Distribution Agreement

In presenting this thesis or dissertation as a partial fulfillment of the requirements for an advanced degree from Emory University, I hereby grant to Emory University and its agents the non-exclusive license to archive, make accessible, and display my thesis in whole or in part in all forms of media, now or hereafter known, including display on the world wide web. I understand that I may select some access restrictions as part of the online submission of this thesis or dissertation. I retain all ownership rights to the copyright of the thesis. I also retain the right to use in future works (such as articles or books) all or part of this thesis.

Signature:

_____ _____

Katherine Lee Carssow 11/30/2011

The Presence of Maternal Hypertension as an Effect Modifier in the Relationship Between Intrapair Birth Weight Discordance and Infant Mortality in Live Twin Births

By

Katherine Lee Carssow

Degree to be awarded: MPH

Epidemiology

_____

Michael R. Kramer

Faculty Thesis Advisor

The Presence of Maternal Hypertension as an Effect Modifier in the Relationship Between Intrapair Birth Weight Discordance and Infant Mortality in Live Twin Births

By

Katherine Lee Carssow

Bachelor of Science in Nursing

University of Pennsylvania

2007

Faculty Thesis Advisor: Michael R. Kramer, PhD

An abstract of

A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University in partial fulfillment of the requirements for the degree of
Master of Public Health
in Epidemiology

2011

Abstract

The Presence of Maternal Hypertension as an Effect Modifier in the Relationship Between Intrapair Birth Weight Discordance and Infant Mortality in Live Twin Births.

By Katherine Carssow

Objective: To determine whether the presence of maternal hypertension interacts with intrapair twin birth weight discordance to affect the association between birth weight discordance and infant mortality among live twin births.

Study Design and Methods: The study used the matched multiple birth data set compiled by the National Center for Health Statistics (NCHS), which contains matched records for all multiple births in the United States from national birth and death certificate data from 1995-2000. Birth weight discordance was expressed as a percentage based on the weight of the larger twin, and classified into 5 categories: <15%, 15-19%, 20-24%, 25-29%, and ≥30%. Infant mortality was defined as any set of twins in which one or more members did not survive the first year of life. Crude prevalence and odds ratios of infant mortality were calculated for each level of birth weight discordance, presence of maternal hypertension, and selected covariates.

Results: The analysis used a total sample size of 289,953 live twin sets. The crude rates of infant mortality in the highest and lowest categories of birth weight discordance were 9.4% and 2.5%, respectively. The unadjusted association between weight discordance and infant mortality was significant both with and without considering the interaction between weight discordance and maternal hypertension. The association between maternal hypertension and birth weight discordance was also significant (OR 1.62, 95% CI 1.54-1.70).When the model associating death with birth weight discordance was adjusted for maternal demographics along with parity, placental abruption, gestational age, and presence of a congenital anomaly, the effect was attenuated. The p-value for the interaction term in the final model was p=0.70.

Conclusion: Interaction between birth weight discordance and maternal hypertension does not appear to effect the association between weight discordance and infant mortality when important covariates are considered.

The Presence of Maternal Hypertension as an Effect Modifier in the Relationship Between Intrapair Birth Weight Discordance and Infant Mortality in Live Twin Births

By

Katherine Lee Carssow

Bachelor of Science in Nursing

University of Pennsylvania

2007

Faculty Thesis Advisor: Michael R. Kramer, PhD

A thesis submitted to the Faculty of the

Rollins School of Public Health of Emory University

In partial fulfillment of the requirements for the degree of

Master of Public Health]

in Epidemiology

2011

Acknowledgements

Sincere gratitude to my faculty advisor, Dr. Michael Kramer, for patience, support, and expertise; Jessie Patton-Levine for her support and advice; and to my parents, Karen & Tim, for their support and encouragement.

Table of Contents

Chapter 1

Background and Literature Review

While the United States has experienced a notable decline in infant mortality over the past several decades, infant death is still a considerable public health concern and an important indicator of the health and wellness of a society. In 2009 the infant mortality rate in the U.S. was 6.8 infant deaths per 1000 births (1), compared with 100 infant deaths per 1000 live births in 1900 (2). However, the U.S. infant mortality rate has seen very little decline since 2000 and remains high relative to other industrialized countries, with the U.S. ranking 29th in the world in infant mortality. The plateau in the U.S. infant mortality rate is the first sustained period without decline since the 1950s. Also of particular concern are the increasingly wide racial and socioeconomic disparities in infant mortality, suggesting a need for increased understanding of the risk factors related to infant death and effective means of prevention (2).

Multiple risk factors for infant mortality have been identified and studied thoroughly. Among the 5 leading causes of infant death, preterm birth and maternal complications rank 2nd and 4th, respectively (3). The most significant maternal complication of pregnancy is maternal hypertension, which contributes heavily to conditions that increase infant mortality. Hypertensive disorders of pregnancy are classified as chronic hypertension, gestational hypertension, preeclampsia, and chronic hypertension with superimposed preeclampsia (4). Current epidemiologic evidence suggests that hypertensive disorders of pregnancy complicate approximately 5-10% of pregnancies worldwide, and pose significant risks to maternal, fetal, and neonatal health. Potential risks to infants of hypertensive mothers are related to two main etiologies: preterm birth and inadequate placental perfusion (7, 9). Preterm birth, defined as a delivery prior to 37 weeks gestation, causes up to 75% of perinatal, neonatal, and infant

mortality in the U.S. (8). Maternal hypertension often necessitates the induction of labor before 37 weeks gestation to prevent maternal and fetal complications (9).

Placental vasoconstriction decreases blood flow to the fetus, causing growth restriction such that infants of hypertensive mothers are often small for gestational age and exhibit immature organ functioning (4,5,7). The vasoconstriction also leads to frequent complications that cause spontaneous preterm labor without other discernible causes. Maternal hypertension is a direct factor in two of the leading causes of infant mortality and often causes multiple complications, making it imperative to consider when examining other factors related the adverse neonatal outcomes.

