	Y	1.68	1.59	1.77	<.0001	0.730
Combined[c]	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	2.08	1.86	2.34	<.0001	0.734
FINAL MODEL[a]	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	1.69	1.60	1.78	<.0001	0.733
Late Preterm Births (n= 671,971)															
Crude[a]	--	--	--	--	--	--	--	--	--	--	2.00	1.90	2.10	<.0001	0.540
Saturated	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	1.57	1.48	1.66	<.0001	0.718
Interaction	N	N	Y	N	Y	N	Y	Y	Y	N	1.85	1.67	2.04	<.0001	0.708
Confounding	N	N	N	Y	Y	N	Y	Y	Y	Y	1.56	1.48	1.65	<.0001	0.712
Combined[c]	N	N	Y	Y	Y	N	Y	Y	Y	Y	1.82	1.65	2.01	<.0001	0.718
FINAL MODEL[a]	N	N	Y	Y	Y	Y	Y	Y	Y	Y	1.55	1.47	1.64	<.0001	0.718

given model; OR= Odds Ratio of Maternal Hypertension for given model (all ORs adjusted unless otherwise indicated); PTB= Preterm Birth; PROM=Premature Rupture of Membranes

[a]Crude OR of Maternal Hypertension

[b]p-value of Maternal Hypertension variable (all p-values of models <0.0001)

[c]Derived from combination of "Confounding" and "Interaction" models

[d]Derived from backwards elimination of "Saturated" model

TABLE III.6 Final Models, by gestational age

Final models exploring the indirect effect (shown below). All models test the formula Neonatal Respiratory Distress Syndrome=Maternal Hypertension + Surfactant + (other risk factors). All models derived from saturated model using backward elimination of non-significant p-values of given risk factors until all remaining risk factors are significant (p-value of all models <0.0001, alpha=0.001)Data from U.S. Birth Certificates with the given inclusion criteria: live, singleton, hospital birth between 24-27 weeks' gestation; Delivery between 2005-2009 and utilized 2003 Revision of Birth certificate; delivery not complicated by antenatal steroids or meconium aspiration syndrome.

Gestational Age	MODEL
All Eligible Births	-4.1972 + 0.5724*(Maternal Hypertension) + 0.1728*(primiparous) + 0.8127*(multiparous with previous PTB) + 0.2649*(chronic diabetes) + 0.7839*(chorioamnionitis) + 0.8744*(cesarean delivery) + 0.6204*(fetal intolerance) + 0.952*(PROM) + 0.1578*(male infant)
Extremely Preterm Births	-1.9477 + 0.3844*(Maternal Hypertension) + 0.1672*(primiparous) + 0.6804*(multiparous with previous PTB) + 0.4374*(chorioamnionitis) + 0.3387*(cesarean delivery) + 0.73*(fetal intolerance) + 0.5057*(PROM)
Very Preterm Births	-3.0665 + 0.5955*(Maternal Hypertension) + 0.2535*(primiparous) + 0.8857*(multiparous with previous PTB) + 0.3504*(chronic diabetes) + 0.6466*(chorioamnionitis) + 0.6968*(cesarean delivery) + 0.6354*(fetal intolerance) + 0.7362*(PROM) + 0.1042*(male infant)
Preterm Births	-3.9175 +0.5552*(Maternal Hypertension) + 0.1540*(primiparous) + 0.7486*(multiparous with previous PTB) + 0.3141*(chronic diabetes) + 0.1481*(gestational diabetes) + 0.4029*(chorioamnionitis) + 0.7099*(cesarean delivery) + 0.6625*(fetal intolerance) + 0.6901*(PROM) + 0.1721*(male infant)
Late Preterm Births	-4.9422 + 0.4804*(Maternal Hypertension) + 0.0769*(multiparous) + 0.7841*(multiparous with previous PTB) + 0.5257*(chronic diabetes) + 0.2260*(gestational diabetes) + 0.4583*(chorioamnionitis) + 0.7560*(cesarean delivery) + 0.6310*(fetal intolerance) + 0.7766*(PROM) + 0.3019*(male infant)

Extremely Preterm=24-27 weeks' gestation; Very Preterm=28-31 weeks' gestation; Preterm=32-34 weeks' gestation; Late Preterm=35-37 weeks' gestation; PTB= Preterm Birth; PROM= Premature Rupture of Membranes

TABLE II.7: Comparing Associations of Maternal Hypertension and Surfactant to Neonatal Respiratory Distress Syndrome, by gestational age

Adjusted Odds Ratios for mHTN and surfactant derived from final models of indirect effect. All models test the formula Neonatal Respiratory Distress Syndrome=Maternal Hypertension + Surfactanta + (other risk factors). Models derived from saturated model using backward elimination of non-significant p-values of given risk factors until all remaining risk factors are significant (p-value of all models <0.0001, alpha=0.001). Data from U.S. Birth Certificates with the given inclusion criteria: live, singleton, hospital birth between 24-27 weeks' gestation; Delivery between 2005-2009 and utilized 2003 Revision of Birth certificate; delivery not complicated by antenatal steroids or meconium aspiration syndrome.

Model by gestational age	aOR[a] Maternal Hypertension	(95% CI)[b]		aOR[a] Surfactant Administration	(95% CI)[b]	
All Eligible Births (n=1,049,473)	1.69	1.64	1.74	59.52	57.35	61.78
Extremely Preterm Births (n=34,164)	1.42	1.30	1.55	19.70	18.14	21.40
Very Preterm Births (n=90,514)	1.70	1.59	1.80	25.81	24.07	27.68
Preterm Births (n=252,824)	1.69	1.60	1.78	37.80	35.18	40.61
Late Preterm Births (n=671,971)	1.55	1.47	1.64	85.61	79.25	92.49

Extremely Preterm=24-27 weeks' gestation; Very Preterm=28-31 weeks' gestation; Preterm=32-34 weeks' gestation; Late Preterm=35-37 weeks' gestation; aOR=Adjusted Odds Ratio; CI= Confidence Interval

[a]Adjsuted OR for given gestational age

[b]All p-values for confidence intervals < 0.05

TABLE II.8: Comparing Odds of Neonatal Respiratory Distress Syndrome in Infants born to Hypertensive Mothers, by Effect Model and Gestational Age

All models derived from saturated model using backward elimination of non-significant p-values of given risk factors until all remaining risk factors are significant (p-value of all models <0.0001, alpha 0.001). Direct Effect Testing: Neonatal Respiratory Distress Syndrome=Maternal Hypertension (without consideration of surfactant, data presented previously); Indirect Effect Testing: Neonatal Respiratory Distress Syndrome=Maternal Hypertension + Surfactant (with consideration of surfactant); Data from U.S. Birth Certificates with the given inclusion criteria: live, singleton, hospital birth between 24-27 weeks' gestation; Delivery between 2005-2009 and utilized 2003 Revision of Birth certificate; delivery not complicated by antenatal steroids or meconium aspiration syndrome.

Model by Gestational Age	OR[a]	(95% CI)[b]		% Difference in OR[c]
All Eligible Births (n=1,076,585)				
Direct Effect	1.77	1.73	1.82	
Indirect Effect	1.69	1.64	1.74	5%
Extremely Preterm Births (n=34,984)				
Direct Effect	1.47	1.36	1.59	
Indirect Effect	1.42	1.30	1.55	3%
Very Preterm Births (n=92,886)				
Direct Effect	1.81	1.72	1.92	
Indirect Effect	1.70	1.59	1.80	7%
Preterm Births (n=259,618)				
Direct Effect	1.74	1.66	1.83	
Indirect Effect	1.69	1.60	1.78	3%
Late Preterm Births (n=689,097)				
Direct Effect	1.62	1.53	1.70	
Indirect Effect	1.55	1.47	1.64	4%

Extremely Preterm=24-27 weeks' gestation; Very Preterm=28-31 weeks' gestation; Preterm=32-34 weeks' gestation; Late Preterm=35-37 weeks' gestation; OR=Odds Ratio; CI=Confidence Interval

[a]aOR for mHTN in final model

[b]All p-values for confidence intervals < 0.05

[c]Percent Difference between aORs for Maternal Hypertension when comparing "Direct Effect" models to "Indirect Effect" models

FIGURES FOR CHAPTER II

FIGURE II.1: Directed Acyclic Graph for Primary and Secondary Analysis

Primary Analysis: Direct Effect of mHTN on RDS; Secondary Analysis: Indirect Effect of mHTN on RDS through SURF

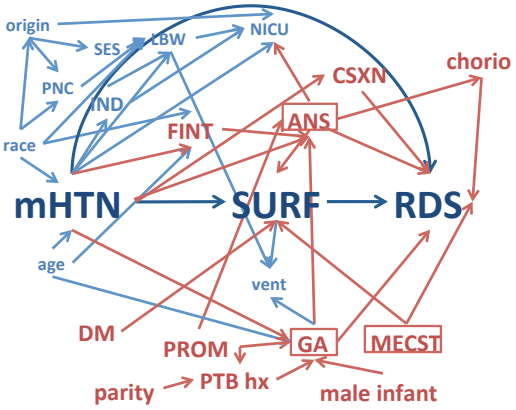

FIGURE III.1: Directed Acyclic Graph

Direct Effect of mHTN on RDS;

