THE ROLE OF INJURY IN NERVOUS SYSTEM BIRTH DEFECTS AND BIRTH TRAUMA DURING THE PERINATAL PERIOD

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Abstract

Injury during the perinatal period can have significant health effects on the pregnant woman, the fetus, and the child; therefore, injuries during pregnancy and during labor and delivery in the form of birth trauma were the focus of this dissertation. Through a three papers format, this dissertation addressed three unique research questions that fell under the overarching theme of injury during the perinatal period. The first paper tested the association between injury during pregnancy and nervous system birth defects through a case control study and the utilization of the Texas Birth Defects Registry. The second paper applied an underutilized semi-automated method of sensitivity analysis to determine the effect of misclassification of injury during pregnancy on the association tested in the first paper. The third paper primarily determined the rate of birth trauma overall and specific types of birth trauma in the United States through the utilization of the HCUP Kids Inpatient Database. Through sophisticated statistical analyses it was determined that there is was an association between injury during pregnancy and nervous system birth defects among breech presentation infants, but no association among normal presentation infants or among the entire study population, even when accounting for exposure misclassification. Additionally, it was found that the national rate estimate of birth trauma in the United States for 2003 was 29 per 1,000 in-hospital births. This rate is higher than a majority of previously published studies; therefore, the occurrence and subsequent burden of birth trauma is

higher than previously thought. The public health significance of this dissertation was to determine if injury during pregnancy could account for some of the 65-70% of unknown causes of birth defects, to determine where in the range of 0.2-37 per 1,000 births the rate of birth trauma actually falls, and to further explore an area of maternal and child health and injury research that is inadequately studied. Therefore, the results of this dissertation suggest that strategies to prevent injuries during pregnancy and birth trauma should be explored, implemented, and subsequently evaluated for effectiveness to reduce maternal, fetal, and infant morbidity and mortality.

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1.0 INTRODUCTION

Based upon post-censal estimates of the United States 2000 census, there were approximately 62,033,402 reproductive aged women (aged 15-44)[1] and 4,112,052 births registered through birth certificates in the United States in 2004.[1] Therefore approximately 6.63% of reproductive aged women were pregnant and gave birth in 2004. Pregnant women are an important and distinctive population for public health research because even though pregnant women generally adopt and maintain a healthier lifestyle, reduce harmful exposures, and visit a health care provider throughout pregnancy, unique complications can arise during pregnancy that effect the health of the pregnant woman, fetus, neonate, child, and ultimately the adult.

Injury during pregnancy is an example of a complication that can endanger the life and wellbeing of both the pregnant woman and her fetus. Although injury is often viewed as a chance occurrence, it should be recognized as a preventable maternal and fetal risk factor for adverse pregnancy, fetal, and infant outcomes. Even if a pregnancy has been uneventful up until the point of labor and delivery, unforeseen events may occur during labor and delivery that could result in an injury in the form of birth trauma to the neonate. Although there are many injuries that can occur to the pregnant woman and her fetus/neonate resulting from trauma during pregnancy or during labor and delivery, this area of research is inadequately studied and is therefore the focus of this dissertation.

This dissertation will explore injury's role during the perinatal period through three epidemiological studies. These studies follow the common theme of injury during pregnancy and labor and delivery, but each paper will focus on a specific issue of interest. The first paper will explore the association between injury during pregnancy and nervous system birth defects. The second paper will conduct a misclassification analysis of the data utilized by the first paper to evaluate the effect of misclassification of injury during pregnancy on the association between injury during pregnancy and nervous system birth defects. The third paper will determine a national estimate of the rate of birth trauma, determine the rates of specific types of birth trauma, and report the rates and odds ratios of birth trauma stratified by demographic, hospital, and various clinical variables.

An introduction to injury during pregnancy, birth defects, misclassification analysis, and birth trauma is provided below along with discussion of potential injury mechanisms related to each of the paper's outcome(s) of interest.

1.1 INJURY DURING PREGNANCY

It has been reported that approximately 6-7% of pregnant women experience trauma during pregnancy,[2] 3.9% of all pregnant women sustain an injury during pregnancy that results in a visit to an emergency department,[3] and 0.3-0.4% of pregnant women will have a trauma related hospital admission.[4] Trauma is defined as an injury or wound to living tissue caused by an extrinsic agent; or a disordered psychic or behavioral state resulting from mental or emotional stress or physical injury; or an agent, force, or mechanism that causes injury.[5]

The causes of traumatic injury during pregnancy are thought to parallel the general population's.[6] This is somewhat intuitive since pregnant women in the United States usually continue their everyday activities throughout pregnancy[7] including work, physical activity, driving, household chores, etcetera. Some of the most frequent causes of injury during pregnancy are motor vehicle crashes, being hit by an object or person, falls, burns, poisoning, being cut or pierced, and overexertion. However, motor vehicle crashes are the primary reported cause of injury during pregnancy.[3,8-16]

It is estimated that 3% of all live births (~120,000 children a year) in the United States are exposed in utero to a police-reported motor vehicle crash[17] and between 1300-5000 fetuses are lost each year due to maternal involvement in motor vehicle crashes.[18,19] Beyond being the primary cause of injury during pregnancy, motor vehicle crashes are also reported to be the primary cause of maternal death during pregnancy,[20,21] hospitalized trauma during pregnancy,[18,22,23] and traumatic fetal injury mortality.[16,24] Furthermore, it has been hypothesized that the number of motor vehicle crashes among women has increased over time due to the changing trends and roles of women and pregnant women in our society. Today's women actually drive more frequently, drive more miles, and drive longer into their pregnancy than women even in the recent past.[9] Therefore, the number of women at risk for injury during pregnancy has likely increased, even when only considering driving and motor vehicle crashes as the mechanism of injury.

Injury during pregnancy is an important public health issue because it has been associated with several adverse fetal and pregnancy outcomes including: substantially increased fetal mortality, maternal death, neonatal deaths, placental abruption, emergency cesarean delivery, spontaneous abortion, still birth, preterm birth, low birth weight, congenital anomalies, brain

damage, disrupted fetal development, disabilities, seizures, preterm premature rupture of the membranes, uterine rupture, fetal distress, and newborn respiratory distress syndrome.[9,16,22,25-33] In addition, brain injury,[34-39] long bone fractures,[40] intra-abdominal injuries,[41,42] and intra-thoracic injuries[34,43] have been reported due to motor vehicle crashes during pregnancy. Although each of the above outcomes is significant for various reasons, nervous system birth defects are the outcome of interest for the first paper of this dissertation.

1.2 BIRTH DEFECTS

About 150,000 infants[44] or 3% of all live born infants are born with a birth defect in the United States each year.[45,46] A birth defect is defined as "an abnormality of structure, function or metabolism (body chemistry) present at birth that results in physical or mental disability, or is fatal."[47] For at least the last 20 years, birth defects have been the leading cause of infant mortality in the United States, accounting for more than 20% of all infant deaths (22.3% for 1995-1998 and 19.6% in 1999).[44,48] However, less than 4% of the infants born with a birth defect will die within the first year of life,[44] with more than 70% of these deaths occurring in the neonatal period.[49] The infants that do survive often face life long challenges and disabilities. Specifically, infants born with birth defects have a greater chance of death and illness including mild health problems, social challenges, long term disability, and reduced quality of life, than infants born without birth defects.[44,48,50]

In 65-70% of birth defect cases, the cause of the birth defect is unknown.[48,51] Since 1967 researchers at the Centers for Disease Control and Prevention (CDC) have been involved in birth defects research and have engaged in a broad range of research activities to learn more about the

causes of birth defects and to develop effective prevention strategies.[48] However, injury during pregnancy has yet to be well examined as a potential cause of or contributing factor to birth defects.

1.2.1 Birth defects and injury overlooked

There are several possible reasons that the association between injury during pregnancy and birth defects has been overlooked as an area of public health concern and research. One reason is that injury during pregnancy is seen by some as a chance occurrence and it is generally believed that events that cause injuries, such as motor vehicle crashes, cannot be predicted or prevented. Injury could also be considered an endemic risk because, there have, and likely always will be, women who sustain injuries during pregnancy. Unlike some of the other hallmark exposures that cause a spike in the rates of certain birth defects, injury during pregnancy is more of a widespread and continual risk. In addition, it is difficult to predict when and if a traumatic event will occur. Nevertheless, the negative effects of injury during pregnancy can be lessened or prevented through injury prevention measures.

Another reason that trauma may not have been explored as a cause of or contributor to birth defects is due to the varying amount of lag time between the exposure (injury) and the outcome (birth/birth defect diagnosis). This lag time can make it difficult to determine a clear association and even more difficult to determine causality between injury and birth defects. So much can happen between the time of an injury and the birth/diagnosis of the birth defect that physicians and the parents of the affected child might not think that an injury sustained during pregnancy could have contributed to or caused a birth defect, especially if the injury was minor. However, several studies have shown that no matter the severity, injury is a significant risk

factor for many adverse pregnancy and fetal outcomes.[28,32,39,52-60] Furthermore, when the potential association between injury during pregnancy and birth defects is tested, injuries that occur at different gestational ages and/or have various severities might have different effects, which could dilute a potential association. Even so, on a case level, if a pregnant woman is involved in a traumatic event (such as a fall or motor vehicle crash) and is not injured or sustains only minor injuries, the possibility for the event or resulting injuries to cause or contribute to a birth defect should not be dismissed.

Another reason that injury's role in birth defects might have been overlooked is that not all birth defects are diagnosed at birth or within the first year of life, and diagnoses after the first year of life are often not included in birth defect registries. It might not be until a parent or physician notices that a child is not reaching their developmental or motor skill milestones that a birth defect is diagnosed. Also, most pregnant women who are injured during pregnancy continue to term, receive very little intervention, and are not followed;[8,11,61] therefore, the link between injury and outcome is often lost. Furthermore, few crash and injury data systems accurately track and capture the magnitudes or trends of injury during pregnancy and their outcomes[9] making it difficult to study the effects of injury during pregnancy.

Funding is another reason that injury's role in birth defects might have been previously overlooked. As can be seen in Figure 1, although the estimated new cases of birth defects per year far out numbers several other pediatric adverse health events, birth defects research does not receive the funding that other pediatric health issues do.[62]

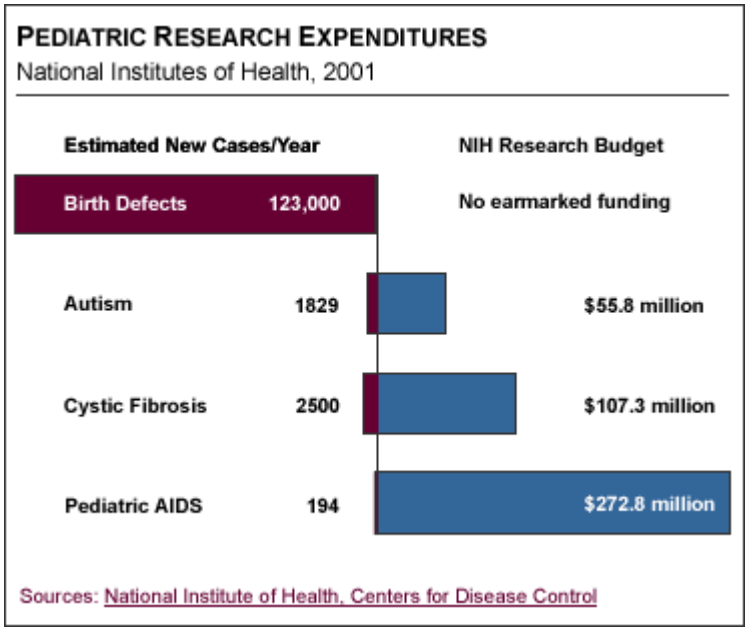

Figure 1. Funding gap[62]

With limited funding, birth defects researchers likely focus their studies on better recognized and established birth defect risk factors than injury during pregnancy. This study will serve as one of the first attempts to systematically determine the association between injury during pregnancy and birth defects.

1.2.2 Nervous system defect focus

As a category, birth defects encompass a myriad of congenital anomalies that could not be adequately researched by a single study. In fact, the definition of birth defects has been used to identify several thousand different birth defects.[47] Therefore, the first paper in this dissertation will focus on nervous system birth defects. Nervous system birth defects were chosen as the primary outcome of interest because they are the most commonly cited birth defects following injury during pregnancy in the literature (based on case studies and series) and there is

"compelling evidence that many neurological disorders which become apparent after birth have their origins during fetal life."[63] Nervous system birth defects also carry the potential to cause life threatening and life long debilitations and are therefore of public health significance. It is important to note that the fetal brain's response to injury, no matter the cause or origin, is different from what is known about the neonatal and infantile periods.[64] Therefore, testing the association between injury during pregnancy and nervous system birth defects will further focus the effects of injury on the fetus and how they might be manifested as nervous system birth defects.

1.2.3 Mechanisms of birth defects from injury

It is generally said organs are more vulnerable to perturbation due to exposure during their development then due to exposure that occurs before or after that organ develops.[65] Due to the continuous development of the nervous system, it is susceptible to exposures and insults beginning very early in pregnancy and lasting throughout and beyond birth. In fact, the central nervous system (CNS) begins to develop just eighteen days post-conception with the induction of the neural plate[66] and within the first month of gestation "specific areas of the CNS begin to form with neruogenesis and migration of cells in the forebrain, midbrain, and hindbrain."[65] Then a "sequence of developmental processes including proliferation, migration, differentiation, synaptogenesis, apoptosis, and myelination" occur.[65] In fact, the central nervous system does not fully mature until myelination is complete (several years after birth).[67] Any alteration in the developmental processes is reported to be able to cause severe nervous system birth defects.[65] Although injury during pregnancy has not been adequately studied as a risk factor for nervous system birth defects, injury during pregnancy could alter or disrupt nervous system

developmental processes through several mechanisms. These include direct injury, reproductive organ injury, iatrogenic effects, hypoxia or ischemia, and stress. These mechanisms may occur independently or in combination of each other.

1.2.3.1 Direct injury

The first mechanism to consider for nervous system birth defects is direct injury. Direct injuries result from mechanical forces that can inflict soft-tissue injuries, bone injuries, and head injury.[68] When a pregnant woman is involved in a traumatic event and/or sustains an injury, her fetus can also sustain direct injuries. Although direct fetal injuries and fractures complicate fewer than 1% of severe blunt abdominal trauma in pregnant women,[6] the most frequently reported category of direct fetal trauma following blunt abdominal trauma is cranial injuries,[6] which could contribute to or cause nervous system birth defects.

As pregnancy progresses, the risk of injury to the pregnant woman and fetus increases primarily due to the increasing size of the developing fetus and uterus.[69] Shah et al. determined that injured pregnant women had a higher reported incidence of serious abdominal injuries, but a lower incidence of chest and serious head injuries than non-pregnant injured women.[11] Since pregnant women are more likely to sustain abdominal trauma when injured, the risk of injury to the fetus is increased through an increased risk of exposure to direct injuries to the maternal abdomen, especially later in pregnancy. It is thought that the fetus is well protected from direct injury during the first 12 weeks of pregnancy, but after that point the uterus reaches the symphysis pubis, protrudes from the abdomen, and continues to grow.[32,69] Some protection may be afforded to the fetus by the encasing amniotic fluid which acts as a shock absorber,[32] but as the fetus grows it becomes a larger target, the amniotic fluid takes up a smaller proportion of the uterus,[32] and the uterine wall continues to get thinner.[69] Therefore, in the later stages of

pregnancy the fetal head is a larger target, is "engaged", it rotates toward the pelvis, the maternal cushion decreases, and it is therefore more vulnerable to injuries overall and injuries related to the maternal pelvis.[6,36,54,69-73] To support this, Klinich et al. found that pregnant women whose fetuses experienced direct injuries were slightly skewed toward later gestational ages with only two occurring in the fifth month, six in the sixth month, eight in the seventh month, eight in the eight month, and ten during the ninth month of pregnancy.[32]

Another possible source of direct injury to the fetus is from direct loading of the pregnant abdomen.[32] An example of direct loading to the pregnant abdomen is when the forces of a seat belt or collision with the steering wheel during a motor vehicle crash cause the fetal head to be mechanically loaded against the bony maternal pelvis or spine.[32] Even with all of the potential forces at the time of a traumatic event or injury, it is believed that fetus' exposure to these forces is diminished due to energy being absorbed by the maternal soft tissues, the uterus, and the amniotic fluid.[6,74] However, this might not be the case as these protective factors change throughout pregnancy (as discussed above).

Direct injury can also cause acute injury, contusions, uterine rupture (especially after the 12th week of gestation when the uterus is no longer fully protected within the pelvis), rupture of the fetal membranes (which can lead to premature birth), fetal skull fractures, intracerebral and/or subdural hemorrhages, and severe maternal hemorrhage.[36,74,75] In addition, retroplacental hemorrhage can then lead to fetomaternal transfusion, fetal anemia, hypovolemia, and hypoxia.[36] Any number of these effects could cause or contribute to a birth defect due to injury during pregnancy.