Twin gestations have an infant mortality rate that is more than five times the rate for singleton gestations (3). According to the CDC's linked birth/infant death data, multiple births accounted for 15% of all infant deaths in 2005, but only accounted for 3% of live births (2,3). Women carrying twins are at an increased risk of developing gestational hypertension. A study of 3650 pregnancies comparing hypertensive disorders in singleton versus twin gestations found a 12.9% pregnancy-specific prevalence of hypertension among women carrying twins versus 6.3% in singleton pregnancies (10). The study also found that among the pregnancies where the mother developed hypertension, the risk of adverse pregnancy outcomes were higher among women carrying twins even when controlling for systolic and diastolic blood pressure. For example, among pregnancies with gestational hypertension, the risk of delivering before 35 weeks gestation was considerably higher among twin gestations than singleton gestations (RR=11.27; 3.37-37.68) (10). In the presence of preeclampsia, the risks of adverse outcomes such as lower birth weights, lower gestational ages at delivery, and risk of cesarean section remain higher among twins versus singletons as well. While the incidence of hypertension and adverse pregnancy outcomes are higher in twin pregnancies versus singletons, among twin pregnancies the mothers who remained normotensive had a higher likelihood of delivering at an earlier gestational age,

suggesting that in twin pregnancies the development of hypertension might have a protective effect. Another possibility is that because hypertension is multifetal pregnancy might increase the risk of fetal death, therefore the twins born alive after a hypertensive pregnancy were already at a relatively lower risk of neonatal death due to some other protective factor than twins born alive to normotensive mothers. Entry into the study required that both twins were born alive, so the exclusion of fetal deaths could have excluded the individuals at highest risk of neonatal death had they survived to delivery.

In recent years, there has been extensive research into the causes and consequences of intrapair birth weight discordance in twins (13). Weight discordance is defined as any disparity in the weight of the larger twin and the smaller twin in a set, but the level at which the discordance becomes clinically significant has been debated. The most frequent determination is that a 15% discordance based on the weight of the larger twin is the most reliable cutoff when considering clinically significant discordance (13,24). The majority of studies determine discordance based on the weight of the larger twin, and consider a difference of 15%-24% moderate discordance and ≥25% severe discordance (19,24). Epidemiologic investigation has found that approximately a quarter of twins are at least 15% discordant (13).

Intrapair birth weight discordance is an important factor in perinatal research because it contributes significantly to fetal and infant death (12-15,17,19). Yalcin et al studied 357 twin live births and found that 33% of sets with >30% weight discordance resulted in neonatal mortality, compared with only 1.5% of sets with <10% weight discordance (27). While some studies have found that the risk of neonatal mortality is not directly increased by the presence of weight discordance (28), the mixed results are often due to differing definitions of weight discordance and difficulty controlling for extraneous factors. Severely weight discordant twins are often small for gestational age, so in assessing neonatal mortality it is difficult to determine the role of weight discordance versus the effects of lower birth weights. One

study of 329 sets of twins found that approximately two-thirds of twins with ≥30% weight discordance were also small for gestational age, and low birth weight is one of the strongest known risk factors for neonatal mortality (29). Despite conflicting reports of the direct risks attributable to weight discordance, most researchers agree the weight discordance often indicates suboptimal growth and developmental compromise in one or both twins in a set, and should be considered a potential risk factor for adverse perinatal outcome and neonatal mortality (30).

Given the conflicting results regarding the link between intrapair birth weight discordance and subsequent neonatal mortality, it is important to continue exploring the mechanisms related to weight discordance and the associated risks to the infant. Given that fetal development and neonatal outcomes are complex and inextricably linked to maternal conditions, one has to consider the maternal factors in researching risk factors for neonatal mortality. Gonzalez-Quintero et al (2003) explored the potential antenatal factors associated with discordant growth in twin pregnancies, and found that preeclampsia was associated with severe weight discordancy (adjusted odds ratio, 1.70, 95% CI 1.21-2.41) after adjusting for parity and placental membranes (23). Various other studies have found that placental pathology and factors that impair optimal placental blood flow can contribute to severe weight discordance (38, 40). The etiology of maternal hypertension and the association between hypertension and multiple pregnancies suggests that birth weight discordance may have different implications in cases where the weight discordance is related to hypertension and cases where weight discordance is associated with other developmental factors. The purpose of this study is to examine the association between intrapair birth weight discordance and neonatal mortality while considering the presence and severity of maternal hypertension as a potentially significant modifier.

Many maternal and infant covariates are important to consider when analyzing infant mortality as an outcome. Maternal demographics such as age, race, and level of education all have an impact on

neonatal outcomes (2-3, 23). Maternal medical history and complications are important predictors of pregnancy and neonatal outcomes (2-3). Placental abruption, when the placenta separates from the uterine lining, is a major cause of preterm birth and poor perinatal and neonatal outcomes, and has been estimated to effect between 10%-40% of preterm births (41). Maternal parity (number of living children) is strongly associated with the risk of adverse pregnancy outcomes (2,3). Preterm birth is unarguably the most important infant risk factor when looking at neonatal outcomes (2). Because maternal factors are an important component in the cause and severity of preterm birth, it is essential to examine a combination of both maternal and infant risk factors in analyzing potential associations with infant mortality.

Chapter 2

Methods

Study Hypothesis:

This study used a cohort follow-up design to test the hypothesis that maternal hypertension during pregnancy and twin birth weight discordance interact to increase the risk of infant mortality among twin gestations.

Sample and Study Population:

The data used in this study is drawn from the matched multiple birth data set, which was compiled by the National Center for Health Statistics (NCHS). This data set contains matched records for all multiple births in the United States from national birth and death certificate data from 1995-2000. To match the separate members of one set of multiples, each member was given a unique set identification number, allowing for the analysis of a complete set of multiples rather than individual member separately. The data provides maternal information such as age, race, parity, demographics, lifestyle, and medical risk factors, as well as infant characteristics such as gestational age at birth, sex, birth weight, congenital anomalies, and many others. Because the data also links death certificate data for each matched set on multiples, information about infant mortality for individuals within a set or for the set as a whole can be ascertained as well. The NCHS reports that 98% of multiple birth records were successfully linked within the data (32). While standard natality records do not enable the matching of individual members of a set of multiples, this data presents the opportunity to analyze characteristics and differences between all members within a set.