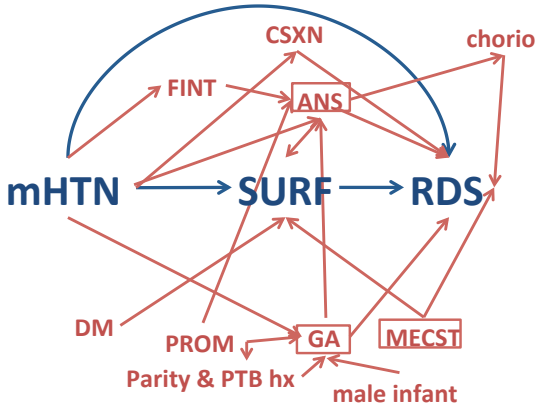

FIGURE II.3: Directed Acyclic Graph for Primary and Secondary Analysis, with Final Risk Factors

Primary Analysis: Direct Effect of mHTN on RDS; Secondary Analysis: Indirect Effect of mHTN on RDS through SURF

LEGEND FOR FIGURES II.1-II.3:

PRIMARY AND SECONDARY INTEREST: mHTN=Maternal hypertension (any diagnosis of hypertension while pregnant); SURF=Exogenous surfactant given to infant (not defined as prophylactic or rescue in birth certificate); RDS=Neonatal respiratory distress syndrome; *INCLUDED RISK FACTORS:* Parity=Number of pregnancies; DM= Maternal diabetes (both chronic and gestational); PTB hx=History of pre-term birth; GA=Gestational age at delivery; MECST=Meconium staining present at delivery; ANS=Antenatal steroids given prior to delivery; Chorio=Chorioamnionitis at delivery; CSXN=Cesarean delivery; FINT=Fetal intolerance during delivery; PROM=Premature rupture of membranes; Male= sex of infant; *CONSIDERED RISK FACTORS:* Origin: Maternal Country of Origin; PNC: Prenatal Care; SES: Maternal socio-economic status; LBW: Low birth weight (<1500g); NICU: Neonatal Intensive Care Unit Admission; Age: Maternal Age; Race: Maternal Race and Ethnicity; Vent: Any neonatal ventilation; IND: Medical induction of labor

Figure III.4: Considered Variables and Potential Causes for Elimination

List of considered variables constructed by literature review, expert opinion and availability on 2003 Revision of U.S. Birth Certificates. Data from U.S. Birth Certificates with the given inclusion criteria: live, singleton, hospital birth between 24-27 weeks' gestation; Delivery between 2005-2009 and utilized 2003 Revision of Birth certificate;Neonatal RDS used proxy of ventilation over 6 hours. MAS used proxy of meconium staining.

		RISK FACTOR	ELIMINATED SECONDARY TO: Literature Review	DAG construction	Excessive Missing Data	CONSIDERED IN MODEL CONSTRUCTION
PRIMARY INTEREST		Maternal Hypertension[a]				X
		Neonatal Respiratory Distress Syndrome				X
SECONDARY INTEREST		Surfactant Administration				X[e]
MATERNAL CONDITIONS	Demographic Information	Age (years)		X		
		Weight Gain During Pregnancy (lbs)***			X	
		Smoking During Pregnancy***			X	
		Married	X			
		Race		X		
		Hispanic Ethnicity and/or origin		X		
		Education	X			
		Socio-economic Status		X		
	Obstetric History	Parity				X[f]
		Previous PTB				X[f]
		Prenatal Care		X		
	Medical History	Chronic Diabetes				X
		Gestational Diabetes				X
		Chorioamnionitis				X
DELIVERY CONDITIONS		Antenatal Steroids Given[b]	X			
		Year of Delivery	X			
		Cesarean Delivery				X
		Operative Vaginal Delivery	X			
		Timing of Delivery (Prolonged or Precipitous)	X			
		Estimated Gestational Age[c]				X
		PROM				X
		MAS[d]	X			
		Fetal Intolerance				X
		Induction of Labor		X		
NEONATAL CONDITIONS		5 minute APGAR**			X	
		Male				X
		Birth Weight (g)		X		
		Ventilation for at least one hour (but less than 6 hours)		X		
		NICU admission		X		
		Antiobiotics Given to Neonate	X			

PTB= Preterm Birth; PROM=Premature Rupture of Membranes; MAS=Meconium Aspiration Syndrome; APGAR=Appearance, Pulse, Grimace, Activity, and Respiration; NICU=Neonatal Intensive Care Unit

[a]Literature review demonstrated consistent combination hypertensive disorders, including Chronic Hypertension, Pregnancy-Induced Hypertension, and Eclampsia, which are the classifications available on the 2003 Revision of the U.S. Birth Certificate

[b]Births with antenatal steroids removed from final dataset

[c]Stratified by gestational age, as suggested by literature review

[d]Births with MAS removed from final dataset

[e]Used only for indirect effect

[f]Combined when studying direct and indirect effects

** 5-10% Missing

*** > 10% Missing

CHAPTER III:

Making Breathing Easier: An Analysis of Birth Certificate Data Examining Maternal Hypertension and Neonatal Respiratory Distress Syndrome

INTRODUCTION

With the 2003 update of the US Birth Certificate, researchers have an increasingly easy, concise, and accessible source of information regarding maternal conditions and perinatal outcomes (22, 33-36). Research has examined the increasing incidence in gestational diabetes and its association with micro- and macrosomia (defined as birth weight less than 2500g and greater than 4000g, respectively) (34, 35), poor fetal lung maturity and PTB. However, unlike diabetes, there is no unified statement on whether mHTN also increases the risk of RDS in the neonate (defined as within the first 28 days post-partum) (2, 8, 12, 14, 16, 17, 40).

Problem Definition

Maternal Hypertension and Neonatal Respiratory Distress Syndrome Torrance et al. (2008) examined lung maturity in infants born to mothers with PIH and HELLP syndrome, respectively (3). They found that, when compared to infants born to normotensive mothers, infants born to mothers with PIH were less likely to demonstrate lung immaturity while infants born to mothers with HELLP were more likely (P=0.02 and P=0.04, respectively) (3). The discussion hypothesized that these variations could be attributed to chronic placental insufficiency from PIH leading to an acceleration of fetal lung maturity, while HELLP syndrome increases oxidative stress, thus compromising lung maturity (3). Langenveld et al. (2011) also found that, compared to infants born to normotensive mothers, the risk of RDS was decreased in infants born to hypertensive mothers (OR 0.81 in PIH, OR 0.69 in pre-eclampsia) (12).

However, others have suggested the opposite, i.e., that mHTN actually increases the risk of RDS. In a 2007 study, Gilbert, Young and Danielsen found that infants born to hypertensive mothers had a significant increase in their odds of RDS (OR 4.0, compared to infants born to normotensive mothers) (13). Since 2000, similar, although not as strong, results have been found by Habli et al. (2007); Baraban, McCoy, and Simon (2008); and Hauth et al. (2000) (2, 4, 15).

Research Objective In response to these observations, this retrospective cohort study aims to examine the relationship between mHTN and neonatal RDS in the viable preterm infant using pre and perinatal information found on birth certificate data, with the goal of finding the total effect that mHTN has on neonatal RDS, if any.

Hypothesis ("*Direct Effect*") Infants delivered to hypertensive mothers will have increased odds of RDS.

METHODS

Subjects and Sample Data on patient characteristics and outcomes came retrospectively from the Centers for Disease Control and Prevention's National Center for Health Statistics public access Research Data Center. All U.S. births from 2005-2009 were examined when they met the following characteristics: live, singleton, hospital births between 24 and 36 completed weeks' gestation using the 2003 revision.

A Priori Analysis Using a review of the literature and verbal discussion with experts in neonatology, a series of a priori directed acyclic graphs (DAGs) were constructed to evaluate the direct effect as well as the covariates.

Measurement All measurements and analyses were conducted using SAS 9.3 (Cary, NC). Given the large sample size and to distinguish the difference between etiologic and statistical significance, this study utilized an alpha of 0.001. Unless otherwise stated, all assumptions for logistic regression (linearity on the log scale) were met. Given the information available on birth certificate, neonatal ventilation over 6 hours is used as a proxy for RDS.

Descriptive Overview The study explored relationships between mHTN, maternal and neonatal risk factors, and neonatal RDS. Possible covariates were divided into three subcategories: *1) maternal characteristics*, which was further subdivided into *a) obstetric history* (primiparity, multiparity, and multiparity with a history of PTB), and *b) medical history* (chronic diabetes, gestational diabetes, and chorioamnionitis)*; 2) delivery conditions* (cesarean delivery, fetal intolerance, and PROM); and *3) neonatal characteristics* (male infant, and surfactant given) (see **APPENDIX 1: VARIABLES** for more information).

Analysis A descriptive analysis gave frequency and percentage for dichotomous variables by all eligible births and after stratification by gestational age. To reflect breakdowns found in the literature and via expert opinion, these were defined as extremely preterm (24-27 weeks), very preterm (28-31 weeks), preterm (32-34 weeks) and late preterm (35-37 weeks) (2, 5, 12, 37). All other analyses continue to investigate by these divisions.

Confounding In order to build an associative model for the total effect of mHTN on neonatal RDS, a table of possible confounders was constructed using simple logistic regression. Covariates found to be significant for both mHTN and RDS were considered confounders for the given division of gestational ages. Unless otherwise stated, confounders were included in the construction of associative models. Of note, surfactant was only considered a confounder in the secondary analysis, which is documented elsewhere.

Interaction Crude logistic regression using interaction terms between gestational age and mHTN assessed potential interaction. In the same manner, interaction was also investigated between mHTN and the previously identified risk factors. A significant *P*-value of the interaction term with mHTN and the risk factor was used as an indication of interaction.