Direct injury may also cause damage to the fetal skull and/or brain which could contribute to or cause the development of a nervous system birth defect. For instance, although

related to the infant and not directly to the fetus, Goldsmith and Plunkett (2004) reference several studies that support the statement that "the structural properties of an infant skull (ease of deformation and decreased threshold to fracture), and the mechanical properties of the infant brain are also different from those of an older child or adult".[76] It should be noted that injury thresholds vary depending on the size of the brain,[76] and therefore would likely be even lower among the fetus versus infant. If this holds true for the fetus, direct injury may cause damage to the fetal skull and/or brain relatively easily. For instance, Twedale notes that a mechanism of injury that is powerful enough to fracture the maternal pelvis may also cause fetal skull fracture and intracranial hemorrhage.[69] Considering everything discussed above, direct injury to the fetus (due to maternal injury during pregnancy or maternal exposure to the forces of a traumatic event) is a potential mechanism of nervous system birth defects.

1.2.3.2 Reproductive organ injuries

Maternal reproductive organ injuries due to injury during pregnancy are another potential mechanism for birth defects. One of the main organs of interest to the health of the pregnancy and fetus is the placenta (Figure 2). The placenta is a vascular organ that transports oxygen, nutrients, and waste between the pregnant woman and the fetus.[32] Trauma during pregnancy can disrupt this transport through placental abruption.[77] Placental abruption is the premature detachment of the placenta and is the primary cause of fetal death due to injury.[7,10] Over 70% of fetal losses result from placental abruption following blunt abdominal trauma.[6] Ananth et al.[78] reported that placental abruption occurs in about 1 of 100 pregnancies[79] and is associated with up to a third of all perinatal deaths.[80-82] Reputed by trauma centers, placental abruption is also the most common complication of motor vehicle crashes during pregnancy occurring in 1%-5% of minor crashes and 20%-50% of severe crashes.[7,10]

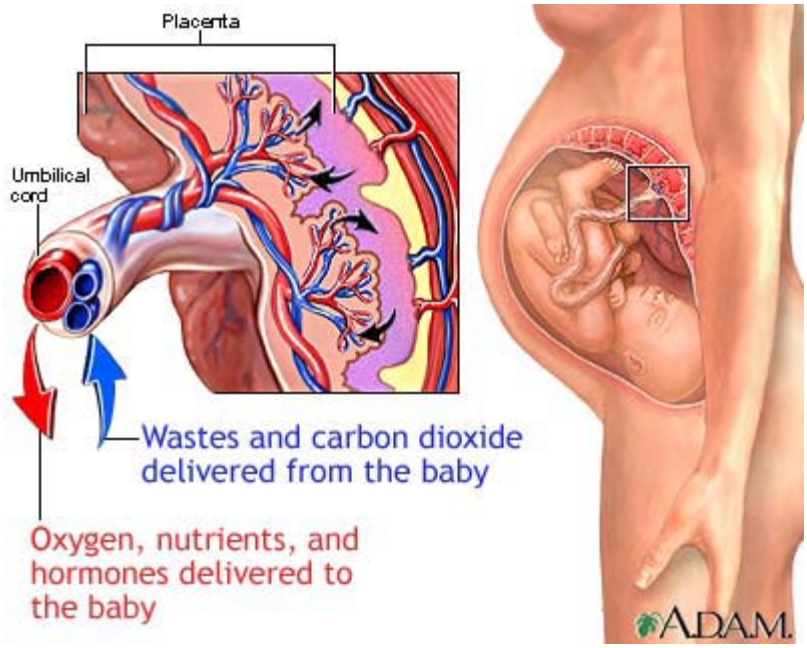

Figure 2. The placenta[83]

Not all of the causes of placental abruption have been identified, but advanced maternal age, multiparity, smoking, cocaine use, hypertensive disorder, intrauterine infection, preterm (prolonged) premature rupture of the membranes, and prior abruption are associated with an increased risk.[78] A review paper by Weintraub et al. (2006) suggests that placental abruption can occur due to the fetus striking the placenta and causing a shear, the fetus pulling the placenta from the umbilical cord, or may be caused by a traumatic deformation that can cause a fluid wave in the uterus, which in turn can create a shearing effect due to tissue differences between the uterus and placenta.[6] Tweddale (2006) also reports that rapid acceleration/deceleration injuries can cause a shearing force strong enough to cause a placental abruption.[69] Abrupt slowing or stopping can also cause injury to the unengaged fetal head.[6,37,74] A traumatic or

injury causing event often involves forces strong enough to cause placental abruption in any of the ways discussed above.

When placental abruption occurs, the uterine wall is not able to properly transport blood and oxygen to the fetus,[77] and depending on the severity of the placental abruption, it could cause a life threatening situation for the fetus.[77] If a placental abruption is concealed or chronic (minor detachment in different areas of the placenta)[77] it is possible that the pregnancy can continue; however, nervous system birth defects and/or developmental disabilities could occur due to a lack of or reduced flow of oxygen or blood (hypoxia and ischemia) to the fetus.

Hagmann et al. (2004) support this association and report that the primary pathogenic mechanisms responsible for intracranial lesions in the fetus following injury during pregnancy is acute placental dysfunction.[54] Acute placental dysfunction can occur due to "maternal shock, placental abruption, or intense uterine vasoconstriction secondary to maternal rise in adrenaline" leading "indirectly to hypoxic-ischemic fetal brain injury."[54,84] Considering the adverse effects of reproductive organ injuries, especially placental abruption, reproductive organ injuries due to injury during pregnancy are an important mechanism to consider for nervous system birth defects.

1.2.3.3 Hypoxia, ischemia, and asphyxia

Hypoxia or ischemia due to placental abruption or other factors such as respiratory and/or cardiac failure in the pregnant woman following injury during pregnancy, are also mechanisms of interest for nervous system birth defects. Hypoxia is defined as a deficiency of oxygen reaching the tissues[5] due to diminished oxygen in the blood supply.[85] Ischemia is decreased oxygenation to a body part[85] due to a deficient blood supply because of the obstruction of the inflow of the arterial blood.[5] Brain injury in the newborn can occur because of hypoxia or

ischemia and often occurs in utero due to placental insufficiency or respiratory or cardiac failure after birth.[85] Both respiratory and cardiac failure can result in asphyxia which affects the blood flow to the brain and other organs.[85] Asphyxia is impaired gas exchange[85] or in other words, "a lack of oxygen or excess of carbon dioxide in the body that is usually caused by interruption of breathing and that causes unconsciousness."[5] The fetus relies on maternal respiratory and cardiac function to obtain adequate amounts of oxygen. Therefore, if a woman is injured during pregnancy and rendered unconscious with inadequate ventilation or worse is killed, the fetus will no longer receive the oxygen it needs and will be in a life threatening situation. Additionally, a non-fatal danger of hypoxia for the fetus or neonate is "selective necrosis of vulnerable areas of the developing brain, which lack both normal circuitry and adequate autoregulation to recover."[85] In fact, 30-40% of neonates and infants with brain injury die and 20-40% of the survivors develop significant neurological impairments.[85-87] Therefore, hypoxia, ischemia, and asphyxia are important mechanisms to consider for nervous system birth defects in fetuses and infants who are in utero at the time of maternal injury or involvement in a traumatic event.

1.2.3.4 Iatrogenic effects

A fourth mechanism for nervous system birth defects following injury during pregnancy is iatrogenic effects. Iatrogenic effects are the outcomes of actions "induced inadvertently by a physician or surgeon or by medical treatment or diagnostic procedures."[88] When a pregnant woman is injured there are two lives to consider and pregnancy complicates the diagnosis and treatment of an injury.[89] Depending on the type and severity of injury, a pregnant woman may be subjected to different treatments, x-rays, or medications in order to treat her injuries and/or save her life. These may in turn affect the health and development of the fetus. Certain tests or treatments can be especially harmful to the fetus if they occur during early pregnancy and

organogenesis. In general, iatrogenic effects are more likely to occur in early pregnancy when a woman does not know[90] or show that she is pregnant and is treated for trauma. Some female trauma patients may have altered mental status or be unable to convey their pregnancy status to health care providers in an emergency room.[90] Therefore, if the pregnancy is not obvious or a patient is not tested for pregnancy, she may be subjected to treatments with the potential to cause iatrogenic effects in the fetus.

For instance, a retrospective four year study of admitted trauma patients reported that 2.9% of women aged 15 to 40 were pregnant at admission of which 11.4% were incidental pregnancies and 7.8% of the incidental pregnancies were newly diagnosed pregnancies.[90] An incidental pregnancy was a pregnancy where the woman did not know she was pregnant or was not able to relay her pregnancy status to the trauma team. The gestational age range of the incidental pregnancies was 3 weeks to 25 weeks gestation.[90] The women with incidental pregnancies were routinely exposed to doses of radiation that exceeded the American College of Obstetricians and Gynecologist recommendation of no more than five rads.[90] The authors reported that the radiation may have been related to the increased risk of developmental or growth abnormalities that was observed by the study.[90]

Considering all that was discussed above, iatrogenic effects due to exposures early in pregnancy when a woman does not know or show she is pregnant or iatrogenic effects that result from treating or attempting to save the life of the pregnant woman in severe injury cases are a potential mechanism for the development of nervous system birth defects following injury during pregnancy.

1.2.3.5 Stress

Nathanielsz et al. point out that humans pass more biological milestones before birth than after; therefore, it is possible that environmental influences, including stress, during fetal life may alter the trajectory of development in a fetus.[91] A pregnant woman involved in or injured by a traumatic event could and likely will endure at least some level of physical, mental, and/or financial stress. However, the literature on how stress related to traumatic events effect pregnancy outcomes is limited.[92] Although psychosocial stress is a different type of stress then psychological stress (which can result after a traumatic event), an association between psychosocial stress and anxiety and shortened pregnancy duration has been shown.[93-96] This association raises the question of whether or not stress related to a traumatic event or injury resulting from a traumatic event may contribute or cause adverse pregnancy outcomes.

The few studies that have been conducted have found stress to be associated with various adverse pregnancy outcomes among various populations of women. For instance, similar to the results of the psychosocial stress studies, a study that examined stress related to a strong earthquake (6.8 magnitude) found that stress, especially in early pregnancy, was associated with a shorter gestation length.[97] The role of stress in pregnancy outcomes has been further explored among pregnant New York women exposed to the terrorist attacks of September 11th. These September 11th studies determined an increased risk of small for gestational age,[98] decrements in birth weight and birth length among term infants,[99] and a shorter gestation and smaller head circumference in infants of women who were in their first trimester on September 11, 2001[99] and were exposed to the destruction of the World Trade Center. Decrements in infant head circumference at birth was also reported among pregnant women with post-traumatic stress symptomatology who were living or working close to the World Trade Center on September 11th

and therefore were considered to be exposed to extreme psychological trauma.[92] Interestingly, among the same women, post-traumatic stress symptomatology and moderate depression were associated with longer gestational durations.[92] A different study by Rich-Edwards et al. also found that women who were pregnant during September 11th had a longer gestational length than women who delivered prior to September 11th.[100] Although it should be noted that Rich-Edwards' study subjects were Boston-area women and the authors had no direct measure of the level of distress experienced by their pregnant population.[100]

Unfortunately stress is difficult to measure, inconsistently characterized, and is rarely assessed. A severe form of stress that has been better studied is Post Traumatic Stress Disorder (PTSD). PTSD is an extreme form of psychological stress/trauma that should be monitored for following traumatic events and disasters. As an example, it has been estimated that nine percent of survivors of serious motor vehicle crashes develop post-traumatic stress symptoms and that many other survivors have PTSD-like reactions.[101] If a pregnant woman developed PTSD following a traumatic event, stress would become a chronic exposure throughout the remainder of her pregnancy and would probably be even more likely than lower levels of stress to cause or contribute to adverse pregnancy or fetal effects.

For instance, preterm delivery is an adverse pregnancy outcome associated with PTSD.[96,102-105] It is important to consider this possible association between PTSD and preterm birth[106] because, preterm delivery increases the risk of developmental, cognitive, and behavioral impairments later in life.[107,108] It is possible that these outcomes are due to alterations or defects of the nervous system. Since stress can result in decrements in infant head circumference at birth[92] it is possible that stress could alter development and cause or contribute to nervous system birth defects. Therefore, stress and in an extreme form PTSD, due to involvement in or injuries

resulting from traumatic events is another mechanism to consider for adverse pregnancy outcomes and nervous system birth defects.

1.2.3.6 Mechanism overview

When considering direct injuries, reproductive organ injuries, hypoxia-ischemia, iatrogenic effects, and stress, injury during pregnancy could and probably is associated with many adverse fetal outcomes including nervous system birth defects. Beyond mechanisms, there have been several case reports and series that have demonstrated injury's role in adverse pregnancy and fetal outcomes. Several of these case reports and series are discussed or highlighted below.

1.2.4 Review of related case reports and series

A majority of the published studies on injury during pregnancy have small sample sizes or are cases series at single institutions.[28] Part of the reason for this is that the data necessary to study injury during pregnancy and its role in maternal and fetal outcomes is simply not available on a national scale. Furthermore, the lack of inclusion of fetal outcomes in injury surveillance systems and vital statistics has resulted in a lack of population based studies.[10] The reality is that injury during pregnancy and its adverse fetal effects, especially related to birth defects, is inadequately studied. Therefore, the literature and current level of knowledge on the role of injury during pregnancy as it relates to birth defects is limited and is based largely on case studies and series. Although cases taken from the literature often focus on more unusual injuries,[32] these cases can be used to generate hypotheses. The previously discussed mechanisms demonstrate how it is biologically plausible for injury during pregnancy to cause or contribute to

the development of nervous system birth defects, but published cases reports and case series further strengthen the possibility of injury's role in nervous system birth defects through actual examples of the effects.

A case report by Bowdler et al. (1987)[37] discusses injuries diagnosed to an infant shortly after birth including cerebral edema and intraventricular and subarachnoid hemorrhage. These injuries were sustained due to a motor vehicle crash that occurred as the pregnant woman was being driven to the hospital while in labor. The pregnant woman was an unbelted passenger when the vehicle she was traveling in was hit broadside on the passenger's side. The woman had to be extricated from beneath the dashboard and was transferred to a medical center after the crash. Her pregnancy had been complicated only by mild preeclampsia and her fetal membranes were intact before the crash, but were ruptured post-crash. The woman had several fractures and crepitus (bone on bone sound often due to a fracture) was heard when the fetal head was palpitated. The fetus was delivered by cesarean section and a 20% placental abruption was present. The infant required no resuscitation and no other external evidence of trauma was found. A skeletal survey showed depressed fractures of the left parietal (upper posterior part of the head) and occipital (posterior part of the skull) bones. A computed tomographic (CT) head scan of the infant revealed "extensive subarachnoid and bilateral intraventricular hemorrhage with generalized brain swelling and diffuse bihemispheric hypodensity suggesting edema." At four months the infant had "motor abnormalities and residual injury to the periventricular white matter."[37] The lack of significant lag time in this case coupled with the evidence of a prior uncomplicated pregnancy, provides strong support for the role of injury during pregnancy in head and brain anomalies that in other instances (or if the exposure occurred earlier in pregnancy) could have resulted in the development of nervous system birth defects.

Another case series of nine case reports by Baethmann et al. (1996)[36] focused on the possible effects of maternal trauma on surviving fetuses. In this case series, trauma occurred in the women between their 23rd and the 37th week of gestation. Seven of the women experienced a motor vehicle crash and two had blunt abdominal trauma. Four of the women experienced severe injuries (cerebral contusion, fractures, or placental abruption) and had emergency cesarean sections. Five of the nine women experienced premature uterine contractions and two had hemorrhages. All of the infants were born between the 30th and 40th week of gestation. Seven of the infants had normal postpartal vital signs, one had to be resuscitated, and one premature infant needed assisted ventilation. The infant's clinical symptoms included "movement disorders (n=3), hydrocephalus (n=2), convulsions (n=1), cerebral palsy (n=1), and normal or no symptoms (n=3). Neuroimaging revealed periventricular leukomalacia (white matter damage) (n=2), localized vascular infarctions (n=2), hemorrhage (n=1), hydrocephalus (n=2), and global brain damage (n=1)." The causative role of trauma was "extremely likely" in one of the cases and "probable but unproved" in the rest.[36] Again the probable association or causation of injury during pregnancy and head and brain anomalies, and therefore nervous system defects, was demonstrated.