The data contains 325,516 sets of twins, 12,157 sets of triplets, and 760 sets of quadruplets. For this analysis only twin gestations are considered, so the members of higher-order sets of multiples were excluded (n=40,660). Additionally, records of unmatched twins were excluded (n=8520). Based on findings from a thorough literature review, records with the following characteristics were also excluded: missing birth weight (n=3885), missing gestational age at birth (n=7,029), missing maternal race (n=5039), fetal death within the set (n=14,413), gestational age less than 23 weeks or greater than 41 weeks (n=22,637), birth weight less than 300 grams (n=3,508), and implausible gestational age and birth weight combinations. The original data is organized so that each member of a set is an individual observation. This study aimed to analyze the twin pair rather than the individual members, so the data was merged based on the set ID numbers so that each observation represented a twin set with information regarding two individual infants and one mother. To further ensure accurate analysis, twin sets with the following characteristics were excluded: inconsistent maternal age within the set (n=6,746), inconsistent maternal race within the set (n=6,271), and inconsistent gestational age within the set (n=18,045). The final data set included 289,953 sets of twins, including 8,790 sets in which a neonatal or infant death occurred.

Variables:

The outcome variable of interest was neonatal or infant death within the twin set, defined as death of a live born infant within the first year of life. The matched multiple birth data set contains a "birthid" variable which denotes sets of live multiple births where all members survived the first year of life and live multiple births where one or more members did not survive the first year of life. This variable was used to create a dichotomous mortality variable, where a positive value indicated that one or more members of a set did not survive the first year. To check for consistency across the data, this variable

was tabulated with "age of death in days" and the ICD (9^{th} revision) cause of death variables within the set. All of the sets in which a death was indicated also contained information regarding age at death and cause of death. Because this study sought to analyze the set of twins rather than the individual members within a set, a positive value for infant death included any case in which either member did not survive the first year. Sets in which both members did not survive the first year were categorized into the same group as sets where one twin survived the first year and one did not.

The main exposure variable of interest was birth weight discordance. Once the data was merged so that each observation represented a complete set of live born twins, the total intra-pair birth weight difference in grams was calculated for each set. The number was then divided by the weight in grams of the larger twin within the set to obtain a discordance percentage. Using these percentages, birth weight discordance was classified into 5 categories: >15% (reference category), 15-19%, 20-24%, 25-29%, and ≥30%. The use of this particular categorization was chosen after a literature review, focusing specifically on studies that used the matched multiple birth data set (17, 19).

The secondary exposure variable of interest was maternal hypertension. The matched multiple birth data reports information on three classes of maternal hypertension: chronic hypertension, pregnancy-induced hypertension, and ecclampsia. Distributions were calculated for each category separately, and then a new variable was created to account for any type of hypertension reported during the pregnancy (see Table 1). A positive value in the new category indicated that one or more types of hypertension were reported during the pregnancy, so sets where more than one type was reported were given the same weight as those where only one type was reported.

Covariates

All information in the matched multiple birth data set is based on what is documented on the birth certificate or death certificate of the individual infant. Maternal race was categorized as white, black, or

other. Maternal age was classified into 5 different categories: <20 years, 20-24 years, 25-29 years, 30-35 years, and >35 years. Maternal education was categorized as (1) less than high school, (2) completed high school, (3) some college, (4) completed college or greater, and (5) unknown. Gestational age at delivery is reported based on either mother's last menstrual period or clinical ultrasound, depending on the method recorded on the birth certificate. Gestational age was categorized into 4 classes: <28 weeks, 28-32 weeks, 33-36 weeks, or ≥37weeks. The data also reported information on any congenital anomalies that were recorded on the infant birth or death certificate. The data contains specific information about 21 different congenital anomalies, as well as a category for any other unknown or unspecified anomalies. Distributions were calculated for each anomaly separately, and a new variable created to represent the presence of any type of anomaly. Presence of congenital anomaly was further classified as present, not present, or unknown or unspecified. Maternal parity was categorized as either nulliparous or multiparous. Adequacy of prenatal care was classified as either (1) early prenatal care (entry in to prenatal care during the first trimester), (2) late prenatal care (entry into prenatal care after the first trimester), or (3) no prenatal care or unknown. Placental abruption was classified as present, not present, or unknown.

Statistical Analyses

The data was analyzed using SAS version 9.3 (SAS institute, Cary, NC). Associations between the outcome (infant mortality), birth weight discordance, maternal hypertension, and potential covariates were assessed using crude mortality risk and obtaining ORs for the exposures and outcome. . Stratified analysis was conducted using the Breslow-Day test for homogeneity to evaluate possible effect modification. Mantel-Haenszel adjusted odds ratios were also calculated to evaluate possible confounding (> 10% change in the odds ratios). Covariates considered as potential confounders by these

methods and the literature included: maternal race, maternal age, maternal education, adequacy of prenatal care, gestational age at delivery, parity, presence of a congenital anomaly, and presence of placental abruption. Effect modification was assessed for selected interactions that were biologically plausible, which included birth weight discordance with maternal hypertension, gestational age with birth weight discordance, and maternal age with gestational age. Unconditional logistic regression models were used to evaluate associations between birth weight discordance and infant mortality. Maternal and infant risk factors were added to the model and eliminated in a step-wise method. Interaction terms were tested for statistical significance using likelihood ratio tests and were kept in the model if $p<0.05$.