Associative Models Associative models not including surfactant were built to explore the direct effect. Variable inflation factor (VIF) assessed collinearity. Confounders and interaction terms found previously with mHTN were added into the associative models unless otherwise stated. C-index assessed goodness of fit for all candidate models. If multiple candidates demonstrated c-indices with less than 10% variation, the more parsimonious model was selected. Non-significant terms were removed via backwards selection.

RESULTS

A Priori Analysis The DAG for the direct effect, in conjunction with the literature review, helped to establish the process for approaching data analysis (**FIGURE III.1**). DAGs for covariates revealed that many typical covariates, including maternal factors (origin, race, age, socio-economic status, prenatal care, and induction of labor) and neonatal factors (low birth weight, NICU admission, and ventilation for at least 1 hour but less than 6 hours) were already controlled for by controlling for descendants (**FIGURE III.2**). Thus, they were not included in analysis (**FIGURE III.3**).

According to trends in the literature, the dataset was restricted to pregnancies not complicated by antenatal steroids or MAS (11, 20, 24, 26) (**FIGURE III.3**). Given that a woman with a history of PTB is by definition multiparous, parity and history of PTB were combined to make one variable "multiparous with a history of PTB" (**FIGURES III.2-III.4**).

Measurement

Descriptive Overview Frequencies and percentages for all risk factors were summarized for the 1,049,473 births eligible for the study (**TABLE III.1**). Analysis of variance (ANOVA) showed that all risk factors varied significantly across gestational ages, with the exception of chronic diabetes (P=0.006). With increasing gestational age, nearly all risk factors trended either up (multiparity, gestational diabetes) or down (RDS, primiparity, multiparity with a previous PTB, chorioamnionitis, cesarean delivery, fetal intolerance, PROM, surfactant administration). The exceptions included chronic diabetes (no trend) and mHTN (peak at 13.7% of births in the very premature cohort) (**TABLE III.1**).

Most risk factors were rare in the all eligible births set, with both the primary exposure (mHTN) and outcome (RDS) impacting 10.6% and 3.6% of eligible pregnancies, respectively. Other rare risk factors included multiparity with a history of PTB, chronic diabetes, gestational diabetes, chorioamnionitis, fetal intolerance, PROM, and surfactant (4.4%, 1.4%, 5.1%, 1.0%,

5.1%, 7.9%, and 1.4% of all eligible births, respectively). However, once viewed by gestational age, the "rareness" of these risk factors was no longer maintained, as some trended down as gestational age increased (RDS, max 20.1%; PROM, max 17.4%; and surfactant administration, max 11.2%, all for extremely preterm births) (**TABLE III.1**). When viewing the extremes of gestational age, these trends remained, with all variance among all risk factors showing significance with the exception of chronic diabetes (P=0.59) (**TABLE III.2**).

Despite literature linking maternal smoking to RDS, maternal smoking was not included in the analysis because over 20% of births did not report smoking status. It is acknowledged that this omission could cause some exposure misclassification. Other variables dropped due to excessive numbers of missing data, as well as a dearth of information in the literature regarding any association with mHTN, included weight gain during pregnancy, with more than 10% missing, and 5 minute APGAR, with over 5% missing (**FIGURE III.4**).

Analysis

Confounding As the alpha was set at 0.001, a two table approach was used to find potential confounders between mHTN and RDS for given gestational ages rather than the typical 10% difference between crude and adjusted ORs. Before stratification by gestational age, the only risk factor that was not found to be a confounder was multiparity with a history of PTB (P=0.010 for association to mHTN) (**TABLE III.3**). This lack of confounding continued after stratification by gestational age (P=0.039, P=0.29, P=0.09, and P=0.016 for association to mHTN for extremely preterm, very preterm, preterm, and late preterm births, respectively) (**TABLES III.3A-III.3D**).

Other risk factors found not to be confounders after stratification for gestational age include gestational diabetes, male infant (P=0.200 and P=0.017 for association to RDS for extremely preterm births, respectively) (**TABLE III.3A**), multiparity without a history of PTB (P

=0.79 for association to RDS for late preterm births), and chorioamnionitis (*P*=0.33 for association to mHTN for late preterm births). (**TABLE III.3D**).

Interaction Interaction was not present between mHTN and gestational age (*P*=0.06 for interaction term) when viewing all eligible births (data not shown). All risk factors considered showed interaction prior to stratification by gestational age (all *P*<0.0001) (**TABLE III.4**).

After stratification, interaction became more complicated. There were no significant interaction terms in the extremely preterm cohort (*P*-values ranging from 0.012 to 0.44). Risk factors primiparity, multiparity, chorioamnionitis, and cesarean delivery had no significant interaction with mHTN. Maternal factors chronic and gestational diabetes had significant interaction in births after 32 weeks' gestation (*P*<0.0001 for preterm and late preterm births). Delivery factors fetal intolerance and PROM had significant interaction even earlier at 28 weeks' gestation (*P*<0.0001 for very preterm, preterm, and late preterm births). Finally, multiparity with a history of PTB showed inconsistent interaction (*P*=0.0211, *P* <0.0001, *P*<0.0001, *P*=0.0092 for increasing gestational ages, respectively), as did male infant (*P*=0.44, *P*=0.0003, *P*=0.66, *P*=0.52 for extremely preterm, very preterm, preterm and late preterm births, respectively) (**TABLE III.4**).

Building Models Candidates for the associative models included the 1) crude, 2) saturated, 3) interactive, 4) confounded, and 5) combined (interactive and confounded) models (**TABLE III.5**). There were no concerns for collinearity, as the VIF for all risk factors in all scenarios was less than 2 (data not shown).

In all eligible births, the combined model was nominally better at discrimination compared to the saturated model (c-index 0.697 compared to 0.696, respectively, <1% variation). However, the saturated candidate had either better discrimination (c-index=0.630, 0.685, and 0.671 for extremely preterm, very preterm, and late preterm births, respectively) or the same discrimination (c-index=0.675 for preterm births) compared to the combined candidates for all gestational ages. As a result, all final models were constructed using backward selection from the

saturated models. Non-significant terms dropped from candidate models included primiparity (late preterm births), multiparity (all models except late preterm births), chronic diabetes (extremely preterm births), gestational diabetes (all eligible, extremely preterm and very preterm births), and male infant (extremely preterm births). All final models showed less than 1% variation in discrimination from their respective saturated candidate (**TABLE III.5**).

All final models showed confounding, with changes in β1 between the crude and adjusted for mHTN of 29%, 20%, 28%, 30%, and 31% (**TABLE III.6**) (crude OR 2.24, 1.62, 2.31, 2.20, 2.00, compared to aOR 1.77, 1.47, 1.81, 1.74, 1.62 for all eligible births and increasing gestational ages, respectively; all $P<0.0001$) (**TABLE III.5**). For final models, see **TABLE III.6**.

DISCUSSION

This large, retrospective cohort attempts to quantify the total effect of mHTN on neonatal RDS. While the literature has not been consistent on the association of mHTN and RDS (2-4, 12, 14, 15, 19), these results show a clear association (aOR mHTN 1.77 for all eligible births, 1.47-1.81, after stratification by gestational age) (**TABLE III.5**). Assuming the validity of birth certificate data, the results point to a harmful association of mHTN on neonatal RDS. This is in contrast to previous studies that suggested mHTN was actually protective against neonatal RDS (3).

Trends Several trends should be taken into account when viewing the data. While most risk factors trend either up or down with increasing gestational age, mHTN (the primary exposure) does not. This is because mothers delivering at earlier gestational ages are removed from the later gestational age pool, a form of preterm delivery bias. Additionally, it may be that obstetricians are more likely to induce labor prior to 34 weeks if it appears that the mHTN is severe, as suggested by Sibai (2000). In contrast, the percentage of births affected by chronic diabetes remains statistically constant with increasing gestational age (ANOVA P=0.006), suggesting that this chronic condition is more easily managed while pregnant than hypertension during pregnancy.

Strengths There is much strength to this study, its size being the most apparent. With over 1,000,000 births, this captures one quarter of U.S. births fitting the eligibility criteria other than the 2003 revision (n=3,867,748) (42). As such, and given the rareness of mHTN, the sample population easily approximates the target population. The ability to decrease the alpha to 0.001 while still finding significance allows a maximization of power. By focusing this study on births delivered between 24 and 36 completed weeks' gestation, researchers can examine those most at risk for neonatal RDS (20, 21), as well as target neonates more likely to receive surfactant (16,

17, 20, 21). Finally, the large dataset allowed for further subdivision according to gestational age, permitting applicability in the clinical setting.

Limitations

The major limitation of this study was that it utilized only publicly available data. This meant that a proxy for RDS had to be utilized (ventilation over 6 hours), and the varying degrees of mHTN had to be combined rather than viewed separately (there is no allotment on the 2003 revision for pre-eclampsia or HELLP syndrome) (3, 12, 14). That said, there is likely some degree of exposure and outcome misclassification.

Furthermore, while the birth certificate should ideally be an accurate source of information, literature reviews have shown that it struggles to identify maternal chronic conditions (22, 33-36) and lack universality in dealing with mothers from different cultures (37, 38). Combination with discharge documentation would aid in overcoming this potential selection bias (33).