A case series by Litmanovitz et al. (2000)[34] reported three women who were involved in separate motor vehicle accidents during the 36th, 26th, and 29th week of gestation. The third case is of interest for the role of injury during pregnancy on nervous system birth defects. Post-crash the third woman sustained multiple facial lacerations and contusions and an hour after hospital admission she had signs of placental abruption. Her infant was delivered through an emergency cesarean section and was in severe respiratory distress. The infant also had "a fracture of the right humerus, consolidation of the right lung, and a corneal opacity, judged to be traumatic in

origin." There were no abnormalities revealed through brain sonography. However, on the seventh day of life the infant had signs of pneumoperitoneum (abnormal state characterized by the presence of gas (as air) in the peritoneal cavity) and an isolated perforation of the terminal ileum was found through laparotomy and it was closed. Over the next three months the infant continued to demonstrate extensive periventricular and subcortical leukomalacia that was attributed to hypoxic brain damage and was determined to be severely microcephalic.[34] This case demonstrates how injury during pregnancy can result in microcephaly, a nervous system birth defect.

Hagmann et al. (2004) presented both a case of fetal intracranial injuries in an infant who was delivered preterm following a maternal motor vehicle crash and a review of the published cases of fetal intracranial hemorrhages after maternal motor vehicle crashes.[54] Hagmann et al.'s case experienced subdural and intracerebral hemorrhages shortly after delivery with little doubt that both lesions were related to the crash.[54] Their review of the literature yielded 22 cases of fetal intracranial hemorrhages following motor vehicle crashes during pregnancy.[54] Of these cases, sixteen were preterm infants of which four were stillborn, six experienced neonatal death, three had abnormal neurologic development, and three had a normal outcome.[54] Six of the 22 cases were term infants of which three were stillborn, one experienced neonatal death, and two had an impaired neurodevelopment.[54] Two of the term infants who experienced a motor vehicle crash only weeks before birth were reported to have posthemorrhagic hydrocephalus at birth.[54] It was determined that the hydrocephalus was likely due to intraventricular hemorrhages in utero because of the crashes.[54] Hagmann et al. noted that subdural hemorrhages and fetal skull fractures have been previously reported as a result of direct traumatic impact [71,109,110] and in Hagmann et al.'s review, six infants had skull fractures associated with subdural hemorrhages

(n=3) and intraventricular hemorrhages (n=3).[54] Once again the evidence of the relationship between injury during pregnancy and head and brain anomalies including nervous system birth defects is presented and plausible.

Work by Leroy-Malherbe et al. (2006) further support the theory that fetal lesions can and sometimes do occur from trauma during pregnancy.[8] They studied eighteen cases of infants/children with a neurological handicap who were exposed in utero to a motor vehicle crash.[8] They found fetal anomalies in six cases between the first and thirtieth day after trauma, five cases of emergency delivery or rapid birth after signs of fetal distress, one infant death soon after birth, and a third of the cases were not followed up.[8] The neurological handicaps that Leroy-Malherbe et al. recorded were congenital microcephaly (n=3), congenital hydrocephalus (n=3), infantile cerebral hemiplegy (n=6), quadriplegy with severe encephalopathy (n=4), diplegy (n=1), clumsiness with cerebellar atrophy (n=1), Moebius syndrome (n=1), mental retardation with autistic features (n=2), learning disability (n=1), and auditory agnosia (n=1).[8] Through their analysis of the brain lesions that related to the timing of trauma, the immediate consequences of the trauma, the pregnancy, and follow up of the child, Leroy-Malherbe et al. proposed four scenarios for brain injury during pregnancy: 1) "Fetal and newborn distress shortly after trauma," 2) "Premature birth shortly after trauma, without other evidence of fetal distress," 3) Ultrasound "observation of fetal brain changes without former signs of fetal distress," and 4) "Neonatal or postnatal revelation of a handicap after uneventful fetal follow-up and birth."[8] Leroy-Malherbe et al.'s findings offer further support of the association, if not a causal role, of injury during pregnancy and nervous system birth defects.

Even in the absence of published case-control and cohort studies, when considering the potential mechanisms and the case reports and series discussed above, it is hard to question that

injury during pregnancy can be a contributing factor or causal for at least some nervous system conditions defined as birth defects. The first study in this dissertation titled "Injury during pregnancy and nervous system birth defects in Texas 1999-2003" will further explore the potential association between injury during pregnancy and nervous system birth defects. This paper begins on page 37.

2.0 EXPOSURE MISCLASSIFICATION ANALYSIS

The Texas Birth Defects Registry (TBDR) was the data source for the first dissertation paper titled "Injury during pregnancy and nervous system birth defects in Texas 1999-2003". This paper tested the association between injury during pregnancy and nervous system birth defects and will be referenced as the TBDR study. Misclassification is a limitation of the TBDR study and may have affected the paper's results. Misclassification usually biases an association toward the null hypothesis;[111] therefore, any amount of misclassification in the TBDR will likely cause an underestimation of the true risk of the association between injury during pregnancy and nervous system birth defects.[112] In order to determine the extent to which exposure misclassification could affect the results of the TBDR paper, specific methods to quantify the effects of exposure misclassification will be employed. There are few methods available that quantify the systematic error for an effect estimate and they are rarely used.[113] The methods that do exist include a semi-automated method of sensitivity analysis to assess systematic errors attributable to misclassification.[113] These methods will be applied to the TBDR data to determine if and how exposure misclassification effected the association between injury during pregnancy (exposure) and nervous system birth defects (outcome) in the TBDR study.

2.1.1 Potential sources of exposure misclassification in the Texas Birth Defects Registry

There are several possible sources of misclassification for injury during pregnancy in the Texas Birth Defects Registry. One scenario that could have resulted in misclassification is if a woman did not seek medical attention for an injury she sustained during pregnancy. In this situation, if a pregnant woman was involved in a traumatic event, such as a fall, motor vehicle crash or abuse, but did not go to an emergency room or hospital, the event and any injuries that may have resulted would not be recorded in a medical record. If the event and any resulting injuries are not recorded in a medical record then they are not reviewed by the TBDR staff and consequently not included in the TBDR as an injury during pregnancy.

Another situation that could have led to exposure misclassification in the TBDR is if a pregnant woman sought medical care at a hospital other than the one she gave birth in. Since the TBDR uses the infant records to identify possible/probable cases of birth defects and then looks back at the related medical records, if a woman was seen in a hospital other than the hospital she gave birth in for injuries or follow up after a traumatic event, the exposure would be missed and therefore misclassified.

Yet another instance where exposure misclassification could have occurred is if a pregnant woman sought treatment for an injury during pregnancy in the same hospital that she gave birth in, but the hospital creates new medical records for each hospitalization. In this scenario the exposure could have been misclassified due to a disconnect between the medical records. A final source of exposure misclassification in the Texas Birth Defects Registry is if a pregnant woman was cared for by an obstetrician in his/her office or at an urgent care center rather than in an emergency department or hospital following an injury or traumatic event. Since

individual offices are not part of the TBDR's active surveillance the registry staff would not have access to the information to properly classify a woman's exposure.

Even with the several sources of misclassification described above it is important to consider that a woman who was injured during pregnancy could report an injury or involvement in a traumatic event to her health care provider at the time of birth. This is a realistic possibility for the study population because it consists of women who had an infant with at least one birth defect. These women would likely be thinking of anything out of the ordinary that occurred during their pregnancy and/or what they might have been exposed to that could have caused an anomaly in their child. However, it would be up to the woman to report an injury during pregnancy and the health care provider to document the injury in the medical record in order for the information to be reviewed and recorded by the TBDR staff.

Unfortunately, the amount of misclassification in the TBDR is unknown and how frequently each of the above situations actually occurs cannot be adequately determined. However, it should be noted that the exposure misclassification is probably less of an issue in the TBDR than in hospitalization studies. A majority of hospitalization studies define exposure based on whether or not a woman was hospitalized for either her injuries or exposure to a traumatic event. This ignores women who were involved in a minor traumatic event or those who are less severely injured or not injured at all. The less severely or non-injured women are often classified as not exposed (due to not being hospitalized) in hospitalization studies, which is clearly misclassification. Regardless of the source of misclassification, it is recognized that misclassification of injury during pregnancy is a limitation of the TBDR study and in order to provide a more accurate estimate of the association between injury during pregnancy and nervous system defects, the second study in this dissertation will further explore the exposure

misclassification of injury during pregnancy in the TBDR study and how exposure misclassification might have altered the study's findings. The misclassification paper titled "Exposure misclassification analysis of injury during pregnancy in the Texas Birth Defects Registry" begins on page 60.

3.0 BIRTH TRAUMA

Birth trauma is defined as injuries sustained during the process of labor and delivery.[114-116] Although improvements in obstetrical care and prenatal diagnosis have caused a decrease in the incidence of birth trauma, it is still a significant cause of neonatal morbidity and mortality.[117] Awari et al.[118] point out that birth trauma is known to result in head injury,[119] brachial plexus,[120-122] clavicle fracture,[123-125] femoral fractures,[126] and spinal cord injuries.[127] Even though some birth injuries are avoidable, no infant is immune to birth injury[68] and most occur even in the presence of skilled obstetrical and neonatal care.[116] Birth trauma has been estimated to occur in 0.2-37 per 1,000 births and is associated with an increase risk of infant morbidity and mortality.[116,127,128]

Some of the risk factors for birth injury include macrosomia, perinatal depression, shoulder dystocia, abnormal presentation of the fetus, the use of instruments during delivery,[116] and second stage labor that is greater than sixty minutes.[129] Furthermore, the risk and type of birth trauma can vary depending on the infant size (i.e., if an infant is large, small, or appropriate for its gestational age).[68] Birth trauma may result from obstetrical manipulation of the fetus to allow for delivery or during a difficult delivery.[116,130]

3.1.1 Birth trauma understudied/overlooked

Birth trauma and its risk factors have not been adequately studied on a national scale. Wen et al. point out that large population studies are needed to examine other important and rare outcomes such as intracranial hemorrhage since the small sample sizes of randomized trials have hampered the ability of the studies to have conclusive results.[131-135] In order to address these gaps in the literature, this study will use a large population based database to determine a national estimate of the rate of birth trauma, determine the rates of specific types of birth trauma, and report the rates and odds ratios of birth trauma stratified by demographic, hospital, and various clinical variables.

3.1.2 Mechanisms of birth trauma

Based on their etiology, the mechanisms for birth trauma can be divided into insults from either mechanical forces during the process of labor and delivery or insults due to hypoxia and ischemia.[117]

3.1.2.1 Mechanical forces during labor and delivery

Mechanical forces during the process of labor and delivery occur naturally as the infant passes through the birth canal; however, the primary cause of birth trauma due to mechanical forces is because of obstetrical manipulation of the fetus during birth. Obstetrical manipulation, specifically operative vaginal delivery, was estimated in 1996 to occur in 5-25% of nulliparous pregnant women.[136] Obstetrical manipulation is used during complicated vaginal deliveries and

can include the use of vacuum extraction, obstetric forceps, cesarean delivery, or any combination of these delivery methods.

Instrumental vaginal delivery (use of a vacuum extractor or obstetric forceps) is integral to obstetrics worldwide.[137] It allows for assisted delivery when "cord prolapse, a non-reassuring fetal heart rate, prolonged second stage labor, intrapartum hemorrhage, exhaustion, heart disease, pulmonary injury, and certain neurological conditions in the mother" arise during labor and delivery.[132,138,139] Nevertheless, instrumental vaginal delivery has been reported to cause rare but serious injuries to the infant.[137] Furthermore, the risk of birth trauma and/or delayed delivery is elevated in infants who are exposed to more than one instrument during a delivery or a failed instrumentation prior to cesarean section.[115,137,138,140] However, a single attempt at instrument delivery with excessive force may be as harmful as multiple instrument use.[137]

The choice of which instrument is the better or safer depends on many factors, not all of which are scientifically evidence based. Forceps were previously preferred to vacuum extraction,[141] but the vacuum extractor has more recently become the instrument of choice in the United States and United Kingdom.[142] This increase in popularity is attributed to the new design of the vacuum cups, which are supposed to reduce the risk of injury to the infant.[133] Despite the vacuum extractor's rising popularity, in 1998 the Food and Drug Administration (FDA) issued a public health advisory to physicians covering the potential risks of using vacuum extraction.[143] This advisory was issued due to an observed increase in the rate of serious neonatal events associated with vacuum extraction in the four years prior to the advisory issue versus the previous 11 years.[143] In addition, randomized trials have shown that the risk of cephalhematoma and retinal hemorrhage is higher in infants delivered with vacuum extraction than forceps.[133,144] On the other hand, vacuum extraction is reported to causes less maternal trauma than forceps[144]

and the risk for infant mortality is reported to be similar between infants delivery by forceps or vacuum extraction.[138] In the end, the physician's choice between using vacuum extraction or obstetric forceps usually is based on tradition and training.[145]

Regardless of whether infants are born with or without obstetrical manipulation they are exposed to a degree of mechanical forces during labor and delivery. As will be discussed below, there are many examples of direct trauma resulting from the events that occur during labor and delivery and it is important to recognize that mechanical forces are a potential and likely mechanism for birth trauma, especially those applied by instruments during delivery.

3.1.2.2 Hypoxia, ischemia, and asphyxia

Another mechanism of interest for birth trauma is hypoxia and ischemia. Regardless of whether hypoxia/ischemia is primary or secondary to another condition, it is "one of the most common forms of injury during the perinatal period."[146] When fetal hypoxia and asphyxia occur the fetal circulatory response is to centralize blood flow in favor of the brain, heart, and adrenals.[147,148] Once circulatory centralization can no longer be maintained circulatory decentralization occurs and severe brain damage, if not fetal death, will results if immediate resuscitation does not occur.[147]

Several events can cause asphyxia throughout pregnancy and during labor. These events can be categorized as chronic, acute catastrophic, and repeated hypoxia.[149,150] "Decreased fetal hemoglobin (e.g., fetomaternal or fetofetal hemorrhage), infection and maternal causes such as systemic hypoxia and reduced uteroplacental blood flow due to hypotension" can cause chronic hypoxia.[149] Maternal trauma is a potential source of maternal systemic hypoxia with resulting fetal hypoxia. Acute catastrophic hypoxia can be caused by "immediate catastrophic events include cord prolapse" and at times cord entanglements, "true knots in the cord, vasa previa,

placental abruption, uterine rupture," and entrapment (such as shoulder dystocia).[149] When asphyxia due to placental abruption is coupled with fetal blood loss due to fetal volume contraction, the impacts of asphyxia can be enhanced.[149] Additionally, during labor "the fetus may be exposed to shorter but frequent episodes" of asphyxia that can "lead to a progressive decompensation over time."[149,150] However, "impaired gas exchange and mild asphyxia" are considered "a normal part of labor and the normal fetus has an enormous ability to respond to the consequent intervals of hypoxia/asphyxia while maintaining the function of essential organs such as the brain and the heart."[149]

Additionally, if an infant begins to knowingly suffer from hypoxia and ischemia during labor and delivery the health care provider knows that they have minutes to deliver and potentially resuscitate the neonate to prevent brain damage. This creates a situation in which a health care provider might be more likely to use vacuum extraction, forceps delivery, and/or cesarean section to quickly deliver the fetus. As previously discussed, instrument delivery puts the infant at an increased risk of birth trauma. Therefore, regardless of whether hypoxia and ischemia causes the birth trauma directly or influences a health care provider to deliver a fetus quickly with the aid of obstetric instruments, which can independently cause birth trauma, hypoxia and/or ischemia are a mechanism of birth trauma.

3.1.2.3 Unknown mechanisms

It is important to note that birth trauma can also occur during uncomplicated deliveries[136,151,152] and in the absence of risk factors.[116] Many of these cases can be explained simply through the mechanical forces that occur during labor and delivery as the infant passes through the birth canal. These infants may not have risk factors, but are still subjected to an amount of mechanical forces that could cause birth trauma. On the other hand, it is possible that

in utero exposures, including injury during pregnancy, may contribute to the number of infants born with birth trauma without any established risk factors. For instance, birth trauma in the form of intracranial hemorrhage has been reported to occur prior to labor[53] and therefore is not by definition a birth trauma. However, if a case of intracranial hemorrhage or other injury to the fetus is not diagnosed until after an infant is born, the injury may be misclassified as a birth trauma. This may explain how some infants who had an otherwise uncomplicated delivery are diagnosed with birth trauma.

3.1.3 Epidemiological studies

There are many epidemiological studies related to birth trauma; however, few are population based, a majority focus on specific topics and birth traumas of interest, some are dated, and some are not conducted in the United States. One of these studies was by Levine et al. (1984)[129] who retrospectively reviewed 13,870 singleton full-term consecutive live births from a major teaching hospital for the years 1974-1977 and 1979-1981. The outcomes of interest and their incidences were brachial plexus (2.6 per 1000), fractured clavicle (2.0 per 1000), and facial nerve injury (7.5 per 1000).[129] Although Levine et al. provide incidence rates of three types of birth trauma, the rates were not inclusive of other types of trauma, the incidence rates were for one hospital, and the study is fairly dated.