Results

The characteristics and medical risk factors among the twin sets stratified by 5 levels of birth weight discordance are shown in Table 1. A total of 289,953 sets of twins were available for analysis. Of these sets, 213,024 (73.5%) were <15% discordant, 28,022 (9.6%) were 15-19% discordant, 22,310 (7.7%) were 20-24% discordant, 12,323 (4.2%) were 25-29% discordant, and 14,274 (4.9%) were ≥30% discordant. In the four separate categorizations of maternal hypertension, the crude prevalence of birth weight discordance was highest amongst sets in which maternal hypertension was present. Severe birth weight discordance (≥30%) was most prevalent among sets where the mother was either <20 years old or >35 years old. The crude prevalence of severe birth weight discordance was highest among preterm births, with the lowest prevalence being seen in gestational ages of ≥37 weeks. Crude prevalence of severe birth weight discordance was markedly higher among sets in which a congenital anomaly was present. The crude prevalence of infant mortality stratified on 5 levels of birth weight discordance showed a progressive increase in mortality with increasing birth weight discordance. Among severely weight

discordant twins, the crude mortality rate was 9.4%, compared with 2.5% in the lowest discordance category.

Table 2 shows the crude infant mortality rates (per 100 live births) by the exposure variables and covariates. The infant mortality rate was highest in the most birth weight discordant group. Across all levels of maternal hypertension, the infant mortality rate was highest amongst the sets where maternal chronic hypertension was present, but lower for sets where pregnancy-induced hypertension is present. A possible explanation for this inconsistency is that birth certificate is could be inaccurate when differentiating between preexisting hypertension and hypertension that is purely pregnancy-induced This possibility is supported by studies examining the reliability of birth certificate data (34, 44). Among the 3 included racial categories, black mothers had the highest crude infant mortality rate. The crude infant mortality rate was also markedly increased among the following groups: young maternal age (<20 years), preterm births, and births where a congenital anomaly was present. Table 3 shows the infant mortality rates by birth weight discordance stratified by maternal hypertension. The infant mortality rate increased with increasing birth weight discordance, however the highest infant mortality rates were seen amongst non-hypertensive mothers and those with unknown hypertensive status. Table 3 also allows for the calculation of rate ratios (RRs) between hypertensive and non-hypertensive mothers for each category of birth weight discordance. The RR in the most severely discordant category was 1.25, compared with 1.91 in the least discordant category, suggesting possible effect measure modification of birth weight discordance and mortality by maternal hypertension.

Multivariate logistic regression models were used to assess the association between birth weight discordance and infant mortality (Table 4 and Table 5). The unadjusted odds showed a progressive increase in the odds ratio (OR) as the level of birth weight discordance increases (Table 4). Adjusting for

demographic factors (Model 2: maternal age, maternal race, and maternal education) strengthened the association between birth weight discordant and mortality. In Model 3, adjusting for maternal and infant risk factors resulted in an attenuation of the OR for the highest level of birth weight discordancy (≥30%) and a slight decrease in the OR for all other levels of birth weight discordance. Table 5 displays the results after an interaction term was included in the model to assess the interaction between birth weight discordancy and maternal hypertension. When the interaction term was included and demographic factors were added to the model, the ORs increased slightly for all levels of birth weight discordance among sets where maternal hypertension was present or information on maternal hypertension was missing. The observations in which information on maternal hypertension was classified as missing showed the most observable difference between the levels of birth weight discordance.

Table 5 shows the results of multivariate analysis for the association between birth weight discordance and infant mortality adjusting for the interaction of maternal hypertension and birth weight discordance. Selected modeling output is reported in the table to demonstrate the significant effect modification of discordance by presence of maternal hypertension. Respective to the ORs found in table 4, where the interaction between maternal hypertension and birth weight discordance is not included, the results showed an increase in the value of the OR across every level of birth weight discordance in sets where maternal hypertension is present. A p-value for the interaction term is included for each model presented in Table 5 to demonstrate that the interaction term was significant in the early models and ceased to be significant in the final model. After adjusting for maternal and infant risk factors, the ORs across all levels of birth discordance and maternal hypertension were attenuated. Among the observations in which information about maternal hypertension is missing, the disparities between levels of birth weight discordance are the most notable. Adjusting for maternal demographic factors does not notably affect the ORs respective to the unadjusted model. When adjusted for

maternal and infant risk factors along with medical risk factors, the ORs are decreased across all levels of birth weight discordance. Overall, the association between birth weight discordance appears to increase with increasing birth weight discordance, however the effect is notably attenuated when adjusted for the following maternal and infant risk factors: gestational age at delivery, maternal parity, presence of placental abruption, and presence of a congenital anomaly.

Because the observations where information on maternal hypertension was missing appeared to influence the ORs between birth weight discordance and infant mortality, the same logistic regression models were run omitting the observations where maternal hypertension was missing. Compared with the results in which missing values were included, the ORs were decreased across all levels of birth weight discordance when the missing values of maternal hypertension were excluded.

Discussion

This study was intended to assess whether the presence of maternal hypertension affects the association between birth weight discordance and infant mortality among twin pregnancies. The results suggest that intra-pair birth weight discordance is strongly associated with subsequent infant mortality, after adjusting for maternal and infant risk factors such as maternal demographics, maternal medical complications, parity, gestational age at delivery, and presence of a congenital anomaly. The presence of maternal hypertension also appears to be associated with risk of infant mortality, although in observations where information regarding maternal hypertension is missing the risk appears to be greater than when hypertension was present (crude infant mortality rates of 3.56 and 3.14, respectively). After the addition of an interaction term to assess for interaction between maternal hypertension and birth weight discordance, the initial results suggested that the association between birth weight discordance and infant mortality was amplified in the presence of maternal hypertension,

In interaction models, among hypertensive mothers the OR for the most severely birth weight discordant group compared to the least discordant group was 6.02 (95% CI 4.90-7.41); in contrast in models without the interaction the adjusted association of the most discordant compared to the least discordant controlling for hypertension was 3.98 (95% CI 3.75-4.24). After adjusting for maternal demographic factors the results remained similar, however the addition of maternal and infant medical risk factors (placental abruption, parity, gestational age, and presence of a congenital anomaly) resulted in an attenuation of the ORs across all levels of birth weight discordance and all categories of maternal hypertension. The addition of medical risk factors also increased the p-value of the interaction term to p=0.699, suggesting no significant interaction between birth weight discordance and maternal hypertension on subsequent infant mortality when controlling for other important risk factors.