Lastly, while many of the risk factors examined should intuitively demonstrate interaction, the impact of such interaction was not statistically strong enough to account in building models. That said, finding interaction among so many risk factors does complicate the picture, and future studies should continue to take possible interaction into account.

TABLES FOR CHAPTER III

TABLE III.1: Descriptive Analysis of Eligible Births, by frequency (%)

Relationships between mHTN, maternal and neonatal risk factors, and neonatal RDS explored, with a descriptive analysis giving frequency and percentage for dichotomous variables by all eligible births and after stratification by gestational age (as reflected by literature review and expert opinion). Bold p-value shows non-significant association (alpha=0.001). Ventilation over 6 hours used as proxy for RDS. Bolded p-values show non-significant association. (alpha=0.001). Data from U.S. Birth Certificates with the given inclusion criteria: live, singleton, hospital birth between 24-27 weeks' gestation; Delivery between 2005-2009 and utilized 2003 Revision of Birth certificate; delivery not complicated by antenatal steroids or meconium aspiration syndrome.

RISK FACTOR		All Eligible Births n= 1,049,473	Extremely Preterm Births n= 34,164	Very Preterm Births n= 90,514	Preterm Births n= 252,824	Late Preterm Births n= 671,971	p value (F- value)[a]
PRIMARY INTEREST	Maternal Hypertension	110,781 (10.6)	4,221 (12.4)	12,293 (13.7)	28,580 (11.4)	65,687 (9.8)	<.0001 (534.17)
	Neonatal Respiratory Distress Syndrome	37,636 (3.6)	6,818 (20.1)	9,431 (10.5)	10,915 (4.3)	10,472 (1.6)	<.0001 (16,448.3)
SECONDARY INTEREST	Surfactant Given	15,071 (1.4)	3,793 (11.2)	4,622 (5.1)	3,674 (1.5)	2,982 (0.5)	<.0001 (12,379.7)
MATERNAL CONDITIONS	Obstetric History						
	Primiparous	408,523 (39.4)	16,193 (48.6)	38,175 (42.9)	99,823 (40.0)	254,332 (38.3)	
	Multiparous	582,196 (56.1)	15,218 (45.7)	46,517 (52.3)	138,016 (55.3)	382,445 (57.5)	<.0001 (375.4)
	Multiparous + previous PTB	46,291 (4.4)	1,900 (5.7)	4,338 (4.9)	11,828 (4.7)	28,225 (4.2)	
	Medical History						
	Chronic Diabetes	14,254 (1.4)	461 (1.4)	1,263 (1.4)	3,590 (1.4)	8,940 (1.3)	**0.006 (4.12)**
	Gestational Diabetes	52,835 (5.1)	822 (2.4)	3,697 (4.1)	12,804 (5.1)	35,512 (5.3)	<.0001 (248.46)
	Chorioamnionitis	10,604 (1.0)	1,206 (3.5)	1,540 (1.7)	2,614 (1.0)	5,244 (0.8)	<.0001 (988.58)
DELIVERY CONDITIONS	Cesarean Delivery	403,404 (38.4)	19,255 (56.4)	43,881 (48.5)	103,097 (40.8)	237,171 (35.3)	<.0001 (4,007.12)
	Fetal Intolerance	53,463 (5.1)	2,414 (7.1)	5,919 (6.5)	13,938 (5.5)	31,192 (4.6)	<.0001 (347.59)
	PROM	82,838 (7.9)	5,901 (17.4)	10,121 (11.3)	25,221 (10.0)	41,140 (6.2)	<.0001 (3,365.89)
NEONATAL CONDITIONS	Male	564,762 (53.7)	18,036 (52.8)	48,091 (53.1)	137,040 (54.2)	361,595 (53.8)	<.0001 (15.6)

Extremely Preterm=24-27 weeks' gestation; Very Preterm=28-31 weeks' gestation; Preterm=32-34 weeks' gestation; Late Preterm=35-37 weeks' gestation; PTB=preterm birth; PROM=premature rupture of membranes

[a]Analysis of Variance

Table III.2: Descriptive Analysis for Eligible Births, by frequency (%) for Extremes of Age (Extremely Preterm Births vs. Late Preterm Births)

Relationships between mHTN, maternal and neonatal risk factors, and neonatal RDS explored, with a descriptive analysis giving frequency and percentage for dichotomous variables by extremely preterm and late preterm births (as reflected by literature review and expert opinion). Bold p-value shows non-significant association (alpha=0.001). Data from U.S. Birth Certificates with the given inclusion criteria: live, singleton, hospital birth between 24-27 weeks' gestation; Delivery between 2005-2009 and utilized 2003 Revision of Birth certificate; delivery not complicated by antenatal steroids or meconium aspiration syndrome.

PREDICTOR		Extremely Preterm Births n= 34,164 (%)	Late Preterm Births n= 671,971 (%)	F Value[a]	p-value[a]
PRIMARY INTEREST	Maternal Hypertension	4,221 (12.4)	65,687 (9.8)	280.89	<.0001
	Neonatal Respiratory Distress Syndrome	6,818 (20.1)	10,472 (1.6)	50159.2	<.0001
SECONDARY INTEREST	Surfactant Given	3,793 (11.2)	2,982 (0.5)	42040	<.0001
MATERNAL CONDITIONS	Obstetric History				
	Primiparous	16,193 (48.6)	254,332 (38.3)	1254.34	<.0001
	Multiparous	15,218 (45.7)	382,445 (57.5)	2036.99	<.0001
	Multiparous + previous PTB	1,900 (5.7)	28,225 (4.2)	159.27	<.0001
	Medical History				
	Chronic Diabetes	461 (1.4)	8,940 (1.3)	**0.29**	**0.59**
	Gestational Diabetes	822 (2.4)	35,512 (5.3)	551.37	<.0001
	Chorioamnionitis	1,206 (3.5)	5,244 (0.8)	2756.27	<.0001
DELIVERY CONDITIONS	Cesarean	19,255 (56.4)	237,171 (35.3)	6459.71	<.0001
	Fetal Intolerance	2,414 (7.1)	31,192 (4.6)	415.42	<.0001
	PROM	5,901 (17.4)	41,140 (6.2)	6837.17	<.0001
NEONATAL CONDITIONS	Male	18,036 (52.8)	361,595 (53.8)	13.11	<0.001

Extremely Preterm=24-27 weeks' gestation; Late Preterm=35-37 weeks' gestation; PTB=preterm birth; PROM=premature rupture of membranes

[a]Analysis of Variance

TABLE III.3 Potential Confounders between Maternal Hypertension and Neonatal Respiratory Distress Syndrome (All eligible births, no stratifcation by gestational age)

Tables of possible confounders constructed using simple logistic regression. Ventilation over 6 hours used as proxy for RDS. Covariates found to be significant for both mHTN and RDS considered confounders for the given division of gestational age. Bolded p-values show non-significant association. (alpha=0.001). Data from U.S. Birth Certificates with the given inclusion criteria: live, singleton, hospital birth between 24-27 weeks' gestation; Delivery between 2005-2009 and utilized 2003 Revision of Birth certificate; delivery not complicated by antenatal steroids or meconium aspiration syndrome.

		MATERNAL HYPERTENSION (%)						RESPIRATORY DISTRESS SYNDROME (%)					
	RISK FACTOR	YES n=110,781 (10.6)	NO n= 935,007 (89.4)	OR [a]	(95% CI)		p-value[c]	YES n=37,636 (3.6)	NO n=1,006,911 (96.4)	OR [b]	(95% CI)		p-value[c]
MATERNAL CONDITIONS	Obstetric History												
	Primiparous	55,405 (13.6)	353,118 (86.4)	---	---	---		16,079 (4.0)	390,888 (96.1)	---	---	---	
	Multiparous	48,453 (8.3)	588743 (91.7)	0.58	0.57	0.59	<0.0001	17,709 (3.1)	562,441 (97.0)	0.77	0.75	0.78	<0.0001
	Multiparous + previous PTB	6,079 (13.1)	40,212 (86.9)	0.96	0.94	0.99	**0.010**	3,401 (7.4)	42,605 (92.6)	1.94	1.87	2.02	<0.0001
	Medical History												
	Chronic Diabetes	5,157 (36.2)	9,097 (63.8)	4.97	4.80	5.15	<0.0001	1,006 (7.1)	13,171 (92.9)	2.08	1.95	2.22	<0.0001
	Gestational Diabetes	12,001 (22.7)	40,834 (77.3)	2.66	2.61	2.72	<0.0001	2,235 (4.3)	50,357 (95.8)	1.20	1.15	1.26	<0.0001
	Chorioamnionitis	924 (8.8)	9,619 (91.2)	0.81	0.76	0.87	<0.0001	1,065 (10.1)	9,461 (89.9)	3.07	2.88	3.27	<0.0001
DELIVERY CONDITIONS													
	Cesarean	67,156 (16.7)	335,083 (83.3)	2.76	2.72	2.79	<0.0001	23,242 (5.8)	378,289 (94.2)	2.68	2.63	2.74	<0.0001
	Fetal Intolerance	10,869 (20.4)	42,450 (79.6)	2.29	2.24	2.34	<0.0001	4,830 (9.1)	48,334 (90.9)	2.92	2.83	3.01	<0.0001
	PROM	5,984 (7.3)	75,998 (92.7)	0.65	0.63	0.67	<0.0001	6,563 (8.0)	75,323 (92.0)	2.62	2.55	2.69	<0.0001
NEONATAL CONDITIONS													
	Surfactant Given	3,075 (20.5)	11,913 (79.5)	2.22	2.13	2.31	<0.0001	10,131 (67.2)	4,940 (32.8)	74.70	72.06	77.44	<0.0001
	Male	57,746 (10.3)	505,072 (89.7)	0.93	0.92	0.94	<0.0001	21,677 (3.9)	540,422 (96.1)	1.17	1.15	1.20	<0.0001

PTB=preterm birth; PROM=premature rupture of membranes

[a]Odds Ratio of given risk factor increasing the likelihood of maternal hypertension

[b]Odds Ratio of given risk factor increasing the likelihood of respiratory distress syndrome

[c]p-value of Maximum Likelihood Estimate

TABLE III.3A Potential Confounders between Maternal Hypertension and Neonatal Respiratory Distress Syndrome (Extremely preterm births, dataset limited to births between 24-27 weeks' gestation)

Tables of possible confounders constructed using simple logistic regression. Ventilation over 6 hours used as proxy for RDS. Covariates found to be significant for both mHTN and RDS considered confounders for the given division of gestational age. Bolded p-values show non-significant association. (alpha=0.001). Data from U.S. Birth Certificates with the given inclusion criteria: live, singleton, hospital birth between 24-27 weeks' gestation; Delivery between 2005-2009 and utilized 2003 Revision of Birth certificate; delivery not complicated by antenatal steroids or meconium aspiration syndrome.