Hughes et al. (1999)[119] conducted a case-control retrospective chart review of a cohort of patients with birth associated head and neck trauma. The most common finding in their cohort was cephalhematoma (56.6%) and they reported a prevalence of birth-associated head and neck injuries of 9.5 per 1000 live births.[119] Although this study was relatively recent and gave a prevalence rate of birth trauma, some descriptive epidemiology, and reported associated risk

factors, it did not provide a national estimate of birth trauma and its findings were focused only on birth trauma to the head and neck.

Awari et al. (2003)[118] is one of the most recent and few studies that considers birth trauma as an overall category. However, this study was conducted at a single hospital in Saudi Arabia. Therefore the generalizability of this study to the United States is limited, but the study findings are still of interest. Awari et al. performed a retrospective analysis of 31,028 consecutive deliveries from January 1986-December 1996 and determined that birth injuries had an incidence of 6.7 per 1,000 live births.[118]

Hankins et al. (2006)[153] is another recent study that explored the incidence of birth trauma among other outcomes. They reviewed the last 10 years of literature using Ovid Medline with several different search terms. The search term used by Hankins et al. relatd to birth trauma was "fetal trauma". From the articles that were identified using this search criteria it was determined that the incidence of significant birth trauma varies from 0.2 to 1-2 per 1,000 births and that a majority of fetal trauma is associated with difficulties during delivery.[153]

The only population based study in the literature was by Tomashek et al. (2006).[154] Tomashek et al. used the National Hospital Discharge Survey to compare "overall and cause-specific morbidity rates attributable to conditions originating in the perinatal period among newborns discharged from US hospitals" in 1989-1990 and 1999-2000.[154] The study population included 55,210 newborns in 1989-90 and 68,678 newborns in 1999-2000.[154] Tomashek et al. calculated morbidity rates using weighted estimates of morbidity diagnoses. They determined that the rates of birth trauma in all newborns was 37.0 per 1,000 newborns in 1989-1990 and 29.2 per 1,000 newborns in 1999-2000 (this was a significant decrease in the rate with a p-value <0.05).[154] These rates are much higher than many of the rates reported by other studies. This

dissertation's birth trauma paper will serve as a comparison to the published studies, but will utilized a different, larger, and more recent data source.

The published studies presented above further illustrate that a national estimate of birth trauma is an important but relatively lacking piece of knowledge in the literature. Much of the other birth trauma literature focuses on birth trauma related to instrument deliveries instead of birth trauma as a whole. Considering that instrument delivery is a primary mechanism for birth trauma, some of the most recent papers on this topic are presented below.

Demissie et al. (2004) conducted a population based study comparing the risk of adverse neonatal and infant outcomes between vacuum and forceps assisted deliveries.[138] Their study population included singleton live births in the United States for the years 1995-1998 and in New Jersey for the years 1989-1993.[138] Demissie et al. determined that vacuum and forceps deliveries had similar neonatal mortalities; however, vacuum extraction was associated with a lower risk of birth injuries (odds ratio=0.69, 95% confidence interval 0.66-0.72) in United States births.[138] In conclusion, it was determined that vacuum extraction was a safe alternative to forceps delivery.[138]

Another study that looked at obstetrical manipulation was a United Kingdom study by O'Mahony et al.(2005) that "reviewed delivery details of intrapartum-related fetal and neonatal deaths with singleton cephalic presentation and birth weight of >2500g in which traumatic cranial or cervical spine injury or substantial difficulty at delivery of the head was a dominant feature."[137] O'Mahony et al. concluded that physical difficulty during deliver and the use of obstetric instruments was almost always associated with cranial traumatic injury.[137] The authors also mentioned that some cases of birth trauma still occurred even without evidence of unreasonable force; however, it was thought that poorly judged and several attempts at vaginal

delivery, when delivery was not progressing or the fetus was showing signs of compromise, were the primary factors involved in birth injuries no matter which instruments were used.[137]

After reviewing the birth trauma literature, the lack of an established population based national rate estimate of birth trauma was identified. Many of the studies in the literature focus on the differences in outcomes between modes of delivery, but only Tomashek et al.'s paper provides a relatively current United States population based national rate estimate of birth trauma. Even so, this dissertation's birth trauma paper will use a more recent, larger, more representative, population based sample than Tomashek et al. It is important to conduct this study because the national burden of birth trauma has yet to be established. In addition, this study will strive to identify new and support previously identified risk factors for birth trauma. The birth trauma paper titled "A national rate estimate and descriptive epidemiology of birth trauma for the United States in 2003" begins on page 78.

4.0 PAPER ONE: INJURY DURING PREGNANCY AND NERVOUS SYSTEM BIRTH DEFECTS IN TEXAS 1999-2003

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Manuscript in Preparation

4.1 ABSTRACT

Background: Injury during pregnancy has been associated with several adverse fetal and pregnancy outcomes; however, the relationship between injury during pregnancy and birth defects has not been adequately studied. Methods: Through a case-control study, the association between injury during pregnancy and nervous system birth defects, diagnosed within the first year of life, was tested utilizing the Texas Birth Defects Registry for the years 1999-2003. Logistic regression was used to determine the unadjusted and adjusted odds ratios (OR) and 95% confidence intervals (95% CI) for the association. Results: Out of the 59,750 infants eligible for this study, 4,144 were diagnosed with a nervous system birth defect, 315 of the infants' mothers

were injured during pregnancy, and 25 of the women who were injured during pregnancy had a subsequent nervous system birth defect. The unadjusted odds ratio for the association between injury during pregnancy and nervous system birth defects was OR=1.16, 95% CI (0.77-1.74), the main effects adjusted OR=0.99, 95% CI (0.63-1.57), and the main effects plus interactions adjusted OR=0.72, 95% CI (0.41-1.27). Among breech presentation infants, the unadjusted odds ratio for the association between injury during pregnancy and nervous system birth defects was OR=2.98, 95% CI (1.45-6.13), the main effects adjusted OR=2.43, 95% CI (1.07-5.51), and the main effects plus interactions adjusted OR=2.44, 95% CI (1.08-5.54). Conclusion: There was a significant association between injury during pregnancy and nervous system birth defects among breech presentation infants in the Texas Birth Defects Registry.

4.2 INTRODUCTION

Injury during pregnancy can endanger the life and wellbeing of the pregnant woman and her fetus. It has been reported that approximately 6-7% of pregnant women experience trauma during pregnancy,[2] 3.9% of all pregnant women sustain an injury during pregnancy that results in a visit to an emergency department,[155] and 0.3-0.4% of pregnant women will have a trauma related hospital admission.[4] The causes of injury during pregnancy are thought to parallel the general population's[6] since pregnant women in the United States usually continue their everyday activities throughout pregnancy.[7] Some of the most frequent causes of injury during pregnancy are motor vehicle crashes, being hit by an object or person, falls, burns, poisoning, being cut or pierced, and overexertion. Motor vehicle crashes are the primary reported cause of serious injury during pregnancy.[3,8-16]

Injury during pregnancy has been associated with several adverse fetal and pregnancy outcomes including: substantially increased fetal mortality, maternal death, neonatal deaths, placental abruption, emergency cesarean delivery, spontaneous abortion, still birth, preterm birth, low birth weight, congenital anomalies, brain damage, disrupted fetal development, disabilities, seizures, preterm premature rupture of the membranes (PPROM), uterine rupture, fetal distress, and newborn respiratory distress syndrome.[9,22,25-33] In addition, brain injury,[34-39] long bone fractures,[40] intra-abdominal injuries,[41,42] and intra-thoracic injuries[34,43] have been reported due to motor vehicle crashes during pregnancy. Although there are many associations between injury during pregnancy and adverse pregnancy and fetal outcomes, the relationship between injury during pregnancy and birth defects has not been adequately studied.

About 150,000 infants[44] or 3% of all live born infants are born with a birth defect in the United States each year.[45,46] For at least the last 20 years, birth defects have been the leading cause of infant mortality in the United States, accounting for more than 20% of all infant deaths (22.3% for 1995-1998 and 19.6% in 1999).[44,156] However, less than 4% of infants born with a birth defect will die within the first year of life,[44] and of those that do, more than 70% of the deaths occur in the neonatal period.[49] The infants that survive with a birth defect often face life long challenges and disabilities including a greater chance of death and illness such as mild health problems, social challenges, long term disability, and reduced quality of life, compared to infants born without birth defects.[44,50,156]

In 65-70% of birth defect cases, the cause of the birth defect is unknown.[51,156] Injury during pregnancy has yet to be well examined as a potential cause of or contributing factor to birth defects and may account for a portion of these unknown causes. Additionally, the literature and current level of knowledge on the role of injury during pregnancy in birth defects is limited

and based largely on case studies and series. Based on the findings from several published cases reports and case series, injury during pregnancy may play a role in the development of nervous system birth defects. It has been reported that any alteration in the developmental processes of the fetus may cause severe nervous system birth defects.[65] It is possible that injury could alter or disrupt nervous system developmental processes through several mechanisms including direct injury, reproductive organ injury, iatrogenic effects, hypoxia or ischemia, and/or stress. Therefore, this study will test the association between injury during pregnancy and nervous system birth defects.

4.3 METHODS

4.3.1 Study design, hypothesis, and specific aims

The purpose of this case-control study is to determine if there is an association between injury during pregnancy and nervous system birth defects in infancy. The study's primary hypothesis is that infants diagnosed with a nervous system birth defect are more likely to have been exposed in-utero to a maternal injury during pregnancy than infants born with other birth defects. The specific aims are to 1) test for an association between injury during pregnancy and nervous system birth defects and 2) determine if injury during pregnancy should be considered a risk factor for the development of nervous system birth defects. This study has been approved by the University of Pittsburgh's Institutional Review Board.

4.3.2 Data collection

Birth defects data were obtained from the Texas Birth Defects Registry (TBDR). The TBDR is maintained by the Birth Defects Epidemiology and Surveillance Branch of the Texas Department of State Health Services (DSHS) which is one of nine centers for birth defects research and prevention established by the Centers for Disease Control and Prevention (CDC).[157] The TBDR is a population-based registry that uses active surveillance and began collecting birth defects data in 1996, with birth defects surveillance becoming statewide in 1999.[158]

Registry data are collected by trained program staff that visit medical facilities to review log books, hospital discharge lists, and other records to create a list of potential birth defect cases.[158] Program staff then review the medical charts of each potential case. If the infant or fetus is determined to have at least one of the birth defects covered by the registry, they are included in the registry and detailed demographic and diagnostic information is abstracted from their records.[158] Quality control procedures are in place for finding cases, abstracting information, and coding defects from the records to help ensure the registry's completeness and accuracy.[158] Records based on abstracted medical information are then matched to vital statistics records including birth certificates and fetal death certificates from the Vital Statistics Unit at the Texas DSHS.[158] Approximately 58% of the birth defect cases in the TBDR have more than one defect.[159] When this occurs, each defect is counted once in the registry (i.e. the data are not mutually exclusive).[159]

4.3.3 Study population

The accessible study population consisted of infants or fetuses included in the Texas Birth Defects Registry (TBDR) during the years 1996-2003 (N=85,845). In order for a fetus or infant to be included in the TBDR, all of the following must be true: the infant or fetus must have a birth defect, the mother's residence at the time of delivery must be in an area covered by the registry (statewide after 1999), the infant or fetus must have a structural birth defect or developmental disability monitored by the registry, and the defect must be diagnosed prenatally or within one year after delivery.[158] This case definition currently includes all pregnancy outcomes (live births, spontaneous fetal deaths, and induced pregnancy terminations) at all lengths of gestation. However, prior to April 5, 2001 the registry did not collect information on birth defects in fetal deaths before 20 weeks gestation.[158]

Inclusion criteria for this study were that the infant was born 1999-2003, was a live birth, and was not diagnosed with any chromosomal birth defects (British Pediatric Association (BPA) code 758). Since statewide surveillance did not begin until 1999, cases prior to 1999 were excluded from the study (N=19,987). Cases classified as a spontaneous fetal death (N=1,547), induced termination of pregnancy (N=1,745), or an unspecified fetal death/pregnancy termination (N=100) were also excluded from this study. Pregnancy outcomes other than live births were excluded due to the possibility of other mechanisms and/or reasons for pregnancy termination effecting the association being tested and due to the inconsistent collection of early pregnancy loss and termination during the study years of interest. Exclusions due to a diagnosis of a chromosomal anomaly (BPA code 758) (N=5,908) were made to allow for the testing of the association between injury during pregnancy and nervous system birth defects above and beyond genetic components. The excluded chromosomal anomalies were: Down syndrome, Patau

syndrome/trisomy 13, Edwards syndrome/trisomy 18, autosomal deletion syndromes, balanced autosomal translocation in normal individuals, other conditions due to autosomal anomalies, gonadal dysgenesis, Klinefelter syndrome, other conditions due to sex chromosome anomalies, and conditions due to anomaly of unspecified chromosomes. After all of these exclusions, the study population consists of 59,750 (69.6% of the accessible population) live born infants without a diagnosed chromosomal anomaly who were included in the Texas Birth Defects Registry (TBDR) for the years 1999-2003.

4.3.4 Definition of cases and controls and exposure of interest

The case definition was diagnosis of a nervous system birth defect as indicated by a British Pediatric Association (BPA) code of 742 in the TBDR. The BPA code 742 includes: encephalocele, microcephalus, reduction deformities of the brain, congenital hydrocephalus, other specified anomalies of the brain, other specified anomalies of the spinal cord, other specified anomalies of the nervous system, and unspecified anomalies of the brain, spinal cord, and nervous system (Appendix A.1). Study controls consisted of all remaining infants in the TBDR, after the exclusions discussed above, that were diagnosed with a birth defect other than a nervous system birth defect. The exposure of interest was maternal injury during pregnancy. An infant was classified as exposed if injury during pregnancy was indicated as a maternal illness, condition, or complication the infant's TBDR record. Maternal injury during pregnancy was a dichotomous variable, but included abdominal trauma, abuse, motor vehicle crash, gun shot wound, or the general category of "injuries during this pregnancy". It is important to note that injury during pregnancy in the TBDR is a crude measurement. No information was available on the timing or severity of injury and due to inconsistent measurement of injury mechanism

between study years, injury mechanism was not analyzed. Additionally, there were limitations to accurately capturing an infant's injury during pregnancy status that will be discussed later in this paper.

4.3.5 Data analysis

The TBDR data required extensive cleaning and recoding of several variables for this study. This was primarily due to a redesign of the TBDR database in 2002. Birth defects cases abstracted on or after February 1, 2002 were abstracted directly into a redesigned database and data from cases prior to that date were transferred into the redesigned database. Not all of the data from cases prior to February 1, 2001 were easily transferable to the new database, resulting in many null fields in the redesigned database for the birth defect cases prior to February 1, 2002. These null fields were addressed in this study by comparing the abstraction forms, abstraction manuals, and data for the old and redesigned databases and where it was appropriate, new variables that combined information from the old and redesigned databases were created. Since data were abstracted from medical records, if a maternal exposure, maternal illness, maternal complication, fetal/infant exposure, fetal/infant illness, or fetal/infant complication was not indicated as occurring in the TBDR data it was consider not to have happened rather than being classified as missing.

All analyses were conducted in SAS 9.1 (SAS Institute INC., Cary, North Carolina). The PROC LOGISTIC procedure was used for univariate and multivariate analysis. The main effects model was built using univariate analysis followed by step-up and then step-down regression. First order interactions among the main effects variables were tested through univariate analysis followed by a global test for interactions and step-down regression. Unadjusted and adjusted

odds ratios were calculated to test the association between injury during pregnancy and nervous system birth defects.

Additional analyses to address potential exposure misclassification of injury during pregnancy in the Texas Birth Defects Registry were performed using a SAS Macro named "sensmac". This macro simulates the data for a misclassified variable (injury during pregnancy in this study) based on user identified sensitivity and specificity values and specification of either non-differential or differential misclassification.[160] For this study, the sensitivity was set to 0.075 to account for the difference between the expected (7%) and observed (0.53%) number of women who were injured during pregnancy. The specificity was set to 1.0 because no woman who was classified as injured during pregnancy was thought to be misclassified. The analyses were performed for the unadjusted, main effects adjusted, and main effects plus interactions adjusted models. The macro was run using 10,000 iterations and non-differential misclassification was indicated. The misclassification was determined to be non-differential since both cases and controls in this study were birth defect cases and subjected to the same data collection efforts and potential biases. The macro outputs three intervals. The first interval is the conventional 95% confidence interval which only accounts for random error. [160] The second and third simulation intervals account for systematic error only and both the systematic and random error, respectively.[160] The methods of the macro are described in more detail elsewhere.[160]

4.4 RESULTS

The study population consisted of 59,750 live born infants without a diagnosed chromosomal anomaly in the Texas Birth Defects Registry for 1999-2003. Out of the 59,750 infants, 4,144

(6.94%) were diagnosed with at least one nervous system birth defect (BPA code 742). The top three most frequent nervous system birth defects were other specified anomalies of brain (N=1,513), congenital hydrocephalus (N=1,159), and microcephalus (N=1,085) (Table 1). Injuries during pregnancy were reported among 315 (0.53%) of the 59,750 infants. Twenty-five (7.94%) of the 315 infants whose mothers were injured during pregnancy were also diagnosed with a nervous system birth defect (Table 2).