Twin sets where information on maternal hypertension was missing appeared to have the most observable differences in ORs across all levels of birth weight discordance, suggesting that these observations could significantly affect the overall associations found between maternal hypertension, birth weight discordance, and infant mortality. A potential explanation for this result could lie in the importance of adequacy of birth certificate data. Studies examining the importance of birth certificate completeness have found that incomplete birth certificates are a marker for high-risk mothers and vulnerable infants (34-36). This explanation is logical because an incomplete birth certificate could indicate a general lack of medical care or ability to accurately recount past medical history. Gould et al (2002) reported that incomplete birth certificates were "most common in the case of women at high risk for poor perinatal outcomes and infants dying within the first day." Although the inclusion of observations with missing information on maternal hypertension caused less clear results in this study, it is important to consider this high-risk group to accurately assess the risk of infant mortality.

It is important to consider the limitations of this study when interpreting the results. The initial exclusions that were necessary to perform an analysis could have caused an exclusion of many high-risk twin pairs with incomplete birth certificates. This study considered the twin pair as the unit of analysis instead of the individual member of the set, so information about individual risk is lost. Because the study used vital statistics data, many potential risk factors were not available for analysis. Information about chorionicity and zygosity are not available, and studies have determined these to be important factors affecting fetal development and neonatal outcome in twin pairs (37). Smoking during pregnancy is a well-documented risk factor for poor infant outcomes, low birth weight, and exacerbation of maternal hypertensive disorders (38-40). However, the information regarding smoking available in this data did not appear to be accurate or sufficient enough to be included in the analysis, likely due to underreporting of smoking in basic birth certificate data (40). The advantages of the data used include having a large sample size, a large sample of infant deaths, and the large number of maternal and infant variables available for analysis.

Chapter 3

Public Health Implications

Infant mortality remains a very important public health concern and indicator of the overall health of a society. While the United States is at the forefront of many medical advances and public health initiatives, the infant mortality rate still reflects a need to improve the screening and treatment of pregnant women, especially in the case of multifetal pregnancies (1). A major hindrance to advances in this area is a lack of understanding of fetal development and the causes of the most important determinant of neonatal outcomes, which is preterm birth. A multitude of maternal factors seem to contribute to preterm birth, low birth weight, and adverse neonatal outcomes, so it is imperative that ample research is dedicated to parsing through the many possible risk factors that are contributing to the high infant mortality rate.

Another factor to consider is the implication of the increasing use of assisted reproductive technology (ART). Reynolds et al (2003) examined trends in the use of ART and its' effect on multiple pregnancies, and suggest that the use of ART is becoming an increasingly important cause of multiple pregnancy. Because the use of the technologies is on the rise, twins could become an increasingly common, so it is imperative to continue to explore the unique risks faced by these infants and their mothers.

This study was designed to contribute to the ongoing research into causes of infant mortality. Because multifetal pregnancies have a significantly increased risk of adverse neonatal outcomes (2-4), the study was unique to twins and considered the specific risks involved that multifetal pregnancy poses on maternal health and ability to maintain a safe pregnancy. Birth weight discordant twins have an even great risk of poor outcomes. Hollier et al (1999) found that severely weight discordant twins were more

like to have adverse perinatal outcomes, even after controlling for gestational age and weight of each individual twin (39). While infant mortality is a clear and easily measured poor pregnancy outcome, it is important to consider other negative consequences of birth weight discordance. Babson et al (1973) carried out a study to test the long-term outcomes of birth weight discordant twins, and found that members of weight discordant sets showed significant differences in height, weight, head circumference, and significant differences in intelligence based on standardized intelligence measures compared with members of non-discordant sets. Os et al (2001) observed a link between weight discordant twins and subsequent problem behavior in children, which often persists into adulthood.

Because maternal hypertension is often exacerbated by multiple pregnancy, and maternal hypertension further complicates fetal growth and development, it seemed pertinent to examine how the presence of maternal hypertension. The results of this study reinforce the need for further inquiry into risk factors for infant mortality in twin pregnancies. In the literature review, it was apparent that most studies of twins still analyze the individual twins rather than the pair as one singular unit of analysis. The availability of the matched multiple birth file offers future researchers the opportunity to analyze the pair as a whole, which could potentially reveal new information about twins and the risks involved in twin pregnancies.

References

1. The World Bank. Mortality rate, infant (per 1,000 live births). Data Table. Retrieved at http://data.worldbank.org/indicator/SP.DYN.IMRT.IN. Accessed June 10th, 2011.

2. MacDorman MF, Mathews TJ. Recent Trends in Infant Mortality in the United States. NCHS data brief, no 9. Hyattsville, MD: National Center for Health Statistics. 2008.

3. Mathews TJ, MacDorman MF. Infant mortality statistics from the 2006 period linked birth/infant death data set. Hyattsville, MD: US Department of Health and Human Services, CDC, National Center for Health Statistics; 2010. National Vital Statistics Reports Vol. 58, no. 17.

4. Hutcheon JA, Lisonkova S, Joseph KS. Epidemiology of pre-eclampsia and the other hypertensive disorders of pregnancy, Best Practice & Research Clinical Obstetrics and Gynaecology (2011).

5. Ray JG, Burrows RF, Burrows EA, Vermeulen MJ. MOS HIP: McMaster outcome study of hypertension in pregnancy. Early Human Development 2001;64:129–43.

6. Ferrazzani S, Luciano R, Garofolo S, D'Andrea V, De Carolis S, Pia De Carolis M, Paolucci V, Romagnoli C, Caruso A. Neonatal outcome in hypertensive disorders of pregnancy. Early Human Development 2011. 87 (6). 445-449.

7. Magee, L., E. Abalos E, von Dadelszen P, Sibai B, Walkinshaw SA (2009). Control of hypertension in pregnancy. Current Hypertension Reports 11(6): 429-436.

8. Goldberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and Causes of Preterm Birth. Lancet 2008, 371: 75-84.

9. Lain KY, Roberts JM. Contemporary concepts of the pathogenesis and management of preeclamsia. Journal of the American Medical Association 2002, 287:3183-3186.

10. Sibai BM, Hauth J, Caritis S, et al. Hypertensive disorders in twin versus singleton gestations. American Journal of Obstetrics and Gynecology 2000, 182(4); 938-942.

11. Blnodel B, Kogan M, Alexander GR et al. The impact of the increasing number of multiple births on the rates of preterm birth and low birthweight: An international study. American Journal of Public Health 2002, 92; 1323-1330.

12. Nawab US, Greenspan JS, Kirkby S et al. Differences in short-term neonatal outcomes between discordant twins. Advances in Neonatal Care 2008, 8(6):334-342.

13. Bagchi S, Salihu HM (2006). Birth weight discordance in multiple gestations: occurrence and outcomes. Journal of Obstetrics and Gynaecology, 26(4):291-6.

14. Blickstein I, Kalish RB. Birthweight discordance in multiple pregnancy. Twin Research, 2003; 6(6):526-31.

15. Tan H, Wen SW, Fung Kee Fung K et al. The distribution of intra-twin birth weight discordance and its association with total twin birth weight, gestational age, and neonatal mortality. European Journal of Obstetrics, Gynecology, and Reproductive Biology. 121(1):27-33.

16. Kalish RB, Branum A, Sharma G et al. Gestational age-specific distribution of twin birth weight discordance. Journal of Perinatal Medicine 2005, 33(2):117-20.

17. Demissie K, Ananth CV, Martin J et al. Fetal and neonatal mortality among twin gestations in the United States: the role of intrapair birth weight discordance. Obstetrics and Gynecology 2002, 100(3):474-480.

18. Blickstein I, Keith LG. Neonatal mortality rates among growth-discordant twins, classified according to the birth weight of the smaller twin. American Journal of Obstetrics and Gynecology 2004, 190(1):170-174.

19. Branum AM, Schoendorf KC. The effect of birth weight discordance on twin neonatal mortality. Obstetrics and Gynecology 2003, 101(3):570-574.

20. Hartley RS, Hitti J, Emanuel I. Size-discordant twin pairs have higher perinatal mortality rates than nondiscordant pairs. American Journal of Obstetrics and Gynecology 2002, 187(5):1173-1178.

21. Amaru RC, Bush MC, Berkowitz RL et al. Is discordant growth in twins an independent risk factor for adverse neonatal outcome? Obstetrics and Gynecology 2004, 103(1):71-6.

22. Sonntag J, Waltz S, Schollmeyer T et al. Morbidity and mortality of discordant twins up to 34 weeks of gestational age. European Journal of Pediatrics 1996, 155(3):224-9.

23. González-Quintero VH, Luke B, O'sullivan MJ et al. Antenatal factors associated with significant birth weight discordancy in twin gestations. American Journal of Obstetrics and Gynecology 2003, 189(3):813-817.

24. Blickstein I, Shoham-Schwartz Z, Lancet M et al. Characterization of the growth-discordant twin. Obstetrics and Gynecology 1987, 70(1):11-15.

25. Riese ML. Discordant and nondiscordant twins: comparative multimethod risk assessment in the neonatal period. Journal of Developmental and Behavioral Pediatrics 2001, 22(2):102-12.

26. Sannoh S, Demissie K, Balasubramanian B et al. Risk factors for intrapair birth weight discordance in twins. The Journal of Maternal-fetal & Neonatal Medicine 2003, 13(4):230-236.

27. Yalçin HR, Zorlu CG, Lembet A et al. The significance of birth weight difference in discordant twins: a level to standardize? Acta Obstetricia Gynecologica Scandinavica 1998, 77(1):28-31.

28. Patterson RM, Wood RC. What is twin birthweight discordance? American Journal of Perinatolgy 1990, 7;217-219.

29. O'Brien WF, Knuppel RA, Scerbo JC et al. Birth weight in twins: an analysis of discordancy and growth retardation. Obstetrics and Gynecology 1986, 67:483-486.

30. Sherer DM, Divon MY. Fetal growth in multifetal gestation. Clinical Obstetrics and Gynecology 1997, 40(4):764-770.

31. National Center for Health Statistics. 1995-2000 Matched multiple birth data set. NCHS CD-ROM. Hyattsville, Maryland: US Department of Health and Human Services, Centers for Disease Control and Prevention, 2000.

32. Martin, J., Curtin, S., Saulnier, M., & Mousavi, J. (2003). Development of the matched multiple birth file. 1995–1998 matched multiple birth dataset. NCHS CD-ROM series 21, no. 13a. Hyattsville, MD: National Center for Health Statistics.

33. Fiscella K. Does prenatal care improve birth outcomes? A critical review. Obstet Gynecol. 1995;85(3):468–479.

34. DiGiuseppe DL, Aron DC, Ranbom L, Harper DL, Rosenthal GE. Reliability of birth certificate data: a multi-hospital comparison to medical records information. Matern Child Health J. 2002;6(3):169–179.

35. Reichman NE, Hade EM. Validation of birth certificate data: a study of women in New Jersey's HealthStart program. Ann Epidemiol. 2001;11(3):186–193.

36. Gould JB, Chavez G, Marks AR, Liu H. Incomplete birth certificates: a risk marker for infant mortality. Am J Public Health. 2002;92(1):79–81.

37. Rydhstroem H. The relationship of birth weight and birth weight discordance to cerebral palsy or mental retardation later in life for twins weighing less than 2500 grams. Am J Obstet Gynecol 1995 Sep;173(3 Pt 1):680-6.

38. Victoria, A., G. Mora, and F. Arias. Perinatal Outcome, Placental Pathology, and Severity of Discordance in Monochorionic and Dichorionic Twins. Obstetrics & Gynecology, 2001. 97(2): p. 310-315.

39. Hollier LM, McIntire DD, Leveno KJ. Outcome of twin pregnancies according to intrapair birth weight differences. Obstet Gynecol 1999;94:1006–10.