		MATERNAL HYPERTENSION (%)						RESPIRATORY DISTRESS SYNDROME (%)					
	RISK FACTOR	YES n= 4,221 (12.4)	NO n= 29,716 (87.6)	OR[a]	(95% CI)		p-value[c]	YES n= 6,818 (20.1)	NO n= 27,162 (79.9)	OR [b]	(95% CI)		p-value[c]
MATERNAL CONDITIONS	Obstetric History												
	Primiparous	2,172 (13.4)	14,021 (86.6)	---	---	---		3,333 (20.7)	12,786 (79.3)	---	---	---	
	Multiparous	1,698 (11.2)	13,520 (88.8)	0.81	0.76	0.87	<0.0001	2,752 (18.2)	12,408 (81.9)	0.85	0.80	0.90	<0.0001
	Multiparous + previous PTB	288 (15.2)	1,612 (84.8)	1.15	1.01	1.32	**0.039**	601 (31.9)	1,286 (68.2)	1.79	1.62	1.99	<0.0001
	Medical History												
	Chronic Diabetes	183 (39.7)	278 (60.3)	4.80	3.97	5.80	<0.0001	121 (26.4)	337 (73.6)	1.44	1.17	1.77	<0.001
	Gestational Diabetes	220 (26.8)	602 (73.2)	2.66	2.27	3.12	<0.0001	178 (21.8)	637 (78.2)	1.12	0.94	1.32	**0.200**
	Chorioamnionitis	73 (6.1)	1,116 (93.9)	0.45	0.36	0.57	<0.0001	380 (31.6)	821 (68.4)	1.89	1.67	2.15	<0.0001
DELIVERY CONDITIONS													
	Cesarean	3,582 (18.7)	15,560 (81.3)	5.10	4.67	5.56	<0.0001	4,450 (23.2)	14,725 (76.8)	1.59	1.50	1.68	<0.0001
	Fetal Intolerance	491 (20.5)	1,907 (79.5)	1.92	1.73	2.13	<0.0001	898 (37.4)	1,504 (62.6)	2.59	2.37	2.82	<0.0001
	PROM	451 (7.7)	5,416 (92.3)	0.54	0.49	0.60	<0.0001	1,647 (28.0)	4,228 (72.0)	1.73	1.63	1.85	<0.0001
NEONATAL CONDITIONS													
	Surfactant Given	630 (16.8)	3,130 (83.2)	1.49	1.36	1.63	<0.0001	2,883 (76.0)	910 (24.0)	21.13	19.47	22.93	<0.0001
	Male	1,995 (11.1)	15,918 (88.9)	0.78	0.73	0.83	<0.0001	3,689 (20.6)	14,257 (79.4)	1.07	1.01	1.13	**0.017**

PTB=preterm birth; PROM=premature rupture of membranes

[a]Odds Ratio of given risk factor increasing the likelihood of maternal hypertension

[b]Odds Ratio of given risk factor increasing the likelihood of respiratory distress syndrome

[c]p-value of Maximum Likelihood Estimate

TABLE III.3B Potential Confounders between Maternal Hypertension and Neonatal Respiratory Distress Syndrome (Very preterm births, dataset limited to births between 28-31 weeks' gestation)

Tables of possible confounders constructed using simple logistic regression. Ventilation over 6 hours used as proxy for RDS. Covariates found to be significant for both mHTN and RDS considered confounders for the given division of gestational age. Bolded p-values show non-significant association. (alpha=0.001). Data from U.S. Birth Certificates with the given inclusion criteria: live, singleton, hospital birth between 24-27 weeks' gestation; Delivery between 2005-2009 and utilized 2003 Revision of Birth certificate; delivery not complicated by antenatal steroids or meconium aspiration syndrome.

		MATERNAL HYPERTENSION (%)						RESPIRATORY DISTRESS SYNDROME (%)					
	RISK FACTOR	YES n= 12,293 (13.7)	NO n= 77,770 (86.4)	OR [a]	(95% CI)		p-value[c]	YES n= 9,431 (10.5)	NO n= 80,668 (89.6)	OR [b]	(95% CI)		p-value[c]
MATERNAL CONDITIONS	Obstetric History												
	Primiparous	6,364 (16.7)	31,811 (83.3)	---	---	---		4,345 (11.4)	33,705 (88.6)	---	---	---	
	Multiparous	5,096 (11.0)	41,421 (89.0)	0.62	0.59	0.64	<0.0001	4,071 (8.8)	42,270 (91.2)	0.75	0.71	0.78	<0.0001
	Multiparous + previous PTB	696 (16.0)	3,642 (84.0)	0.96	0.88	1.04	**0.29**	888 (20.6)	3,426 (79.4)	2.01	1.86	2.18	<0.0001
	Medical History												
	Chronic Diabetes	535 (42.4)	728 (57.6)	4.82	4.30	5.39	<0.0001	246 (19.6)	1,007 (80.4)	2.12	1.84	2.44	<0.0001
	Gestational Diabetes	963 (26.1)	2,734 (74.0)	2.33	2.16	2.52	<0.0001	469 (12.7)	3,217 (87.3)	1.26	1.14	1.39	<0.0001
	Chorioamnionitis	100 (6.6)	1,426 (93.5)	0.44	0.36	0.54	<0.0001	330 (21.6)	1,195 (78.4)	2.41	2.13	2.73	<0.0001
DELIVERY CONDITIONS													
	Cesarean	9,878 (22.6)	33,804 (77.4)	5.32	5.08	5.57	<0.0001	6,309 (14.4)	37,368 (85.6)	2.34	2.24	2.45	<0.0001
	Fetal Intolerance	1,491 (25.3)	4,404 (74.7)	2.30	2.16	2.45	<0.0001	1,328 (22.6)	4,553 (77.4)	2.74	2.57	2.93	<0.0001
	PROM	851 (8.5)	9,199 (91.5)	0.56	0.52	0.60	<0.0001	1,802 (17.9)	8,271 (82.1)	2.07	1.96	2.19	<0.0001
NEONATAL CONDITIONS													
	Surfactant Given	1,144 (24.9)	3,446 (75.1)	2.21	2.06	2.37	<0.0001	3,247 (70.3)	1,375 (29.8)	30.28	28.28	32.42	<0.0001
	Male	6,154 (12.9)	41,691 (87.1)	0.87	0.84	0.90	<0.0001	5,217 (10.9)	42,647 (89.1)	1.10	1.06	1.15	<0.0001

PTB=preterm birth; PROM=premature rupture of membranes

[a]Odds Ratio of given risk factor increasing the likelihood of maternal hypertension

[b]Odds Ratio of given risk factor increasing the likelihood of respiratory distress syndrome

[c]p-value of Maximum Likelihood Estimate

TABLE III.3C Potential Confounders between Maternal Hypertension and Neonatal Respiratory Distress Syndrome (Preterm birth, dataset limited to births between 32 and 34 weeks' gestation)

Tables of possible confounders constructed using simple logistic regression. Ventilation over 6 hours used as proxy for RDS. Covariates found to be significant for both mHTN and RDS considered confounders for the given division of gestational age. Bolded p-values show non-significant association. (alpha=0.001). Data from U.S. Birth Certificates with the given inclusion criteria: live, singleton, hospital birth between 24-27 weeks' gestation; Delivery between 2005-2009 and utilized 2003 Revision of Birth certificate; delivery not complicated by antenatal steroids or meconium aspiration syndrome.