Differences between maternal, exposure, infant and pregnancy, geographical, and paternal variables were explored between infants who were and were not exposed to a maternal injury during pregnancy. These comparisons showed that a higher percentage of women who were injured during pregnancy were younger in age, Black or Hispanic, and born in the United States when compared to women who were not injured during pregnancy (Table 3). Additionally, a higher percentage of women who were injured during pregnancy also reported alcohol use during pregnancy and tobacco use during pregnancy than women who were not injured during pregnancy (Table A.2). When comparing infant and pregnancy variables, a higher percentage of infants whose mother was injured during pregnancy were breech presentation at delivery, had hydramnios, and had umbilical cord complications than infants whose mother was not injured during pregnancy (Table A.3). There were also some differences in the percentage of women injured during pregnancy compared to women not injured during pregnancy for their Texas Public Health Region of residence; however no clear urban or rural pattern emerged (Table A.4 and Figure A.4.1). A majority of the exposure (Table A.2) and infant and pregnancy variables (Table A.3) did not differ between infants who were and were not exposed to a maternal injury during pregnancy and there were no note worthy differences among paternal variables (Table A.5) and exposure status.

The unadjusted odds ratio (OR) for the association between injury during pregnancy and nervous system birth defects was OR=1.16 with a 95% confidence interval (95% CI) of (0.77-1.74) and a p-value of 0.4835. The main effects model adjusted for infant gender, gestational age at birth, maternal race (White vs. non-White), maternal education (greater or less than high school), low birth weight, tobacco use during pregnancy, number of birth defects, hydramnios, breech presentation, and umbilical cord complications. The adjusted odds ratio, 95% CI, and p-value for injury during pregnancy were OR=0.99, 95% CI (0.63-1.57), and p-value=0.9735. The Hosmer-Lemeshow goodness of fit test showed no lack of fit for the main effects model (p-value=0.0613); however, a few first order interactions were significant to the model.

The significant interactions were gender by low birth weight, hydramnios by low birth weight, breech presentation by low birth weight, and breech presentation by injury during pregnancy. The Hosmer-Lemeshow goodness of fit test showed no lack of fit for the main effects plus interactions model (p-value=0.1121). The adjusted odds ratio, 95% CI, and p-value for the main effects plus interactions model for injury during pregnancy were OR=0.72, 95% CI (0.41-1.27), and p-value=0.2528. Respectively, the main effects model and the main effects plus interactions model used only 56,020 (93.75%) and 45,438 (76%) of the 59,750 infants due to missing data in some of the modeled variables.

Due to the significant interaction between breech presentation and injury during pregnancy (p-value=0.0161) a stratified analyses was performed to further explore the role of breech presentation as it relates to injury during pregnancy and nervous system birth defects. In the study population, there were 6,001 infants diagnosed with a breech presentation and 53,749 infants with a normal presentation. Of the infants with a breech presentation 40 were exposed to a maternal injury during pregnancy and 610 were diagnosed with a nervous system birth defect

(data not shown). The unadjusted odd ratio, 95% CI, and p-value for injury during pregnancy among infants diagnosed with a breech presentation was OR=2.98, 95% CI (1.45-6.13), and p-value=0.003 compared to OR=0.82, 95% CI (0.49-1.38), and p-value=0.4533 for infants with a normal presentation. The main effects adjusted odd ratio, 95% CI, and p-value for injury during pregnancy among infants diagnosed with a breech presentation was OR=2.43, 95% CI (1.07-5.51), and p-value=0.0340 compared to OR=0.73, 95% CI (0.42-1.29), and p-value=0.2837 for infants with a normal presentation. The main effects plus interactions adjusted odd ratio, 95% CI, and p-value for injury during pregnancy among infants diagnosed with a breech presentation was OR=2.44, 95% CI (1.08-5.54), and p-value=0.0324 compared to OR=0.73, 95% CI (0.41-1.29), and p-value=0.2749 for infants with a normal presentation. Therefore among infants diagnosed with a breech presentation, the infants who were exposed to a maternal injury during pregnancy were more likely to be diagnosed with a nervous system birth defect than those who were not exposed to a maternal injury during pregnancy (Table 4).

The results of the exposure misclassification analyses using sensmac showed a slight increase in the odds ratios for the unadjusted analyses and a change in the direction of the odds ratio for the main effects and main effects plus interaction adjusted analyses, when accounting for exposure misclassification. However, the conclusions of the original analysis, no association between injury during pregnancy and nervous system birth defects among live born infants with a non-chromosomal birth defect who were included in the TBDR 1999-2003 remained, even when accounting for misclassification of injury during pregnancy (Table 5). The slightly increased odds ratios and the change in direction of the odds ratios showed that the exposure misclassification biased the original analyses toward the null, but not enough to effect the overall conclusion of no association.

When accounting for exposure misclassification in the breech presentation stratified analyses, the odds ratio for the association between injury during pregnancy and nervous system birth defects remained was even higher and remained statistically significant among breech presentation infants (Table 6). For infants with normal presentation the odds ratios increased slightly when exposure misclassification was accounted for, but there remained no association between injury during pregnancy and nervous system birth defects in the normal presentation infants (Table 7).

4.5 DISCUSSION

In the absence of testing for an association between injury during pregnancy and nervous system birth defects by other published case-control and cohort studies, the results of this study can only be compared to those of case reports and series. It is important to note that some of these comparisons are difficult to make due to different study populations, case definitions, and exposure definitions. Even so, case reports and series have reported a range of central nervous system and nervous system related fetal/neonatal outcomes following trauma during pregnancy including: cerebral edema, intraventricular and subarachnoid hemorrhage, [37] movement disorders, hydrocephalus, convulsions, cerebral palsy, periventricular leukomalacia, localized vascular infarctions, hemorrhage, hydrocephalus, global brain damage,[36] subdural and intracerebral hemorrhages,[54] congenital microcephaly, congenital hydrocephalus, infantile cerebral hemiplegy, quadriplegy with severe encephalopathy, diplegy, clumsiness with cerebellar atrophy, Moebius syndrome, mental retardation with autistic features, learning disability, auditory agnosia,[8] and at 3-4 months follow up: motor abnormalities, residual injury to the

periventricular white matter,[37] and extensive periventricular and subcortical leukomalacia determined to be microcephaly.[34] Additionally, a literature review by Hagmann et al. of 22 cases of fetal intracranial hemorrhages after a motor vehicle crash during pregnancy reported cases of abnormal neurologic development, impaired neurodevelopment, posthemorrhagic hydrocephalus at birth, and skull fractures associated with subdural hemorrhages and intraventricular hemorrhages.[54] Although published case reports and series were the driving force of this study's hypothesis, the results of this study did not support an association between injury during pregnancy and nervous system birth defects among live born infants with a non-chromosomal anomaly who were included in the TBDR 1999-2003. However, stratified analyses found a significant association between injury during pregnancy and nervous system birth defects among infants diagnosed with breech presentation.

4.5.1 Strengths and limitations

There are several strengths to this study. The first is the choice of the data source. Since trauma during pregnancy is relatively rare, it is ideal to study using large secondary data sources[14] such as the TBDR. Additionally, many studies that examine the role of trauma during pregnancy focus on hospitalization or fetal death reviews,[27] but by using the TBDR, the women who were injured during pregnancy did not have to have been hospitalized for their injury or experience the severe outcome of fetal death to be included in this study.

Another strength of this study is that both cases and controls were identified from the TBDR. Since the data source was the same for both cases and controls, both groups were subjected to the same active surveillance data collection efforts. This is a study strength because, any amount of recall bias should be approximately the same among cases and controls since both

groups experienced birth defects as a pregnancy outcome. This essentially means that cases and controls are equally likely to think about what potentially adverse exposures occurred during pregnancy that could have led to a birth defect, including injury during pregnancy. Therefore, since recall regarding exposure affects cases and controls to the same extent, there is no bias.[112] This was also the basis of choosing non-differential misclassification for the exposure misclassification analyses.

There are also some limitations of the TBDR. To begin with there is the potential for exposure misclassification. We anticipated that 6-7% of the women in the TBDR would have been injured during pregnancy based on previous estimates in the literature.[2] However, only 0.53% of the women in the TBDR were classified as being injury during pregnancy. Likely sources of misclassification for injury during pregnancy in the TBDR are: if a woman did not seek medical attention for an injury she sustained during pregnancy, if she sought medical care at a hospital other than the one she gave birth in, if hospitals created new medical records for each hospitalization, or if the pregnant woman's injury was cared for by an obstetrician in his/her office versus in a hospital. However, it is possible that a woman who was injured during pregnancy could report an injury to her health care provider at the time of birth and maybe likely to do so if the birth defect is diagnosed at birth. Even so, this is speculation and cannot be adequately determined. The probable misclassification of injury during pregnancy in the TBDR could have caused an underestimation of the true association of injury during pregnancy on nervous system birth defects[112] and according to the exposure misclassification results, there was in fact a degree of underestimation of the association between injury during pregnancy and nervous system birth defects. Nevertheless, the association remained insignificant even when accounting for exposure misclassification of injury during pregnancy in the TBDR.

Another limitation was the potential for the TBDR to miss cases of birth defects that were eligible for inclusion into the registry. For instance, birth defect cases are not included in the registry if they are diagnosed beyond an infant's first year of life (other than cases of fetal alcohol syndrome). Therefore, children that were diagnosed with a birth defect after they turn one year of age were not included in the TBDR and were missed cases. This is an important limitation to consider when looking at nervous system birth defects because nervous system birth defects might not be diagnosed until later in life when a child is not meeting developmental milestones. Another way cases could be missed is if they were diagnosed outside of Texas or in prenatal diagnostic facilities or private physicians' offices (which are not included in the TBDR).[161]

Another and an actual source of missed cases was due to severe flooding that occurred during Tropical Storm Allison in June of 2001. Several hospitals in Houston were affected by the flooding and lost medical records. The Birth Defects Epidemiology and Surveillance Branch estimates that between 1999 and 2000 that there were about 50 infants and fetuses born with birth defects at Houston hospitals that may be missing from the TBDR due to the flooding and loss of medical records. However, these fifty cases only equal approximately 1% of the 5,133 infants and fetuses in the registry born during 1999 and 2000 to residents of Public Health Region 6 (which includes the city of Houston).[161] Even though there are potential and known cases missing from the TBDR, these missed cases should not be significant enough to alter the results or findings of this study.

Another study limitation is the limited information pertaining to injury during pregnancy. Injury during pregnancy in the TBDR is somewhat of a crude measurement and it does not including injury timing or severity information. Timing of injury information is important to

assess when available because the various regions of the brain form at different times; therefore, the timing of insults, their severity, and nature will likely determine the type or pattern of brain injury, how the neurological disorder is expressed, and the extent to which the individual's functioning abilities will be affected.[63,162] When available, assessing the timing of injury in future studies should be done to help identify windows of vulnerability for adverse nervous system outcomes following injury during pregnancy. It has also been shown that regardless of the severity of a pregnant woman's injury, the pregnancy and/or fetus can still experience adverse outcomes and even fetal death.[29,41,58,89,163-167] Therefore, similar to injury timing, when available injury severity should be analyzed to further explore different types or severities of adverse maternal and fetal outcomes following various severities of injury.

A potential study or data limitation is that on February 1, 2002 the TBDR implemented new data collection software. Cases abstracted before the implementation of the new software (affecting most cases delivered before 2001), were likely to have several fields with null values, and some fields had values but were collected under different rules and definitions.[158] These fields were identified and analyzed with care as discussed in the methods section.

A final study limitation is that injury during pregnancy could vary by region, maternal risk-taking behavior, geographic and seasonal/climatic factors, social and cultural issues, or variations in maternal driving.[10] By only studying the state of Texas some of these potential differences cannot be assessed. Nevertheless, the TBDR is a vast source of information and there are many geographic, seasonal, and even social and cultural variations within the state of Texas that were assessed in this study.

4.5.2 Future research

This study's significant finding of an association between injury during pregnancy and nervous system birth defects among breech presentation infants merits further exploration. It is unknown what is actually driving this association; however, it can be speculated that through direct injury, reproductive organ injury, iatrogenic effects, hypoxia or ischemia, and/or stress, an injury during pregnancy may disrupt a developmental pathway leading to a nervous system birth defect which in turn affects the normal rotation of the fetus and results in breech presentation. Since the association between injury during pregnancy and nervous system birth defects was not present among normal presentation infants, there may be specific injuries, timing of injury, or severity of injury that results in a nervous system birth defect that in turn results in breech presentation. Therefore, specific avenues of interest for further research of this association are the timing of injury, the severity of injury, the specific types of nervous system birth defects among breech versus normal presentation infants, as well as the position of the fetus at the time of injury (if this can be accurately assessed). This finding raises more questions than it answers, but may be key to reducing further infant morbidity and mortality associated with injury during pregnancy, nervous system birth defects, and breech presentation.

Going beyond this study's scope and overall outcome of nervous system birth defects, there are many more birth defects, specific nervous system birth defects, and other neuro-related outcomes that could/should be assessed in future studies. Especially since neurodevelopmental disabilities affect 3-8% of the 4 million babies born each year in the United States[168] and the cause of fewer than 25% of neurodevelopmental disabilities such as dyslexia, attention deficit hyperactivity disorder (ADHD), intellectual retardation, and autism is known.[168] It is possible that injury during pregnancy through the mechanisms discussed in this paper may be associated

with some of these outcomes. Support for these hypotheses could be garnered from Morris et al. who reported that about 40% of the neonates that survived emergency cesarean section following maternal trauma in their study had moderate to serious disabilities, many had neurobehavioral dysfunction and poor school performance.[57] Therefore, the association between injury during pregnancy and other neuro-related outcomes should be considered.

Although this was the first case-control study to test the association between injury during pregnancy and nervous system birth defects; due to data limitations and the specific birth defects study population, this study should be repeated if/when possible and the association among infants with a breech presentation should be further explored. With limited data sources that include both the exposure and outcomes of interest, future studies will likely require the utilization of linkage procedures. Additionally, if current and future data collection efforts included injuries during pregnancy as an exposure of interest during pregnancy or injury surveillance systems included injury during pregnancy as a required reportable event, more studies looking at the various adverse maternal, fetal, and child outcomes of injury during pregnancy would be able to be conducted. In turn, the results of these studies could be used for targeted prevention of injury during pregnancy to reduce maternal, fetal, and child morbidity and mortality.

4.6 CONCLUSION

Among the entire study population, injury during pregnancy, as reported in the TBDR, was not associated with nervous system birth defects even when accounting for exposure misclassification. However a significant association between injury during pregnancy and

nervous system birth defects was determined among breech presentation infants through stratified analyses. This study should be repeated with data that contains more injury specific information such as timing, severity, and mechanism of injury to determine if an association exists among specific types or severities of injury or when the injury occurs at a specific gestational age, and to further explore the association among breech presentation infants. In conclusion, although injury is often viewed as a chance occurrence, it should be recognized as a preventable risk factor for adverse pregnancy, fetal, and infant outcomes including nervous system birth defects among breech presentation infants.