40. Fraser D, Picard R, Picard E, Leiberman JR. Birth weight discordance, intrauterine growth retardation, and perinatal outcomes in twins. Journal of Reproductive Medicine 1994;39:504-508.

41. Babson SG, Phillips DS. Growth and development of twins dissimilar in size at birth. N Engl J Med 1973;289:937– 40.

42. Reynolds MA, Schieve LA, Martin JA, Jeng G, Macaluso M. Trends in multiple births conceived using assisted reproductive technology, United States, 1997–2000. Pediatrics.2003;111 :1159– 1162.

43. Os, J.v., Wichers, M. Danckaerts, M. Van Gestel, S. Derom, C. Vlietinck, R. A prospective twin study of birth weight discordance and child problem behavior. Biological Psychiatry, 2001. 50(8): p. 593-599.

44. Lydon-Rochelle MT, Holt VL, Cardenas V, Nelson JC, Easterling TR, Gardella C, et al. The reporting of pre-existing maternal medical conditions and complications of pregnancy on birth certificates and in hospital discharge data. Am J Obstet Gynecol 2005;193:125–3.

Table 1. Distributions of Maternal and Newborn Characteristics by Birth Weight Discordance

	Birth Weight Discordance				
N=289,953	<15% (n=213,024)	15-19% (n=28,022)	20-24% (n=22,310)	25-29% (n=12,323)	≥30% (n=14,274)
Maternal Race					
White (n=230,126)	73.5%	9.7%	7.7%	4.3%	4.9%
Black (n=48,593)	73.7%	9.6%	7.8%	4.2%	4.8%
Other (n=11,234)	72.7%	9.6%	7.7%	4.5%	5.5%
Maternal Hypertension					
Hypertension-All Categories					
Present (n=28,608)	67.9%	10.7%	9.2%	5.3%	7.0%
Not Present (n=257,632)	74.1%	9.5%	7.5%	4.1%	4.7%
Missing (n=3,713)	73.4%	10.1%	7.0%	4.7%	4.9%
Chronic Hypertension					
Present (n=2,984)	67.5%	10.1%	8.3%	5.3%	8.7%
Not Present (n=283,256)	73.5%	9.7%	7.7%	4.2%	4.9%
Missing (n=3,713)	73.4%	10.1%	7.0%	4.7%	4.9%
Pregnancy-induced Hypertension					
Present (n=23,837)	68.0%	10.7%	9.3%	5.4%	6.6%
Not Present (n=262,403)	74.0%	9.6%	7.6%	4.1%	4.8%
Missing (n=3,713)	73.4%	10.1%	7.0%	4.7%	4.9%
Ecclampsia					
Present (n=2,880)	66.3%	11.3%	9.6%	5.1%	7.8%
Not Present (n=282,524)	73.5%	9.6%	7.7%	4.2%	4.9%
Missing (n=3,713)	73.4%	10.1%	7.0%	4.7%	4.9%
Maternal Age					
<20 (n=19,303)	74.3%	9.1%	7.5%	4.2%	5.0%
20-24 (n=54,310)	75.2%	9.3%	7.2%	3.9%	4.4%
25-29 (n=78,109)	74.0%	9.7%	7.5%	4.2%	4.6%
30-35 (n=96,410)	73.0%	9.8%	7.9%	4.3%	5.1%
>35 (n=41,821)	71.0%	10.0%	8.4%	4.6%	6.0%
Maternal Education					
Less than high school (n=44,327)	74.3%	9.4%	7.5%	4.1%	4.8%
High school (n=86,882)	73.7%	9.6%	7.7%	4.2%	4.8%
Some college (n=66,060)	73.8%	9.6%	7.5%	4.3%	4.8%
College or Greater (n=87,468)	72.7%	9.9%	7.9%	4.4%	5.2%
Unknown (n=5,216)	73.1%	9.6%	7.9%	4.6%	4.9%
Gestational Age at Delivery					
<28 weeks (n=9,582)	71.3%	9.0%	7.3%	4.2%	8.2%
28-32 weeks (n=30,785)	68.0%	8.8%	8.2%	5.0%	10.0%
33-36 weeks (n=121,383)	72.4%	9.8%	8.0%	4.5%	5.3%
≥ 37 weeks (n=128,203)	76.0%	9.8%	7.3%	3.8%	3.0%
Congenital Anomaly					
Present (n=4,937)	61.9%	9.9%	9.9%	6.5%	11.9%
Not Present (n=273,719)	73.8%	9.7%	7.7%	4.2%	4.8%
Missing or not classified (n=11,297)	71.8%	9.9%	7.9%	4.4%	6.0%
Prenatal Care					
No Prenatal Care (n=2,626)	72.8%	10.0%	7.5%	3.4%	6.3%
Prenatal Care in First Trimester (n=241,901)	73.5%	9.7%	7.7%	4.2%	4.9%
Prenatal Care After First Trimester (n=34,111)	74.2%	9.5%	7.4%	4.3%	4.4%
Missing (n=11,315)	71.9%	10.0%	7.7%	4.5%	5.9%
Parity					
Nulliparous (n=107, 789)	73.7%	9.7%	7.6%	4.2%	4.8%
Multiparous (n=151, 891)	73.5%	9.7%	7.7%	4.2%	4.9%
Missing (n=30,273)	73.0%	9.6%	8.1%	4.3%	5.2%
Placental Abruption					
Yes (n=3,696)	73.4%	9.6%	7.8%	4.4%	6.0%
No (n=283,453)	73.5%	9.7%	7.7%	4.3%	4.9%
Missing (n=2804)	72.9%	9.6%	7.4%	4.6%	5.2%
Infant Mortality Rate*	2.5%	2.9%	3.1%	4.3%	9.4%

*Percentage of sets within the birth weight discordance category where at least oneinfant did not survive the first year of life.