		MATERNAL HYPERTENSION (%)						RESPIRATORY DISTRESS SYNDROME (%)					
	RISK FACTOR	YES n= 28,520 (11.4)	NO n= 223,301 (88.7)	OR[a]	(95% CI)		p-value[c]	YES n= 10,915 (4.3)	NO n= 240,702 (95.7)	OR [b]	(95% CI)		p-value[c]
MATERNAL CONDITIONS	Obstetric History												
	Primiparous	14,303 (14.3)	85,520 (85.7)	---	---	---		4,632 (4.7)	94,774 (95.3)	---	---	---	
	Multiparous	12,430 (9.0)	125,586 (91.0)	0.81	0.76	0.87	<0.0001	5,185 (3.77)	(96.2)	0.80	0.77	0.84	<0.0001
	Multiparous + previous PTB	1,623 (13.7)	10,205 (86.3)	0.95	0.90	1.01	**0.09**	991 (8.4)	10,759 (91.6)	1.89	1.76	2.03	<0.0001
	Medical History												
	Chronic Diabetes	1,358 (37.8)	2,232 (62.2)	4.94	4.62	5.30	<0.0001	299 (8.4)	3,274 (91.6)	2.04	1.81	2.31	<0.0001
	Gestational Diabetes	3,071 (24.0)	9,733 (76.0)	2.64	2.53	2.76	<0.0001	766 (6.0)	11,968 (94.0)	1.44	1.34	1.56	<0.0001
	Chorioamnionitis	218 (8.4)	2,383 (91.6)	0.71	0.62	0.82	<0.0001	206 (8.0)	2,384 (92.1)	1.92	1.67	2.22	<0.0001
DELIVERY CONDITIONS													
	Cesarean	18,805 (18.3)	83,965 (81.7)	3.19	3.11	3.28	<0.0001	6,598 (6.4)	96,026 (93.6)	2.30	2.21	2.40	<0.0001
	Fetal Intolerance	2,987 (21.5)	10,913 (78.5)	2.27	2.18	2.37	<0.0001	1,442 (10.4)	12,416 (5.2)	2.80	2.64	2.97	<0.0001
	PROM	1,853 (7.4)	23,257 (92.6)	0.60	0.57	0.63	<0.0001	1,873 (7.5)	23,190 (92.5)	1.95	1.85	2.05	<0.0001
NEONATAL CONDITIONS													
	Surfactant Given	772 (21.1)	2,892 (78.9)	2.12	1.95	2.30	<0.0001	2,272 (61.8)	1,402 (38.2)	44.87	41.84	48.12	<0.0001
	Male	14,811 (10.9)	121,714 (89.2)	0.90	0.88	0.92	<0.0001	6,355 (4.7)	129,999 (95.3)	1.19	1.14	1.23	<0.0001

PTB=preterm birth; PROM=premature rupture of membranes

[a]Odds Ratio of given risk factor increasing the likelihood of maternal hypertension

[b]Odds Ratio of given risk factor increasing the likelihood of respiratory distress syndrome

[c]p-value of Maximum Likelihood Estimate

TABLE III.3D Potential Confounders between Maternal Hypertension and Neonatal Respiratory Distress Syndrome (Late preterm births, dataset limited to births between 35-37 weeks' gestation)

Tables of possible confounders constructed using simple logistic regression. Ventilation over 6 hours used as proxy for RDS. Covariates found to be significant for both mHTN and RDS considered confounders for the given division of gestational age. Bolded p-values show non-significant association. (alpha=0.001). Data from U.S. Birth Certificates with the given inclusion criteria: live, singleton, hospital birth between 24-27 weeks' gestation; Delivery between 2005-2009 and utilized 2003 Revision of Birth certificate; delivery not complicated by antenatal steroids or meconium aspiration syndrome.

		MATERNAL HYPERTENSION (%)						RESPIRATORY DISTRESS SYNDROME (%)					
	RISK FACTOR	YES n= 65,687 (9.8)	NO n= 604,220 (90.2)	OR[a]	(95% CI)		p-value[c]	YES n= 10,472 (1.6)	NO n= 658,379 (98.4)	OR [b]	(95% CI)		p-value[c]
MATERNAL CONDITIONS	Obstetric History												
	Primiparous	32,566 (12.8)	221,766 (87.2)	---	---	---		3,769 (1.5)	(98.5)	---	---	---	
	Multiparous	29,229 (7.6)	353,216 (92.4)	0.56	0.55	0.57	<0.0001	5,701 (1.5)	(98.5)	1.01	0.97	1.05	**0.79**
	Multiparous + previous PTB	3,472 (12.3)	24,753 (87.7)	0.96	0.92	0.99	**0.016**	921 (3.3)	27,134 (96.7)	2.25	2.09	2.42	<0.0001
	Medical History												
	Chronic Diabetes	3,081 (34.5)	5,859 (65.5)	5.03	4.81	5.26	<0.0001	340 (3.8)	8,553 (96.2)	2.55	2.28	2.85	<0.0001
	Gestational Diabetes	7,747 (21.8)	27,765 (78.2)	2.78	2.70	2.85	<0.0001	822 (2.3)	34,535 (97.7)	1.54	1.43	1.65	<0.0001
	Chorioamnionitis	533 (10.2)	4,694 (89.8)	1.05	0.96	1.14	**0.33**	149 (2.9)	5,061 (97.1)	1.86	1.58	2.20	<0.0001
DELIVERY CONDITIONS	Cesarean	34,891 (14.7)	201,754 (85.3)	2.26	2.22	2.30	<0.0001	5,885 (2.5)	230,170 (97.5)	2.39	2.30	2.48	<0.0001
	Fetal Intolerance	5,900 (19.0)	25,226 (81.0)	2.27	2.20	2.33	<0.0001	1,162 (3.8)	29,861 (96.3)	2.63	2.47	2.80	<0.0001
	PROM	2,829 (6.9)	38,126 (93.1)	0.67	0.64	0.70	<0.0001	1,241 (3.0)	39,634 (97.0)	2.10	1.98	2.23	<0.0001
NEONATAL CONDITIONS	Surfactant Given	529 (17.8)	2,445 (82.2)	2.00	1.82	2.20	<0.0001	1,729 (58.0)	1,253 (42.0)	103.70	96.14	111.86	<0.0001
	Male	34,786 (9.7)	325,749 (90.4)	0.96	0.95	0.98	<0.0001	6,416 (1.8)	353,519 (98.2)	1.36	1.31	1.42	<0.0001

PTB=preterm birth; PROM=premature rupture of membranes

[a]Odds Ratio of given risk factor increasing the likelihood of maternal hypertension

[b]Odds Ratio of given risk factor increasing the likelihood of respiratory distress syndrome

[c]p-value of Maximum Likelihood Estimate

TABLE III.4 Interactions between Risk factors and Surfactant

Crude logistic regression using interaction terms between risk factors and mHTN assessed potential interaction. A significant P-value of the interaction term for surfactant and the risk factor in question was used as an indication of interaction. Bolded p-values show non-significant association (alpha=0.001). Models constructed as follows: Neonatal respiratory distress syndrome = maternal hypertension + risk factor + maternal hypertension AND risk factor. When considering all eligible births, p=0.06 for "Maternal Hypertension AND gestational age" interaction term; Data from U.S. Birth Certificates with the given inclusion criteria: live, singleton, hospital birth between 24-27 weeks' gestation; Delivery between 2005-2009 and utilized 2003 Revision of Birth certificate; delivery not complicated by antenatal steroids or meconium aspiration syndrome.

	MATERNAL CONDITIONS						DELIVERY CONDITIONS			NEONATAL CONDITIONS	
	Obstetric History			Medical History							
Model by Gestational Age	Primi-parous	Multi-parous	Multiparous + previous PTB	Chronic Diabetes	Gestational Diabetes	Chorio-amnionitis	Cesarean	Fetal Intolerance	PROM	Male	Surfactant Given
All Eligible Births[a] (n=1,049,473)	<0.0001 Y	<0.0001 Y	<0.0001 Y	<0.0001 Y	<0.0001 Y	<0.0001 Y	<0.0001 Y	<0.0001 Y	<0.0001 Y	<0.0001 Y	--
Extremely Preterm Births (n=34,164)	**0.0994** N	**0.0174** N	**0.0211** N	**0.6052** N	**0.0181** N	**0.3419** N	**0.012** N	**0.0164** N	**0.0225** N	**0.44** N	--
Very Preterm Births (n=90,514)	**0.6931** N	**0.0572** N	<.0001 Y	**0.012** N	**0.0022** N	**0.0034** N	**0.1154** N	<0.0001 Y	<0.0001 Y	**0.0003** Y	--
Preterm Births (n=252,824)	**0.4045** N	**0.003** N	<0.0001 Y	<0.0001 Y	<0.0001 Y	**0.0021** N	**0.0024** N	<.0001 Y	<.0001 Y	**0.6643** N	--
Late Preterm Births (n= 671,971)	**0.6704** N	**0.2329** N	**0.0092** N	**0.0181** Y	<0.0001 Y	**0.0789** N	**0.258** N	<.0001 Y	0.001 Y	**0.5207** N	--

Extremely Preterm=24-27 weeks' gestation; Very Preterm=28-31 weeks' gestation; Preterm=32-34 weeks' gestation; Late Preterm=35-37 weeks' gestation; Y=Interaction Present; N=No interaction present; PTB= Preterm Birth; PROM=Premature Rupture of Membranes

[a]Using p value of "Surfactant AND Risk Factor" interaction term for given gestational age

*"Maternal Hypertension AND Risk Factor" interaction term unsignificant

**"Maternal Hypertension AND Risk Factor" interaction term significant

TABLE III.5: Variables used in Model Construction, by gestational age

Associative models not including surfactant were built to explore the direct effect (shown below). Confounders and interaction terms found previously with mHTN and surfactant were added into the associative models unless otherwise stated. C-index assessed goodness of fit for all candidate models. If multiple candidates demonstrated c-indices with less than 10% variation, the more parsimonious model was selected. Non-significant terms were removed via backwards selection. Bold p-value shows non-significant association (alpha=0.001). All models, including crude, test the formula: Neonatal Respiratory Distress Syndrome=Maternal Hypertension + (risk factors marked "Y"). Data from U.S. Birth Certificates with the given inclusion criteria: live, singleton, hospital birth between 24-27 weeks' gestation; Delivery between 2005-2009 and utilized 2003 Revision of Birth certificate; delivery not complicated by antenatal steroids or meconium aspiration syndrome.