4.7 PAPER ONE TABLES

Table 1: Frequency of Nervous System Birth Defects in Texas 1999-2003

	Diagnosed with specific nervous system birth defect			
Type of Nervous System Birth Defect (BPA code)	**Yes**	**%**	**No**	**%**
Number of infants with any nervous system birth defect (742)	4,144	6.94	55,606	93.06
Other specified anomalies of brain (742.4)	1,513	2.53	58,237	97.47
Congenital hydrocephalus (742.3)	1,159	1.94	58,591	98.06
Microcephalus (742.1)	1,085	1.82	58,665	98.18
Reduction deformities of brain (742.2)	927	1.55	58,823	98.45
Other specified anomalies of spinal cord (742.5)	303	0.51	59,447	99.49
Encephalocele (742.0)	118	0.20	59,632	99.80
Other specified anomalies of nervous system (742.8)	82	0.14	59,668	99.86
Unspecified anomalies of brain, spinal cord and nervous system (742.9)	9	0.02	59,741	99.98

Table 2: Frequency and Percent of Injury During Pregnancy by Nervous System Defects in Texas 1999-2003

		Injury During Pregnancy			
Type of Nervous System Birth Defect (BPA code)	**N**	**Yes**	**%**	**No**	**%**
Number of infants with any nervous system birth defect (742)	4,144	25	0.60	4,119	99.40
Other specified anomalies of brain (742.4)	1,513	8	0.53	1,505	99.47
Congenital hydrocephalus (742.3)	1,159	4	0.35	1,155	99.65
Microcephalus (742.1)	1,085	9	0.83	1,076	99.17
Reduction deformities of brain (742.2)	927	7	0.76	920	99.24
Other specified anomalies of spinal cord (742.5)	303	3	0.99	300	99.01
Encephalocele (742.0)	118	1	0.85	117	99.15
Other specified anomalies of nervous system (742.8)	82	1	1.22	81	98.78
Unspecified anomalies of brain, spinal cord and nervous system (742.9)	9	0	0.00	9	100.00

Table 3: Maternal Variables by Injury During Pregnancy Status, Texas Birth Defects Registry 1999-2003

			Injury During Pregnancy				Missing
Maternal Variables	**N**	**%**	**Yes**	**%**	**No**	**%**	**N**
Age Group							0
<20	8,754	14.65	64	20.32	8,690	14.62	
20-24	16,150	27.03	104	33.02	16,046	27.00	
25-29	15,514	25.96	75	23.81	15,439	25.98	
30-34	12,159	20.35	50	15.87	12,109	20.37	
35-39	5,895	9.87	18	5.71	5,877	9.89	
40+	1,278	2.14	4	1.27	1,274	2.14	
Ethnicity							38
White	24,634	41.25	120	38.10	24,514	41.27	
Black	6,513	10.91	43	13.65	6,470	10.89	
Hispanic	26,821	44.92	146	46.35	26,675	44.91	
Other	1,744	2.92	6	1.90	1,738	2.93	
Birth Place							833
United States	42,814	71.66	250	81.43	42,564	72.62	
Mexico	11,678	19.54	38	12.38	11,640	19.86	
Other	4,425	7.41	19	6.19	4,406	7.52	
High School Education							1,662
Less than High School Education	18,457	31.77	94	31.23	18,363	31.78	
Greater than High School Education	39,631	68.23	207	68.77	39,424	68.22	

Table 4: Logistic Regression Results for the Association Between Injury During Pregnancy and Nervous System Birth Defects, Stratified by Breech and Non-Breech Presentation

Stratified Analyses	OR	95% CI	P-Value
Breech Presentation			
Unadjusted Analysis	2.98	(1.45-6.13)	0.003
Main Effects Adjusted Analysis	2.43	(1.07-5.51)	0.034
Main Effects Plus Interactions Analysis	2.44	(1.08-5.54)	0.032
Non-Breech Presentation			
Unadjusted Analysis	0.82	(0.49-1.38)	0.453
Main Effects Adjusted Analysis	0.73	(0.42-1.29)	0.284
Main Effects Plus Interactions Analysis	0.73	(0.41-1.29)	0.275

Table 5: Sensmac Sensitivity Analysis Results, 10,000 Iterations, Sensitivity=0.075, Specificity=1.0

Analyses	OR	95% CI
Original Unadjusted Analysis	1.16	(0.77-1.74)
Sensmac Unadjusted Intervals		
Conventional Analysis	1.16	(0.77-1.76)
Sensitivity Analysis	1.17	(1.05-1.31)
Total Error Analysis	1.17	(0.77-1.80)
Original Main Effects Adjusted Analysis	0.99	(0.63-1.57)
Sensmac Main Effects Adjusted Intervals		
Conventional Analysis	1.00	(0.63-1.56)
Sensitivity Analysis	1.16	(1.03-1.31)
Total Error Analysis	1.16	(0.73-1.85)
Original Main Effects Plus Interactions Adjusted Analysis	0.72	(0.41-1.27)
Sensmac Main Effects Plus Interactions Adjusted Analysis		
Conventional Analysis	0.72	(0.40-1.27)
Sensitivity Analysis	1.14	(0.99-1.30)
Total Error Analysis	1.13	(0.63-2.06)

Table 6: Stratified Sensmac Sensitivity Analysis Results, Breech Presentation, 10,000 Iterations, Sensitivity=0.095, Specificity=1.0

Analyses	OR	95% CI
Original Unadjusted Analysis	2.98	(1.45-6.13)
Sensmac Unadjusted Intervals		
Conventional Analysis	2.99	(1.45-6.03)
Sensitivity Analysis	3.38	(2.69-4.23)
Total Error Analysis	3.38	(1.59-7.28)
Original Main Effects Adjusted Analysis	2.43	(1.07-5.51)
Sensmac Main Effects Adjusted Intervals		
Conventional Analysis	2.44	(1.08-5.53)
Sensitivity Analysis	3.35	(2.60-4.25)
Total Error Analysis	3.34	(1.43-7.85)
Original Main Effects Plus Interactions Adjusted Analysis	2.44	(1.08-5.54)
Sensmac Main Effects Plus Interactions Adjusted Analysis		
Conventional Analysis	2.45	(1.08-5.70)
Sensitivity Analysis	3.35	(2.61-4.28)
Total Error Analysis	3.35	(1.41-7.79)

Table 7: Stratified Sensmac Sensitivity Analysis Results, Non-Breech Presentation 10,000 Iterations, Sensitivity=0.073, Specificity=1.0

Analyses	OR	95% CI
Original Unadjusted Analysis	0.82	(0.49-1.38)
Sensmac Unadjusted Intervals		
Conventional Analysis	0.82	(0.49-1.40)
Sensitivity Analysis	0.81	(0.71-0.93)
Total Error Analysis	0.82	(0.47-1.40)
Original Main Effects Adjusted Analysis	0.73	(0.42-1.29)
Sensmac Main Effects Adjusted Intervals		
Conventional Analysis	0.73	(0.42-1.30)
Sensitivity Analysis	0.81	(0.69-0.93)
Total Error Analysis	0.81	(0.44-1.46)
Original Main Effects Plus Interactions Adjusted Analysis	0.73	(0.41-1.29)
Sensmac Main Effects Plus Interactions Adjusted Analysis		
Conventional Analysis	0.73	(0.41-1.29)
Sensitivity Analysis	0.81	(0.69-0.93)
Total Error Analysis	0.80	(0.44-1.44)

5.0 PAPER TWO: EXPOSURE MISCLASSIFICATION ANALYSIS OF INJURY DURING PREGNANCY IN THE TEXAS BIRTH DEFECTS REGISTRY

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5.1 ABSTRACT

Background: Case studies and case series have suggested an association between injury during pregnancy and several nervous system and nervous system related fetal/neonatal outcomes. However, when the association between injury during pregnancy and nervous system birth defects was tested through a case-control study utilizing the Texas Birth Defects Registry, no association was found prior to stratification by breech presentation. A limitation of this case-control study was likely exposure misclassification of injury during pregnancy. Methods: Through an underutilized semi-automated probabilistic sensitivity analysis, a SAS macro named sensmac, this study corrected for systematic error due to misclassification of injury during

pregnancy and re-tested the association between injury during pregnancy and nervous system birth defects. Results: After accounting for exposure misclassification, there remained no association between injury during pregnancy and nervous system birth defects among the entire study population and normal presentation infants; whereas, the statistically significant association remained and was heightened among breech presentation infants. Through increases and changes in the direction of the odds ratios when systematic error, and therefore exposure misclassification, was taken into account, the hypothesis that exposure misclassification biased the association toward the null hypothesis was supported. Conclusion: Even when accounting for exposure misclassification, there was only an association between injury during pregnancy and nervous system birth defects among live born breech presentation infants with a non-chromosomal anomaly in the Texas Birth Defects Registry 1999-2003. Sensmac is a valuable tool that can be used to determine the extent to which data and associations are affected by exposure misclassification.

5.2 INTRODUCTION

Case studies and case series have suggested an association between injury during pregnancy and several nervous system and nervous system related fetal/neonatal outcomes including: cerebral edema, intraventricular and subarachnoid hemorrhage,[37] movement disorders, hydrocephalus, convulsions, cerebral palsy, periventricular leukomalacia, localized vascular infarctions, hemorrhage, hydrocephalus, global brain damage,[36] subdural and intracerebral hemorrhages,[54] congenital microcephaly, congenital hydrocephalus, infantile cerebral hemiplegy, quadriplegy with severe encephalopathy, diplegy, clumsiness with cerebellar atrophy, Moebius syndrome,

mental retardation with autistic features, learning disability, auditory agnosia,[8] and at 3-4 months follow up: motor abnormalities, residual injury to the periventricular white matter,[37] and extensive periventricular and subcortical leukomalacia determined to be microcephaly.[34] Additionally, a literature review by Hagmann et al. of 22 cases of fetal intracranial hemorrhages after a motor vehicle crash during pregnancy reported cases of abnormal neurologic development, impaired neurodevelopment, posthemorrhagic hydrocephalus at birth, and skull fractures associated with subdural hemorrhages and intraventricular hemorrhages.[54]

When the association between injury during pregnancy and nervous system birth defects was tested by a case-control study that utilized data from the Texas Birth Defects Registry (TBDR) for the years 1999-2003 (n=59,750), no association was found among the entire study population and in normal presentation infants after stratification by breech presentation and a significant association was determined among breech presentation infants. The case-control study was paper one of this dissertation, was titled "Injury during pregnancy and nervous system birth defects in Texas 1999-2003", and will be referred to as the TBDR study throughout this manuscript. Although no association was found between injury during pregnancy and nervous system birth defects for the entire study population and in normal presentation infants in the TBDR study, exposure misclassification is thought to have affected the results of the TBDR study and possibly caused an underestimation of the association.

5.2.1 Potential sources of exposure misclassification in the Texas Birth Defects Registry

There are several possible sources of misclassification for injury during pregnancy in the Texas Birth Defects Registry. For instance, if a pregnant woman was involved in a traumatic event, such as a fall, motor vehicle crash or abuse, but did not go to an emergency room or hospital her

injury during pregnancy status could have been misclassified. This would have occurred because she did not seek medical attention at an emergency room or hospital and therefore the event and any resulting injuries would not be recorded in a medical record. Consequently, if the data are not in a medical record then it is not reviewed by TBDR staff and not included in the TBDR. Another source of exposure misclassification for injury during pregnancy in the Texas Birth Defects Registry is if a pregnant woman sought care for her injury in any other location than an emergency room or hospital, such as a private obstetrician's office. Since individual offices are not part of the TBDR's active surveillance, the registry staff would not have access to the information to properly classify a woman's exposure.

Yet another instance that could have led to exposure misclassification in the TBDR is if a pregnant woman sought medical care at a hospital other than the one she gave birth in. The TBDR uses the infant records to identify possible/probable cases of birth defects and then looks back at the related medical records; therefore, if a woman was seen in a hospital other than the hospital she gave birth in for injuries or follow up after a traumatic event, the exposure would be missed and therefore misclassified. A final source of potential exposure misclassification is if a pregnant woman sought treatment for an injury during pregnancy in the same hospital that she gave birth in, but the hospital creates new medical records for each hospitalization. In this scenario the exposure could have been misclassified due to a disconnect between medical records, even for the same person.

Even with the several potential sources of misclassification described above, it is important to consider that a woman who was injured during pregnancy could report an injury or involvement in a traumatic event to her health care provider at the time of birth. This is a realistic possibility for this study population because it consists of women who had an infant

with at least one birth defect. Women who gave birth to an infant with a birth defect would very likely be thinking of anything out of the ordinary that occurred during their pregnancy and/or what they might have been exposed to that could have caused an anomaly in their child. Even if a woman considered an injury during pregnancy as a possible cause or contributing factor to the birth defect, it would be up to the woman to report an injury during pregnancy to her healthcare provider and the healthcare provider to document it in the medical record in order for the information to be reviewed and recorded by the TBDR staff and included in the TBDR.

Regardless of the source of misclassification, it is recognized that misclassification of injury during pregnancy is a limitation of the TBDR study. Although there are few methods available that quantify the systematic error for an effect estimate and they are rarely used,[113] this study will employ one of these methods by using a semi-automated method of sensitivity analysis to assess systematic errors attributable to misclassification.[113] This will help to quantify the extent to which exposure misclassification affected the association between injury during pregnancy and nervous system birth defects in the TBDR study.

5.3 METHODS

5.3.1 Study Design, purpose, hypothesis, specific aims

This study is a semi-automated probabilistic sensitivity analysis. Its purpose is to correct for systematic error due to misclassification using a previously described method[113] and SAS macro that has been programmed to further address the issue of misclassification.[160] The study's hypothesis is that misclassification of injury during pregnancy in the Texas Birth Defects

Registry caused an underestimation of the association of injury during pregnancy and nervous system defects in the TBDR study. The specific aims are to 1) apply an underutilized method of probabilistic sensitivity analysis, 2) quantify the effects of misclassification of injury during pregnancy, and 3) provide simulated intervals that incorporate systematic and random error in order to better represent the association between injury during pregnancy and nervous system defects had exposure misclassification not occurred.

5.3.2 The SAS macro sensmac

Fox, Lash, and Greenland[160] developed a SAS macro that extends Lash and Fink's[113] semi-automated probabilistic sensitivity analysis and corrects for several sources of bias. The SAS macro, called "sensmac", simulates the data for a misclassified variable based on user identified sensitivity and specificity values.[160] The macro also allows for specification of either non-differential or differential misclassification. After the macro is run, three intervals and graphs of the distributions are output. The first interval is the conventional odds ratio and 95% confidence interval. This interval only accounts for random error. [160] The second and third simulation intervals account for systematic error only and both the systematic and random error, respectively.[160] The methods of the macro are described in more detail elsewhere.[113,160]

5.3.3 Selection of sensitivity and specificity

Misclassification of injury during pregnancy was a known limitation of the Texas Birth Defects Registry (TBDR). To quantify the misclassification, the sensitivity and specificity of identifying a woman as being injured during pregnancy in the TBDR were calculated. The sensitivity and

specificity were estimated based on a comparison of the observed and expected number of women identified as injured during pregnancy in the TBDR. The literature reports that 6-7% of women are injured during pregnancy;[2] however, only 0.53% of the women in the TBDR were classified as injured during pregnancy. Therefore, the observed number of women classified as injured during pregnancy in the TBDR was 315/59,750 and the expected number, using the 7% from the literature, was 4,183/59,750. Thus the TBDR only had a sensitivity of 0.075 (315/4,183) for identifying women who were injury during pregnancy (Table 8). On the other hand we are confident that the women who were classified as injured during pregnancy in the TBDR are correctly classified; therefore a specificity equal to 1.0 was used for the analyses. The same methods for determining the sensitivity and specificity for the breech presentation stratified analyses were used and resulted in a sensitivity of 0.095 (40/420) and specificity of 1.0 for the breech presentation infants and a specificity of 0.073 (275/3,762) and a sensitivity of 1.0 for the normal presentation infants.

5.3.4 Data analysis

The misclassification of injury during pregnancy in the Texas Birth Defects Registry was specified as non-differential misclassification in the macro. The misclassification in the TBDR was determined to be non-differential misclassification because, the sensitivity and specificity of the exposure classification should be similar for the cases and controls, but still less than 100%.[111] The exposure classification should be the same for cases (infants with nervous system defects) and controls (infants with other birth defects) in the TBDR study because both cases and controls are cases by definition in the TBDR (infants with birth defects). Therefore, data for both the cases and controls in the TBDR study were collected in the same manner with an equal

likelihood for misclassification among cases and controls. The non-differential misclassification specification in the macro will result in the program defining two probability distributions based on the sensitivity (0.075, 0.095, or 0.073) and specificity (1.0) input by the user and then randomly choosing a specificity and sensitivity from the distributions.[160] For these analyses the macro was instructed to run 10,000 iterations in order to calculate the three intervals and was run to determine the unadjusted and adjusted results.

For exploration, sensmac was also run in four different ways: with 50,000 iterations, using various ranges of sensitivity to allow for wider ranges of expected injuries (3-7% and 5-7%), using differential misclassification, and using a specificity less than one. The analyses using 50,000 iterations mirrored that of the 10,000 iterations analyses for the entire study population above (sensitivity=0.075 and specificity=1.0), but was used to determine if more iterations would result in more precise results. The wider ranges of expected injuries were used to see if the results would vary when considering that the number of women injured during pregnancy might not be exactly the 7% from the literature. Specifically, sensmac was run comparing the observed 0.53% in the TBDR and the expected 7%, 5-7%, and 3-7% of women injured during pregnancy. These ranges were selected while keeping in mind that motor vehicle crashes are the leading cause of injury during pregnancy[3,8-16] and it is estimated that 2-3% of live births in the United States are exposed in-utero to a police reported motor vehicle crash.[17,27] Therefore when considering motor vehicle crashes and all other injury mechanisms the ranges of 3-7% and 5-7% were deemed reasonable to compare to the observed percent. These ranges were tested using unadjusted analysis and 1,000 iterations.