Table 2: Distribution of Infant Mortality Rates* (per 100 births)	
Birth Weight Discordance	
<15%	2.54
15-19%	2.87
20-24%	3.14
25-29%	4.3
≥30%	9.41
Maternal Race	
White (n=230,126)	2.7
Black (n=48,593)	4.88
Other (n=11,234)	2.71
Maternal Hypertension	
Hypertension-All Categories	
Present (n=28,608)	1.96
Not Present (n=256,847)	3.14
Missing (n=3,713)	3.56
Chronic Hypertension	
Present (n=2,984)	3.85
Not Present (n=283,256)	3.02
Missing (n=3,713)	3.56
Pregnancy-induced Hypertension	
Present (n=23,837)	1.67
Not Present (n=262,403)	3.15
Missing (n=3,713)	3.56
Ecclampsia	
Present (n=2,880)	2.81
Not Present (n=282,524)	3.03
Missing (n=3,713)	3.56
Maternal Age	
<20 (n=19,303)	5.78
20-24 (n=54,310)	4.04
25-29 (n=78,109)	2.94
30-35 (n=96,410)	2.35
>35 (n=41,821)	2.19
Maternal Education	
Less than high school (n=44,327)	4.25
High school (n=86,882)	3.38
Some college (n=66,060)	2.79
College or Greater (n=87,468)	2.16
Unknown (n=5,216)	4.72
Gestational Age at Delivery	
<28 weeks (n=9,582)	43.34
28-32 weeks (n=30,785)	6.36
33-36 weeks (n=121,383)	1.36
≥ 37 weeks (n=128,203)	0.8
Congenital Anomaly	
Present (n=4,937)	17.16
Not Present (n=273,719)	2.74
Missing or not classified (n=11,297)	3.89
Prenatal Care	
No Prenatal Care (n=2,626)	10.78
Prenatal Care in First Trimester (n=241,901)	2.81
Prenatal Care After First Trimester (n=34,111)	3.35
Missing (n=11,315)	4.99

*Infant mortality refers to sets in which one or more infants did not survive the first year of life

Table 3.

Infant Mortality Rate by Birth Weight Discordance Among Hypertensive Mothers

Discordance	Mortality Rate (per 100 live twin births)
<15%	1.38
15-19%	1.86
20-24%	1.64
25-29%	2.7
≥30%	7.75

Infant Mortality Rate by Birth Weight Discordance Among Non-Hypertensive Mothers

Discordance	Mortality Rate(per 100 live twin births)
<15%	2.64
15-19%	3.01
20-24%	3.34
25-29%	4.51
≥30%	9.66

Infant Mortality Rate by Birth Weight Discordance (Hypertension unknown)

Discordance	Mortality Rate(per 100 live twin births)
<15%	3.46
15-19%	1.78
20-24%	3.68
25-29%	5.21
≥30%	10.5

Table 4. Odds ratio and confidence intervals using logistic regression modeling† for MMB 1995-2000*, with death as the outcome varaible and birth weight discordance as the main exposure variable.

Birth Weight Discordance	Model 1			Model 2			Model 3		
	OR	95% CI		OR	95% CI		OR	95% CI	
<15% (reference)	1.00			1.00			1.00		
15-19%	1.13	1.05	1.22	1.17	1.08	1.26	1.19	1.09	1.30
20-24%	1.24	1.15	1.35	1.27	1.17	1.38	1.23	1.12	1.35
25-29%	1.72	1.57	1.89	1.74	1.58	1.92	1.72	1.55	1.91
≥30%	3.98	3.75	4.24	4.20	3.94	4.48	2.92	2.72	3.15

†Selected modeling output represented in the table

*Matched Multiple Birth Data Set, 1995-2000

Model 1: Unadjusted

Model 2: Adjusted for demographic factors: maternal age, race, and education

Model 3: Adjusted for demographic factors, along with gestational age at delivery, parity, placental abruption,and presence of a congenital anomaly.

Table 5. Odds ratio and confidence intervals using logistic regression modeling† for MMB 1995-2000*, with death as the outcome varaible and birth weight discordance as the main exposure variable, and including the interaction between birth weight discordance and

Birth Weight Discordance	Model 1			Model 2			Model 3		
Where Hypertension is Present	OR	95% CI		OR	95% CI		OR	95% CI	
<15% (reference)	1.00			1.00			1.00		
15-19%	1.36	1.02	1.81	1.45	1.08	1.95	1.24	0.91	1.69
20-24%	1.19	0.86	1.65	1.21	0.87	1.70	1.00	0.71	1.42
25-29%	1.99	1.43	2.78	2.12	1.51	2.99	1.55	1.08	2.23
≥30%	6.02	4.90	7.41	6.41	5.18	7.94	2.86	2.27	3.60
Where Hypertension is not Present									
<15% (reference)	1.00			1.00			1.00		
15-19%	1.14	1.05	1.23	1.17	1.08	1.27	1.19	1.09	1.30
20-24%	1.27	1.17	1.38	1.30	1.19	1.42	1.25	1.14	1.38
25-29%	1.75	1.59	1.92	1.75	1.59	1.94	1.75	1.56	1.95
≥30%	3.94	3.68	4.20	4.12	3.85	4.41	2.94	2.72	3.18
Where Hypertension is Missing									
<15% (reference)	1.00			1.00			1.00		
15-19%	0.48	0.21	1.10	0.57	0.25	1.33	0.39	0.08	1.84
20-24%	1.05	0.52	2.12	1.05	0.50	2.20	1.78	0.44	7.14
25-29%	1.22	0.56	2.67	1.23	0.53	2.87	0.61	0.09	4.00
≥30%	3.66	2.20	6.10	4.55	2.70	7.63	2.42	0.86	6.80
p-value for interaction term**			**0.005**			**0.006**			**0.699**

†Selected modeling output represented in the table

*Matched Multiple Birth Data Set, 1995-2000

**Interaction between maternal hypertension and birth weight discordance

Model 1: Unadjusted model of infant death on birth weight discordance and including the interaction between maternal hypertension and birth weight discorda

Model 2: Adjusted for demographic factors: maternal age, race, and education

Model 3: Adjusted for demographic factors, along with gestational age at delivery, parity, placental abruption,and presence of a congenital anomaly

ınce