	MATERNAL CONDITIONS						DELIVERY CONDITIONS			NEONATAL CONDITIONS	OUTCOMES				
	Obstetric History			Medical History											
Model by Gestational Age	Primi-parous	Multi-parous	Multiparous + previous PTB	Chronic Diabetes	Gestational Diabetes	Chorio-amnionitis	Cesar- ean	Fetal Intoler-ance	PROM	Male	OR	(95% CI)		p-value[b]	c-index
All Eligible Births (n=1,049,473)															
Crude[a]	--	--	--	--	--	--	--	--	--	--	2.24	2.19	2.30	<.0001	0.550
Saturated	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	1.78	1.73	1.83	<.0001	0.696
Interaction	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	2.02	1.49	2.74	<.0001	0.697
Confounding	N	Y	N	Y	Y	Y	Y	Y	Y	Y	1.76	1.72	1.81	<.0001	0.693
Combined[c]	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	2.02	1.49	2.74	<.0001	0.697
FINAL MODEL[a]	Y	N	Y	Y	N	Y	Y	Y	Y	Y	1.77	1.73	1.82	<.0001	0.696
Extremely Preterm Births (n=34,164)															
Crude[a]	--	--	--	--	--	--	--	--	--	--	1.62	1.51	1.74	<.0001	0.529
Saturated	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	1.47	1.36	1.59	<.0001	0.630
Interaction	N	N	N	N	N	N	N	N	N	N	--	--	--	--	--
Confounding	N	Y	Y	Y	N	Y	Y	Y	Y	Y	1.62	1.50	1.75	<.0001	0.620
Combined[c]	N	Y	Y	Y	N	Y	Y	Y	Y	Y	1.62	1.50	1.75	<.0001	0.620
FINAL MODEL[a]	Y	N	Y	N	N	Y	Y	Y	Y	N	1.47	1.36	1.59	<.0001	0.628
Very Preterm Births (n=90,514)															
Crude[a]	--	--	--	--	--	--	--	--	--	--	2.31	2.20	2.43	<.0001	0.561
Saturated	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	1.81	1.72	1.92	<.0001	0.685
Interaction	N	N	Y	N	N	N	N	N	Y	Y	2.90	2.68	3.13	<.0001	0.624
Confounding	N	Y	N	Y	N	Y	Y	Y	Y	N	1.79	1.70	1.89	<.0001	0.677
Combined[c]	N	Y	Y	Y	N	Y	Y	Y	Y	Y	2.12	1.96	2.30	<.0001	0.684
FINAL MODEL[a]	Y	N	Y	Y	N	Y	Y	Y	Y	Y	1.81	1.72	1.92	<.0001	0.685
Preterm Births (n=252,824)															
Crude[a]	--	--	--	--	--	--	--	--	--	--	2.20	2.10	2.30	<.0001	0.551
Saturated	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	1.62	1.53	1.70	<.0001	0.675
Interaction	N	N	Y	Y	Y	N	N	Y	Y	N	2.47	2.32	2.61	<.0001	0.629
Confounding	N	Y	N	Y	Y	Y	Y	Y	Y	Y	1.73	1.65	1.82	<.0001	0.670
Combined[c]	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	2.02	1.90	2.15	<.0001	0.675
FINAL MODEL[a]	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	1.74	1.66	1.83	<.0001	0.675
Late Preterm Births (n= 671,971)															
Crude[a]	--	--	--	--	--	--	--	--	--	--	2.00	1.90	2.10	<.0001	0.540
Saturated	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	1.69	1.60	1.78	<.0001	0.671
Interaction	N	N	N	Y	Y	N	N	Y	Y	N	2.09	1.97	2.22	<.0001	0.600
Confounding	N	N	N	Y	Y	N	Y	Y	Y	Y	1.61	1.53	1.70	<.0001	0.662
Combined[c]	N	N	N	Y	Y	N	Y	Y	Y	Y	1.84	1.73	1.95	<.0001	0.663
FINAL MODEL[a]	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	1.62	1.53	1.70	<.0001	0.670

OR= Odds Ratio of Maternal Hypertension for given model (all ORs adjusted unless otherwise indicated); PTB= Preterm Birth; PROM=Premature Rupture of Membranes

[a]Crude OR of Maternal Hypertension

[b]p-value of Maternal Hypertension variable (all p-values of models <0.0001)

[c]Derived from combination of "Confounding" and "Interaction" models

[d]Derived from backwards elimination of "Saturated" model

TABLE III.6 Final Models, by gestational age

Final models exploring the indirect effect (shown below). All models test the formula Neonatal Respiratory Distress Syndrome=Maternal Hypertension + Surfactant + (other risk factors). All models derived from saturated model using backward elimination of non-significant p-values of given risk factors until all remaining risk factors are significant (p-value of all models <0.0001, alpha=0.001)Data from U.S. Birth Certificates with the given inclusion criteria: live, singleton, hospital birth between 24-27 weeks' gestation; Delivery between 2005-2009 and utilized 2003 Revision of Birth certificate; delivery not complicated by antenatal steroids or meconium aspiration syndrome.

Gestational Age	MODEL
All Eligible Births	-4.1972 + 0.5724*(Maternal Hypertension) + 0.1728*(primiparous) + 0.8127*(multiparous with previous PTB) + 0.2649*(chronic diabetes) + 0.7839*(chorioamnionitis) + 0.8744*(cesarean delivery) + 0.6204*(fetal intolerance) + 0.952*(PROM) + 0.1578*(male infant)
Extremely Preterm Births	-1.9477 + 0.3844*(Maternal Hypertension) + 0.1672*(primiparous) + 0.6804*(multiparous with previous PTB) + 0.4374*(chorioamnionitis) + 0.3387*(cesarean delivery) + 0.73*(fetal intolerance) + 0.5057*(PROM)
Very Preterm Births	-3.0665 + 0.5955*(Maternal Hypertension) + 0.2535*(primiparous) + 0.8857*(multiparous with previous PTB) + 0.3504*(chronic diabetes) + 0.6466*(chorioamnionitis) + 0.6968*(cesarean delivery) + 0.6354*(fetal intolerance) + 0.7362*(PROM) + 0.1042*(male infant)
Preterm Births	-3.9175 +0.5552*(Maternal Hypertension) + 0.1540*(primiparous) + 0.7486*(multiparous with previous PTB) + 0.3141*(chronic diabetes) + 0.1481*(gestational diabetes) + 0.4029*(chorioamnionitis) + 0.7099*(cesarean delivery) + 0.6625*(fetal intolerance) + 0.6901*(PROM) + 0.1721*(male infant)
Late Preterm Births	-4.9422 + 0.4804*(Maternal Hypertension) + 0.0769*(multiparous) + 0.7841*(multiparous with previous PTB) + 0.5257*(chronic diabetes) + 0.2260*(gestational diabetes) + 0.4583*(chorioamnionitis) + 0.7560*(cesarean delivery) + 0.6310*(fetal intolerance) + 0.7766*(PROM) + 0.3019*(male infant)

Extremely Preterm=24-27 weeks' gestation; Very Preterm=28-31 weeks' gestation; Preterm=32-34 weeks' gestation; Late Preterm=35-37 weeks' gestation; PTB= Preterm Birth; PROM= Premature Rupture of Membranes

FIGURES FOR CHAPTER III

FIGURE III.1: Directed Acyclic Graph

Direct Effect of mHTN on RDS

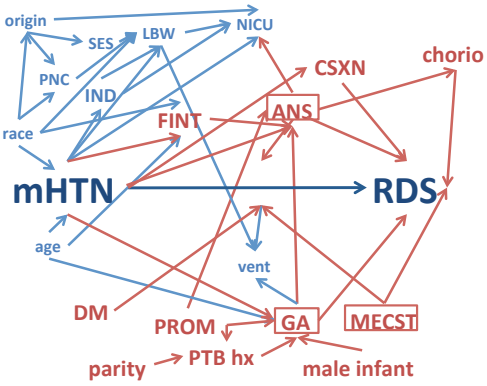

FIGURE III.2: Directed Acyclic Graph, with all Considered Variables

Direct Effect of mHTN on RDS

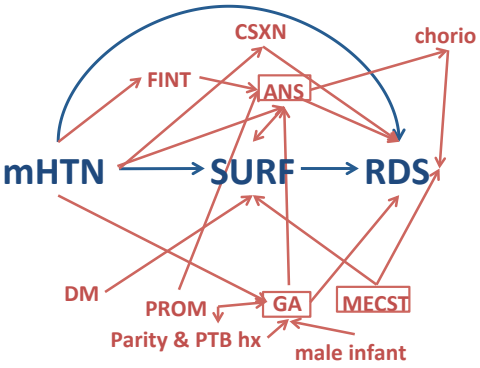

FIGURE III.3: Directed Acyclic Graph, with all Final Variables

Direct Effect of mHTN on RDS

LEGEND FOR FIGURES III.1-III.3:

HYPOTHESIS: mHTN=Maternal hypertension (any diagnosis of hypertension while pregnant); RDS=Neonatal respiratory distress syndrome; *INCLUDED RISK FACTORS:* Parity=Number of pregnancies; DM= Maternal diabetes (both chronic and gestational); PTB hx=History of pre-term birth; GA=Gestational age at delivery; MECST=Meconium staining present at delivery; ANS=Antenatal steroids given prior to delivery; Chorio=Chorioamnionitis at delivery; CSXN=Cesarean delivery; FINT=Fetal intolerance during delivery; PROM=Premature rupture of membranes; Male= sex of infant; *CONSIDERED RISK FACTORS:* Origin: Maternal Country of Origin; PNC: Prenatal Care; SES: Maternal socio-economic status; LBW: Low birth weight (<1500g); NICU: Neonatal Intensive Care Unit Admission; Age: Maternal Age; Race: Maternal Race and Ethnicity; Vent: Any neonatal ventilation; IND: Medical induction of labor

Figure III.4: Considered Variables and Potential Causes for Elimination

List of considered variables constructed by literature review, expert opinion and availability on 2003 Revision of U.S. Birth Certificates. Data from U.S. Birth Certificates with the given inclusion criteria: live, singleton, hospital birth between 24-27 weeks' gestation; Delivery between 2005-2009 and utilized 2003 Revision of Birth certificate;Neonatal RDS used proxy of ventilation over 6 hours. MAS used proxy of meconium staining.