Although the misclassification of injury during pregnancy in the TBDR is considered non-differential misclassification, sensmac was run with the differential misclassification

specifications and 1,000 iterations for exploratory comparison of the non-differential to differential results. The last explorational analysis was to run sensmac using a specificity less than 1.0 with 1,000 iterations. Since there were only 315 women classified as injured during pregnancy out of 59,750 in the TBDR, even when testing the hypothetical situation of 165 of the 315 women being falsely identified as injured during pregnancy, the specificity range remained narrow with a minimum of 0.997 and a maximum of 1.0 and the sensitivity range had a minimum of 0.0358 and maximum of 0.075.

5.4 RESULTS

After running sensmac with 10,000 iterations, a sensitivity of 0.075, and a specificity of 1.0, the unadjusted intervals were determined for the association between injury during pregnancy and nervous system birth defects. The first interval for the unadjusted analysis, the conventional analysis, reported an odds ratio (OR) of 1.16 and a 95% confidence interval (95% CI) of 0.77 to 1.77. This interval only accounts for random error. According to the first interval, there is no association between injury during pregnancy and nervous system birth defects as was also determined by the TBDR study (unadjusted OR=1.16 95% CI=0.77-1.74). The second interval, the sensitivity analysis, accounts for systematic error only and reported an OR=1.17 and a 95% CI=(1.05-1.31). Therefore, when only accounting for systematic error, injury during pregnancy was associated with nervous system birth defects. The third interval, the total error analysis, accounts for both systematic and random error and reported an OR=1.17 and a 95% CI=(0.77-1.80). Since the third interval accounts for both random and systematic error, this interval is the main interval of interest and shows that overall when accounting for both systematic and random

error there is again no association between injury during pregnancy and nervous system birth defects (Table 9).

Using 10,000 iterations and the same values for sensitivity and specificity as indicated above, the main effects adjusted analysis (adjusted for infant gender, gestational age at birth, maternal race (White vs. non-White), maternal education (greater or less than high school), low birth weight, tobacco use during pregnancy, number of birth defects, hydramnios, breech presentation, and umbilical cord complications) had the following results. For the first interval, the conventional analysis, the reported OR=1.00 with a 95% CI=(0.63-1.56). Therefore, when only accounting for random error there was no association between injury during pregnancy and nervous system birth defects as was also determined by the TBDR study (OR=0.99 95% CI=0.63-1.57). The second interval, the sensitivity analysis, reported an OR=1.16 with a 95% CI=(1.03-1.31). Thus, when accounting for systematic error only, the direction of the odds ratio changed and there was a positive association between injury during pregnancy and nervous system birth defects. The third interval, the total error analysis, reported an OR=1.61 and a 95% CI=(0.73-1.85). Although the direction of the odds ratio changed from the original analyses, when accounting for both systematic and random error there remained no association between injury during pregnancy and nervous system birth defects (Table 9).

Again using 10,000 iterations and a sensitivity of 0.075 and a specificity of 1.0, the main effects model plus interactions (main effects as listed above and including gender by low birth weight, hydramnios by low birth weight, breech presentation by low birth weight, and breech presentation by injury during pregnancy interactions), had the following results. For the conventional analysis the reported OR=0.72 with a 95% CI=(0.40-1.27). Therefore, again as with the previous results and the results in the TBDR study (OR=0.72 95% CI=0.41-1.27) there was

no association between injury during pregnancy and nervous system birth defects for the first interval or original analyses. The sensitivity analysis reported an OR=1.14 with a 95% CI=(0.99-1.30). Different from the sensitivity analysis results for the unadjusted and main effects, there was no association between injury during pregnancy and nervous system birth defects for the second interval when accounting for the main effects and interactions. The total error analysis reported an OR=1.13 and a 95% CI=(0.63-2.06). Therefore, although the direction of the odds ratio changed when accounting for both systematic and random error, there was no association between injury during pregnancy and nervous system birth defects adjusting for the main effects and interactions. (Table 9)

After running sensmac in the normal presentation infants (n=53,749) with 10,000 iterations, a sensitivity of 0.073, and a specificity of 1.0, there was no change in the odds ratio for the unadjusted analyses and a slight increase in the odds ratio for the main effects adjusted and main effects plus interaction adjusted models after accounting for exposure misclassification. Additionally, the overall conclusion of no association between injury during pregnancy and nervous system birth defects remained (Table 10). After running senmac to account for exposure misclassification in the breech presentation infants (N=6,001) with 10,000 iterations, a sensitivity of 0.095, and a specificity of 1.0, the odds ratio increased in each of analyses and the significant association between injury during pregnancy and nervous system birth defects remained (Table 11).

The results of the exploratory analyses showed little variation in the above results. For instance, when the sensmac was run using 50,000 iterations instead of 10,000 the results were essentially the same (Table 12). The second set of exploratory analyses that tested various expected injury ranges, resulted minimal differences in the odds ratios and confidence intervals

and no difference in the conclusions of no association between injury during pregnancy and nervous system birth defects. The first range compared the observed 0.53% of women classified as injured during pregnancy in the TBDR to the expected 7% from the literature. This range used a minimum and maximum sensitivity of 0.075 and a specificity of 1.0. The first range had a total error analysis OR=1.16 with a 95% CI=(0.77-1.79). The second range used a minimum sensitivity of 0.075, a maximum sensitivity of 0.105, and a specificity of 1.0. This range compared the observed 0.53% to an expected 5-7% of women classified as injured during pregnancy. By widening the range, the results account for a possible lower percent of women injured during pregnancy than is estimated in the literature. The second range had a total error analysis OR=1.16 with a 95% CI=(0.75-1.86). The third range used a minimum sensitivity of 0.075, a maximum sensitivity of 0.176, and a specificity of 1.0. This ranged compared the observed 0.53% to an expected 3-7% of women classified as injured during pregnancy. The third range had a total error analysis OR=1.17 with a 95% CI=(0.76-1.75). Using different ranges of expected injury during pregnancy did not alter the results enough to warrant further examination.

When sensmac was run using differential misclassification there were no differences among the differential and non-differential results (data not shown). Additionally, when sensmac was run using the hypothetical situation that 165 of the 315 women were incorrectly classified as injured during pregnancy to test a specificity less than one (sensitivity min=0.0358 and max=0.075, specificity min=0.997 and max=1.0) the OR=1.28 with a 95% CI=(0.79-1.96). This was a slightly higher odds ratio and slightly wider confidence interval than the comparison analysis that used a sensitivity of 0.075 and specificity of 1.0 (OR=1.16, 95% CI=(0.77-1.79);

however, the conclusions drawn of no association between injury during pregnancy and nervous system birth defects are the same.

5.5 DISCUSSION

Although the conclusion of no association between injury during pregnancy and nervous system birth defects in the Texas Birth Defects Registry (TBDR) study did not change among the entire study population and normal presentation infants when misclassification of injury during pregnancy was taken into account by the SAS macro sensmac, the analyses performed in this manuscript demonstrated an under utilized method to better quantify an odds ratio and 95% confidence interval when a known misclassification exists. Since sensmac is able to account for both random and systematic error, we were able to report secondary odds ratios and 95% confidence intervals with more confidence than the original TBDR study's analyses allowed. The increase in or change in direction of the odds ratio when accounting for systematic error alone and both random and systematic error, showed the misclassification of injury during pregnancy in the TBDR did in fact bias the association toward the null hypothesis of no association.

Selecting the proper sensitivity and specificity for sensmac took some consideration. Several papers report that 6-7% of women are injured during pregnancy;[11-14,30,54,89,169-172] however, this percent is solely based on a clinical paper that was published in 1963.[2] In 2005, Ikossi et al. acknowledge that the true incidence of injury during pregnancy is unknown due to a lacking comprehensive national trauma database;[14] however, a current incidence of all trauma during pregnancy has yet to be determined and most authors still report the 6-7% from 1963.

When considering how things have changed in our society since 1963, including the role of women, it is hard to believe that the widely reported statistic of trauma occurring in 6-7% of pregnancy women is accurate 45 years later. However, it is possible that trade-offs may have occurred to keep this percent somewhat accurate. For example, women drive much more today than they did in 1963 increasing their risk of a motor vehicle crash, but there have also been significant improvements in road and motor vehicle safety which could counter balance the increased risk of motor vehicle crash and subsequent injury due to an increased exposure.

When deciding what percent to use to calculate the expected number of women injured during pregnancy in the TBDR and the corresponding sensitivity to input into sensmac, I used the more recent motor vehicle crash during pregnancy literature as a baseline. Knowing that motor vehicle crashes are the primary cause of injury during pregnancy and that crashes occur in up to 3% of all live births (even though not all crashes result in an injury), I estimated that on the low end 3% of women are injured during pregnancy when accounting for all injury mechanisms. If the 3% were doubled to account for the other less frequent causes of injury during pregnancy, it would still only be 6%; therefore, expecting 7% of women to be injured during pregnancy was not unreasonable. When I tested various ranges of sensitivity to account for an expected 5-7% and 3-7% of women injured during pregnancy in the exploratory analysis, the results did not vary much. Therefore, I compared the observed 0.53% (for the entire study population), 0.51% (for the normal presentation infants), and 0.67% (for the breech presentation infants) of women injured during pregnancy in the TBDR to an expected 7% for the main analyses of this paper. Nevertheless, a recent and accurate population based percentage of women injured during pregnancy should be determined to update the 1963 statistic.

The TBDR is one of the only databases that includes information on injury during pregnancy and birth defects, but the data is limited in detail for injury during pregnancy. Specifically, there is no timing of injury, severity of injury, or consistent mechanism of injury information available. If the injuries were better classified, an association between a specific type, severity, or mechanism of injury and nervous system birth defects (or a specific nervous system birth defect) might have been identified in the entire study population or the normal presentation infants. Future studies should account for timing of injury, injury severity, and injury mechanisms when available.

5.6 CONCLUSION

This study determined that the misclassification of injury during pregnancy in the Texas Birth Defects Registry caused an underestimation of the association of injury during pregnancy and nervous system defects in the TBDR study. Nevertheless, after accounting for misclassification of injury during pregnancy in the Texas Birth Defects Registry, the conclusions of the TBDR study remained. The SAS macro sensmac is a valuable tool that provides a better representation of the odds ratio and corresponding 95% confidence interval when misclassification is a known study bias and can be used to determine the extent to which data and tested associations are affected by exposure misclassification.

5.7 PAPER TWO TABLES

Table 8: Relation Between Indication of Injury During Pregnancy in the Texas Birth Defects Registry and Expected Results Based on Estimations from the Literature

	Expected Results from Literature (7% of Women Injured During Pregnancy)		
Texas Birth Defects Registry	Injured During Pregnancy	Not Injured During Pregnancy	Total
Injured During Pregnancy	315	0	315
Not Injured During Pregnancy	3,868	55,567	59,435
Total	4,183	55,567	59,750

Sensitivity= 315/4,183=**0.075**
Specificity= 55,567/55,567=**1.00**

Table 9: Sensmac Sensitivity Analysis Results, 10,000 Iterations, Sensitivity=0.075, Specificity=1.0

Analyses	OR	95% CI
Original Unadjusted Analysis	1.16	(0.77-1.74)
Sensmac Unadjusted Intervals		
Conventional Analysis	1.16	(0.77-1.76)
Sensitivity Analysis	1.17	(1.05-1.31)
Total Error Analysis	1.17	(0.77-1.80)
Original Main Effects Adjusted Analysis	0.99	(0.63-1.57)
Sensmac Main Effects Adjusted Intervals		
Conventional Analysis	1.00	(0.63-1.56)
Sensitivity Analysis	1.16	(1.03-1.31)
Total Error Analysis	1.16	(0.73-1.85)
Original Main Effects Plus Interactions Adjusted Analysis	0.72	(0.41-1.27)
Sensmac Main Effects Plus Interactions Adjusted Analysis		
Conventional Analysis	0.72	(0.40-1.27)
Sensitivity Analysis	1.14	(0.99-1.30)
Total Error Analysis	1.13	(0.63-2.06)

Table 10: Stratified Sensmac Sensitivity Analysis Results, Non-Breech Presentation

10,000 Iterations, Sensitivity=0.073, Specificity=1.0

Analyses	OR	95% CI
Original Unadjusted Analysis	0.82	(0.49-1.38)
Sensmac Unadjusted Intervals		
Conventional Analysis	0.82	(0.49-1.40)
Sensitivity Analysis	0.81	(0.71-0.93)
Total Error Analysis	0.82	(0.47-1.40)
Original Main Effects Adjusted Analysis	0.73	(0.42-1.29)
Sensmac Main Effects Adjusted Intervals		
Conventional Analysis	0.73	(0.42-1.30)
Sensitivity Analysis	0.81	(0.69-0.93)
Total Error Analysis	0.81	(0.44-1.46)
Original Main Effects Plus Interactions Adjusted Analysis	0.73	(0.41-1.29)
Sensmac Main Effects Plus Interactions Adjusted Analysis		
Conventional Analysis	0.73	(0.41-1.29)
Sensitivity Analysis	0.81	(0.69-0.93)
Total Error Analysis	0.80	(0.44-1.44)

Table 11: Stratified Sensmac Sensitivity Analysis Results, Breech Presentation, 10,000 Iterations,

Sensitivity=0.095, Specificity=1.0

Analyses	OR	95% CI
Original Unadjusted Analysis	2.98	(1.45-6.13)
Sensmac Unadjusted Intervals		
Conventional Analysis	2.99	(1.45-6.03)
Sensitivity Analysis	3.38	(2.69-4.23)
Total Error Analysis	3.38	(1.59-7.28)
Original Main Effects Adjusted Analysis	2.43	(1.07-5.51)
Sensmac Main Effects Adjusted Intervals		
Conventional Analysis	2.44	(1.08-5.53)
Sensitivity Analysis	3.35	(2.60-4.25)
Total Error Analysis	3.34	(1.43-7.85)
Original Main Effects Plus Interactions Adjusted Analysis	2.44	(1.08-5.54)
Sensmac Main Effects Plus Interactions Adjusted Analysis		
Conventional Analysis	2.45	(1.08-5.70)
Sensitivity Analysis	3.35	(2.61-4.28)
Total Error Analysis	3.35	(1.41-7.79)

Table 12: Sensmac Exploratory Sensitivity Analysis Results, 50,000 Iterations, Sensitivity=0.075, Specificity=1.0

Analyses	OR	95% CI
Original Unadjusted Analysis	1.16	(0.77-1.74)
Sensmac Unadjusted Intervals		
Conventional Analysis	1.16	(0.77-1.75)
Sensitivity Analysis	1.17	(1.05-1.31)
Total Error Analysis	1.17	(0.77-1.78)
Original Main Effects Adjusted Analysis	0.99	(0.63-1.57)
Sensmac Main Effects Adjusted Intervals		
Conventional Analysis	0.99	(0.63-1.56)
Sensitivity Analysis	1.16	(1.03-1.31)
Total Error Analysis	1.16	(0.73-1.86)
Original Main Effects Plus Interactions Adjusted Analysis	0.72	(0.41-1.27)
Sensmac Main Effects Plus Interactions Adjusted Analysis		
Conventional Analysis	0.72	(0.40-1.27)
Sensitivity Analysis	1.14	(1.00-1.23)
Total Error Analysis	1.14	(0.63-2.05)

6.0 PAPER THREE: A NATIONAL RATE ESTIMATE AND DESCRIPTIVE EPIDEMIOLOGY OF BIRTH TRAUMA FOR THE UNITED STATES IN 2003

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6.1 ABSTRACT

Objectives: To estimate the national rate of birth trauma, determine the rates of specific types of birth trauma, and report the rates and odds ratios of birth trauma stratified by demographic, hospital, and clinical variables. Methods: A cross-sectional study was conducted using 890,582 in-hospital birth discharges from the 2003 Healthcare Cost and Utilization Project Kids' Inpatient Database. A neonate was defined as having birth trauma if their hospital discharge record contained an ICD-9-CM diagnosis code from 767.0 to 767.9. Weighted data were used to calculate rates for all birth traumas and specific types of birth traumas and rates and odds ratios by demographic, hospital, and clinical variables. Weighted data represented a national estimate

of 3,920,787 in-hospital births. Results: Birth trauma was estimated to occur in 29 per 1,000 births, which extrapolates to a birth trauma diagnosis in 111,989 in-hospital births for the United States in 2003. The three most frequently diagnosed birth traumas were injuries to the scalp, other injuries to the skeleton, and fracture of the clavicle. Independent risk factors for birth trauma included male gender, Asian/Pacific Islander race, living in urban or wealthy areas, being born in Western, urban, and/or teaching hospital, a co-diagnosis of high birth weight, intrauterine hypoxia and birth asphyxia, instrument delivery, malpresentation, and other complications during labor and delivery. Conclusion: Physicians and midwives should consider birth trauma risk factors, including those identified in this study, during labor and delivery in order to prevent birth trauma and therefore reduce infant morbidity and mortality.