RISK FACTOR			ELIMINATED SECONDARY TO: Literature Review	DAG construction	Excessive Missing Data	CONSIDERED IN MODEL CONSTRUCTION
PRIMARY INTEREST		Maternal Hypertension[a]				X
		Neonatal Respiratory Distress Syndrome				X
SECONDARY INTEREST		Surfactant Administration				X[e]
MATERNAL CONDITIONS	Demographic Information	Age (years)		X		
		Weight Gain During Pregnancy (lbs)***			X	
		Smoking During Pregnancy***			X	
		Married	X			
		Race		X		
		Hispanic Ethnicity and/or origin		X		
		Education	X			
		Socio-economic Status		X		
	Obstetric History	Parity				X[f]
		Previous PTB				X[f]
		Prenatal Care		X		
	Medical History	Chronic Diabetes				X
		Gestational Diabetes				X
		Chorioamnionitis				X
DELIVERY CONDITIONS		Antenatal Steroids Given[b]	X			
		Year of Delivery	X			
		Cesarean Delivery				X
		Operative Vaginal Delivery	X			
		Timing of Delivery (Prolonged or Precipitous)	X			
		Estimated Gestational Age[c]				X
		PROM				X
		MAS[d]	X			
		Fetal Intolerance				X
		Induction of Labor		X		
NEONATAL CONDITIONS		5 minute APGAR**			X	
		Male				X
		Birth Weight (g)		X		
		Ventilation for at least one hour (but less than 6 hours)		X		
		NICU admission		X		
		Antiobiotics Given to Neonate	X			

PTB= Preterm Birth; PROM=Premature Rupture of Membranes; MAS=Meconium Aspiration Syndrome; APGAR=Appearance, Pulse, Grimace, Activity, and Respiration; NICU=Neonatal Intensive Care Unit

[a]Literature review demonstrated consistent combination hypertensive disorders, including Chronic Hypertension, Pregnancy-Induced Hypertension, and Eclampsia, which are the classifications available on the 2003 Revision of the U.S. Birth Certificate

[b]Births with antenatal steroids removed from final dataset

[c]Stratified by gestational age, as suggested by literature review

[d]Births with MAS removed from final dataset

[e]Used only for indirect effect

[f]Combined when studying direct and indirect effects

** 5-10% Missing

*** > 10% Missing

CHAPTER IV:

Public Health Implications and Possible Future Directions

PUBLIC HEALTH IMPLICATIONS

Direct Effect of Maternal Hypertension on Neonatal Respiratory Distress Syndrome Assuming the validity of birth certificate information, this study establishes an association between mHTN and neonatal RDS after adjustment for risk factors, including maternal obstetric and medical history, birth information, and characteristics of the neonate (aOR mHTN direct effect 1.77 for all eligible births, ranging 1.47-1.62 by gestational age). In contrast to previous research, this study's unusually large sample size and small alpha give it substantial power. Public health officials and healthcare providers should be aware of such a relationship when counseling women of reproductive age with a history of hypertension, as well as in their clinical discretion regarding the infant during the neonatal period.

Indirect Effect with Exogenous Surfactant Administration The secondary analysis shows that exogenous surfactant administration does little, if any, to decrease the total effect of mHTN on neonatal RDS (% Differences between direct effect aOR for mHTN and indirect effect aOR for mHTN ranging from 3%-7% by gestational age). Thus, despite the many advances made in perinatology and neonatology since 1980, surfactant cannot be the only answer to addressing neonatal RDS. Further action and intervention should happen prior to delivery.

Other considerations With the recognition that labor and delivery can be a hectic time, especially in the high-risk patient (a category under which all deliveries in this study would qualify), there needs to be improvement in the documentation of the birth certificate. Better documentation during prenatal care could aid in the consolidation of information in hospitals that have electronic medical records. Physicians and registered nurses could use the models established by CNMs to improve their documentation (33). In order to continue using birth

certificates for pregnancies complicated with mHTN, information regarding pre-eclampsia and HELLP syndrome must be included with the current classifications of cHTN, PIH, and eclampsia.

POSSIBLE FUTURE DIRECTIONS

While the association between mHTN and RDS is strong, causality cannot be confirmed. Perhaps the association results from increased oxidative stress in utero, as suggested by Torrance, et al. (2008). Perhaps it is caused iatrogenically from obstetric guidelines to induce labor in severely hypertensive women after 24 weeks' gestation (41). Future studies should consider the various mechanisms of mHTN without exclusion of cHTN and parity. Additionally, a study investigating PTB complicated by mHTN and the association with induction of labor by various gestational ages could prove useful.

With respect to surfactant administration, there is no conclusive clinical guideline or protocol established for administration of surfactant other than when a clinician deems a neonate to be "high risk" (16, 17, 20). A risk assessment of antenatal, perinatal, and neonatal factors available on the birth certificate could help to establish a screen to objectively identify neonates at risk of RDS, as well as allow for more efficient and standardized communication of that risk between delivery and NICU teams. Studies investigating trends in surfactant administration by hospital, region, and season could better establish if variations in surfactant administration are supply or user dependent. Given the results of Kirmeyer and Martin (2007) and Lee, et al. (2011), it would be interesting to investigate surfactant administration not only by gestational age but also by maternal race and ethnicity.

A follow-up study to this one should also include antenatal steroid use in order to investigate whether antenatal steroids can act synergistically with surfactant to decrease the risk of neonatal RDS in infants born to hypertensive mothers. As some have suggested that antenatal steroid administration decreases the likelihood of surfactant administration despite a lack of

decrease in RDS among babies born to hypertensive mothers (25), it could prove interesting to investigate this proposition with a prospective study, ideally in a randomized controlled trial.

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APPENDIX

APPENDIX 1: Definitions of Selected Risk Factors

All definitions from Williams' Obstetrics, unless otherwise noted. Citation: Cunningham FG, Leveno KJ, Bloom SL, Hauth JC, Rouse DJ, Spong CY, eds. Williams Obstetrics. 23rd ed. New York: McGraw-Hill; 2010. http://www.accessmedicine.com/content.aspx?aID=6036563. Accessed November 28, 2012.

PRIMARY INTEREST	Maternal Hypertension (mHTN)	Blood pressure over 140/90 at any point in pregnancy
	Neonatal Respiratory Distress Syndrome (RDS)	Increased work of breathing due to a deficiency of surfactant, suspected in infants with increased respiratory rate, nasal flaring and grunting, often confirmed by a chest x-ray showing "ground glass opacities"[a]
SECONDARY INTEREST	Surfactant Given	Including both prophylactic and rescue doses
MATERNAL CONDITIONS	Obstetric History	
	Primiparous	Women who were pregnant for the first time
	Multiparous	Women who were pregnant before current pregnancy, regardless of outcome of previous pregnancies.
	Preterm birth (PTB)	Delivery before 37 completed weeks of gestation
	Medical History	
	Chronic Diabetes	Fasting glucose > 126 or Hemoglobin A1C > 6.5 when not pregnant
	Gestational Diabetes	Fasting glucose > 126 or Hemoglobin A1C > 6.5 when pregnant, which resolves after delivery
	Chorioamnionitis	Infection of the gestational sac
DELIVERY CONDITIONS	Cesarean delivery	Delivery through incision in the uterus
	Fetal Intolerance	Also known as fetal distress, a grouping of signs on fetal heart monitoring that suggest the fetus cannot tolerate a continuation of pregnancy and needs urgent delivery
	Premature Rupture of Membranes (PROM)	Spontaneous breaking of the amniotic sac prior to onset of labor, often a sign of intrauterine infection
NEONATAL CONDITIONS	Male Infant	As defined on birth certificate

[a]Defintion from Tintinalli's Emergency Medicine. Citation: Wood KS, Gordon PV. Chapter 4. Neonatal and Pediatric Transport. In: Tintinalli JE, Stapczynski JS, Cline DM, Ma OJ, Cydulka RK, Meckler GD, eds. Tintinalli's Emergency Medicine: A Comprehensive Study Guide. 7th ed. New York: McGraw-Hill; 2011. http://www.accessmedicine.com/content.aspx?aID=6348312. Accessed November 28, 2012