6.2 INTRODUCTION

Birth trauma is defined as an injury sustained by the neonate during the process of labor and delivery.[114-116] Birth trauma usually results from trauma sustained during a difficult delivery or secondary to obstetrical manipulation of the fetus to allow for delivery.[116,130] The incidence of birth trauma has reportedly decreased over time due to improvements in obstetrical care and prenatal diagnosis;[117] however, birth trauma still occurs even in the presence of highly skilled obstetrical and neonatal care.[116]

In studies conducted primarily at single hospitals, birth trauma has been estimated to occur in 2-7% of all deliveries and is associated with an increased risk of infant morbidity and mortality.[116,127,128] The few studies that provide population based national birth trauma estimates report rates ranging from 0.2 to 37 birth traumas per 1,000 births.[118,153,154] The various birth

trauma definitions, study populations, and methods used throughout the birth trauma literature make comparisons among or meta-analyses of studies difficult. Due to the minimal number of population based studies and the inconsistencies among the published birth trauma rates, the rate of birth trauma in the United States remains unclear.

The purpose of this study was to determine the rate of birth trauma in the United States through the utilization of a population based sample of in-hospital births. The specific aims were to a) determine a national estimate of the rate of birth trauma, b) determine the rates of specific types of birth trauma and, c) report the rates and odds ratios of birth trauma stratified by demographic, hospital, and various clinical variables.

6.3 MATERIALS AND METHODS

The data source for this study was the 2003 Healthcare Cost and Utilization Project (HCUP) Kids' Inpatient Database (KID). The KID is an ongoing part of HCUP sponsored by the Agency for Healthcare Research and Quality (AHRQ). The KID is the only database on children's hospital use, outcomes, and charges in the United States.[173] The 2003 KID collected hospital discharge data from 3,438 community, non-rehabilitation hospitals in 36 states (AZ, CA, CO, CT, FL, GA, HI, IA, IL, IN, KS, KY, MD, MA, MI, MN, MO, NC, NE, NH, NJ, NV, NY, OH, OR, RI, SC, SD, TN, TX, UT, VA, VT, WA, WI, WV) for the year 2003.[173] Hospital discharges from federal hospitals (Veterans Administration, Department of Defense, and Indian Health Service hospitals), long-term hospitals, psychiatric hospitals, alcohol/chemical dependency treatment facilities, and hospital units within institutions (like prisons) are excluded from the KID.[173] KID is described in further detail elsewhere.[174]

Only in-hospital births were included in this study. In-hospital births were identified in KID as a record with a principal or secondary diagnosis code ranging between V3000 and V3901 (with the last two digits of "00" or "01") and where the patient was not transferred from another facility.[173] After this exclusion, the study sample consisted of 890,582 in-hospital birth discharges from the 2003 KID. Discharge weights were applied to the study sample to adjust the data to represent nationwide birth discharges and obtain national estimates. The KID discharge weights were developed using the American Hospital Association (AHA) universe as the standard and by post-stratification of hospitals on ownership/control, bed size, teaching status, rural/urban location, geographic region, and hospital type (children's hospital or other).[173] After applying the weights, the data represented a weighted national estimate of 3,920,787 in-hospital birth discharges for 2003.

Birth trauma was defined as an International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis code from 767.0 to 767.9 (Appendix B) in any one of the fifteen diagnosis variables in the KID. The ICD-9-CM was "the official system of assigning codes to diagnoses and procedures associated with hospital utilization in the United States" in 2003.[175] Birth trauma was further classified by specific type, including subdural and cerebral hemorrhage (ICD-9-CM 767.0), injuries to the scalp (ICD-9-CM 767.1), fracture of the clavicle (ICD-9-CM 767.2), other injuries to the skeleton (ICD-9-CM 767.3), injury to the spine and spinal cord (ICD-9-CM 767.4), facial nerve injury (ICD-9-CM 767.5), injury to the brachial plexus (ICD-9-CM 767.6), other cranial and peripheral nerve injuries (ICD-9-CM 767.7), other specified birth trauma (ICD-9-CM 767.8), and birth trauma, unspecified (ICD-9-CM 767.9).

All analyses were conducted on the weighted data using SPSS 15.0 (SPSS Inc., Chicago, IL) and SAS version 9.1 (SAS Institute Inc., Cary, North Carolina). SAS's PROC

SURVEYFREQ[176] procedure was used to determine the national estimates of all birth trauma and specific types of birth trauma. These estimates were then used to calculate the rates of all birth trauma and specific types of birth trauma. SAS's PROC SURVEYLOGISTIC [177,178] procedure with the total number of primary sampling units in the study population to compute a finite population correction for Taylor series variance estimation was used to calculate odds ratios, 95% confidence intervals (95% CI), and p-values for several demographic, hospital, and clinical variables. The STRATA, CLUSTER, and WEIGHT statements were also used to specify sample design information in the PROC SURVEYLOGISTIC procedure and to take into account KID's sampling design. This study was approved by the University of Pittsburgh's Institutional Review Board.

6.4 RESULTS

All of the following results are based on the weighted data. The rate of reported birth trauma was 28.56 or approximately 29 per 1,000 in-hospital births (Table 13). This rate extrapolates to a birth trauma diagnosis in approximately 111,989 in-hospital births for the United States in 2003. Injuries to the scalp were the primary type of birth trauma (20.06 per 1,000 births) followed by other injuries to the skeleton (3.70 per 1,000 births), and fracture of the clavicle (2.43 per 1,000 births) (Table 13).

Males had a higher rate and odds ratio of reported birth trauma than females (Table 14). By race, Asian or Pacific Islanders had the highest rate and odd ratio of birth trauma (Table 14). When the data were stratified by location of the patient (based on an urban to rural designation for the patient's county of residence), all patient locations had a reduced rate and odds ratios of

birth trauma compared to patients in large metropolitan locations (Table 14). The data also suggested that patients living in neighborhoods with the two lowest median household income categories (based on the patient's zip code of residence) had lower rates and odds ratios for birth trauma compared to the neighborhoods with the highest median household income (Table 14). When the data were stratified by payer information, only those with Medicare had a significantly reduced odds ratio of reported birth trauma compared to those with private payer (Table 14).

Figure 3 presents the rates per 1,000 in-hospital births of reported birth trauma by state. The 2003 KID includes 36 of the 50 United States; therefore, not all states are represented in Figure 3. The average rate of birth trauma was 27.24 per 1,000 births across all 36 participating states, but the rate ranged from 15.3 cases of reported birth trauma in South Carolina to 57.5 cases of reported birth trauma in Maryland per 1,000 in-hospital births (Figure 3).

Hospitals in the Western United States reported the highest rate and only increased odds ratio of birth trauma, when compared to Southern hospitals (Table 15). There were no significant differences in the rates or odds ratios of birth trauma in among hospitals with different bed sizes (Table 15). When comparing location of the hospital, urban hospitals had a higher rate and odds ratio of reported birth trauma than rural hospitals (Table 15). Stratification by teaching status showed that teaching hospitals had a higher rate and odds ratio of birth trauma than non-teaching hospitals (Table 15). Taking both location and teaching status into account, urban teaching and urban non-teaching hospitals had higher rates and odds ratios of birth trauma than rural hospitals (Table 15).

Of the infants diagnosed with birth trauma 6.8% were co-diagnosed with a complication of labor and delivery; whereas, only 0.9% of the infants not diagnosed with birth trauma were diagnosed with a complication of labor and delivery (data not shown). The corresponding odds

ratio for any complication of labor and delivery for all birth trauma was highly significant (OR=7.93, 95% CI (7.12-8.83) (Table 16). The most frequently diagnosed complications of labor and delivery for infants with reported birth trauma were delivery by vacuum extractor (2.6%) followed by other malpresentation, malposition, and disproportion (2.0%) and forceps delivery (0.9%) (Table 16). Comparatively, only 0.1% of infants without birth trauma were diagnosed with each of the above complications (data not shown). These three complications also had the highest unadjusted odds ratios for the all birth trauma category (Table 16). The diagnosis of a complication of labor and delivery was also highly significant for each of the specific types of birth trauma (Table 16). However, the prevalence of each complication of labor and delivery varied to some degree by the type of birth trauma reported (Table 16).

Infants with low birth weight (<2500 grams) had a lower rate and lower odds ratio of reported birth trauma than normal birth weight infants (2500-3999 grams) (Table 17). Infants with high birth weight (≥4000 grams) had an increased rate and increased odds ratio of reported birth trauma compared to normal birth weight infants (Table 17). Similarly, infants with the Clinical Classification Software (CCS)[179] category diagnosis of short gestation, low birth weight, and/or fetal growth retardation had a lower rate and odds ratio of reported birth trauma than infants without this CCS diagnosis (Table 17). Infants diagnosed with the CCS category of intrauterine hypoxia and birth asphyxia had a higher rate and odds ratio of birth trauma compared to those without this CCS diagnosis (Table 17).

A much higher rate of neonates with birth trauma were considered complicated in-hospital births (Table 18). However, some neonates that were considered to have uncomplicated in-hospital births (in-hospital birth with a Diagnosis Related Group of 391=normal newborn) still experienced birth trauma with a rate of 17.46 cases of birth trauma per 1,000 in-hospital births

(Table 18). The average length of stay for all in-hospital births was 5.27 or approximately five days with a median of two days. The rate of reported birth trauma was highest in neonates with a length of stay equal or greater than five days (Table 18). The odds ratio of birth trauma in the length of stay category of five or more days was not significantly different than infants with a length of stay of two days (Table 18). The average number of diagnoses for all in-hospital births was 2.3 and the average number of procedures was 0.76. The rate and odds ratio of reported birth trauma was highest in those with five diagnoses and three or more procedures (Table 18). Additionally, as the number of procedures increased so did the rates and odds ratios of reported birth trauma (Table 18). Similarly, as the total hospital charges increased so did the rate and odds ratio of reported birth trauma (Table 18). In addition, a higher percent of infants with reported birth trauma compared to those without birth trauma had over $2,585 in total charges (28.6% vs. 24.0%) (data not shown).

When looking at the All Patient Refined Diagnoses Related Group (APR-DRG) severity of illness indicator, those with a major loss of function had the highest rate and highest odds ratio of reported birth trauma followed by moderate loss of function (Table 18). Comparatively, the average APR-DRG severity of illness for all in-hospital births was 1.23 or minor loss of function. Using the APR-DRG risk of mortality indicator, those with a major likelihood of dying had the highest rate and odds ratio of reported birth trauma followed by moderate likelihood of dying. Whereas, the average APR-DRG risk of mortality indicator for all in-hospital births was 1.03 or a minor likelihood of dying. Interestingly, the rate of birth trauma was higher in the infants that did not die during hospitalization versus those who died during hospitalization. Compared to neonates who did not die during hospitalization, the nenonates that died during hospitalization were 41% less likely to have a reported birth trauma (Table 18).

6.5 DISCUSSION

This study's reported birth trauma rate of 28.56 per 1,000 births is higher than many other published rates, but is similar to the rate reported in Tomashek et al. for the years 1999-2000.[154] Tomashek et al. is one of the few studies in the literature that provided a recent national estimate of birth trauma. Their national estimates were derived from the National Hospital Discharge Survey and included 55,210 newborns in 1989-90 and 68,678 newborns in 1999-2000.[154] Tomashek et al. estimated that the rate of birth trauma in all newborns was 37.0 per 1,000 newborns in 1989-1990 and 29.2 per 1,000 newborns in 1999-2000.[154] Similarly, a seven year study conducted in Finland and published in 1990 reported the rate of major birth trauma as 31.6 per 1,000 live births.[180]

Other studies have reported much lower rates of birth trauma. Hankins et al. (2006), through an Ovid Medline literature review restricted to the previous 10 years of literature using the search term "fetal trauma", estimated that the incidence of significant birth trauma varies from 0.2 to 2 per 1,000 births.[153] At a single hospital in Saudi Arabia, Awari et al. (2003) determined that birth injuries had an incidence of 6.7 per 1,000 live births through a retrospective review of the medical records of 31,028 consecutive deliveries from January 1986 to December 1996.[118] The reported rate in Awari et al. is higher than Hankins et al., but much lower than the rate reported in the current study and by Tomashek and colleagues.

Interestingly, this study showed that Asian or Pacific Islanders were more likely to experience birth trauma; however, there were not any clear reasons for the increased risk. For instance, only 1.3% of the Asian or Pacific Islander infants experienced any complications of labor and delivery compared to 1% in all births. Furthermore, of the Asian or Pacific Islander infants with a reported birth weight, 85.9% were normal weight and only 5.7% had a high birth

weight compared to a high birth weight in 9.2% of all births. Some of the increased risk could be due to the fact that Asian or Pacific Islander neonates primarily lived in the wealthiest neighborhoods (41.8%) and were born in urban (95.6%), and Western hospitals (50%). Another possibility for the increased risk could be anatomical, including pelvic, differences among Asian or Pacific Islander women; however, further research is needed.

It is important to point out that neonates with birth trauma have a reduced rate and odds ratio of death during their hospitalization. We speculate that in some cases, choices are made or procedures are performed during labor and delivery to protect the health and lives of both the pregnant woman and fetus, even if they increase the risk of birth trauma. For instance, if a fetus is known to be experiencing hypoxia or birth asphyxia, a physician may make the decision to use vacuum extraction or forceps delivery to reduce the risk of potential adverse health effects due to a lack of oxygen. Although the instrument delivery may cause birth trauma, the benefits of using the instrument to resolve hypoxia/asphyxia will likely outweigh the risks of birth trauma.

Additionally, the birth trauma rate in "normal newborns" with uncomplicated in-hospital births was approximately 18 diagnosed birth traumas per 1,000 in hospital births. This rate is only 11 fewer cases per 1,000 in-hospital births than the overall rate of 29 cases of birth trauma per 1,000 in hospital births. This raises the question of what is an acceptable or normal rate of birth trauma? Even during an uncomplicated natural vaginal delivery the neonate is exposed to several forces as it passes through the birth canal that can cause birth trauma. Therefore, it isn't unreasonable to believe that the birth trauma rate will never be zero and that a specific rate, perhaps approximately 18 per 1,000 in-hospital births, should be considered an acceptable and normal baseline of birth trauma.

This study has several strengths. The Kids' Inpatient Database provides current, quality controlled, and reliable national data with a much larger sample size and more recent data than any previously published birth trauma study. The large sample size also allowed for rate calculations of specific types of birth trauma as well as stratification of the data by key variables.

Our study was limited by the fact that not all data elements in the KID are provided by each state.[173] Therefore, some of the analyses used incomplete data. This has the potential to bias some of the results, but with such a large sample size and through the use of advanced statistical procedures, any resulting biases would be very limited. Another limitation is the possible variation among hospital coding practices. The data in KID rely solely on hospital provided data and are therefore only as complete and accurate as the hospital reports allow. Another potential limitation is that it is unknown whether it is the hospital, the population it serves, or a combination thereof, that is driving the increased risk of birth trauma. Further research is needed to explore this issue. A final limitation is the possibility of confounding. Only diagnoses of birth trauma were taken into account for analyses and, although a majority of birth trauma cases had the same average number of diagnoses as in-hospital births without birth trauma, the potential for confounding due to other diagnoses should be kept in mind when interpreting results.

There are several clinical and public health implications of this study. Through a population based national estimate it was determined that the rate of birth trauma in the United States is higher than a majority of studies have previously reported. Physicians and midwives may have the ability to decrease the number and rate of infants diagnosed with birth trauma by recognizing perinatal risk factors for birth trauma and using technologic advancements (such as ultrasonography and fetal monitory) before attempting a vaginal delivery.[181] In addition, further

birth trauma research, including more in-depth classification (such as an expansion of the work done by Pressler[181]) and follow-up of infants who are diagnosed with birth trauma, will better quantify the morbidity and mortality of birth trauma by type and among infants and women with various birth trauma risk factors. Prevention of birth trauma will also reduce the number of stresses that it places on the health care system because, neonates with birth trauma were shown in this study to have higher costs, greater lengths of stay, and have more medical procedures than neonates not diagnosed with birth trauma. Simply stated, preventing birth trauma will reduce infant morbidity and mortality and reduce the stresses it places on the health care system.

6.6 PAPER THREE TABLES AND FIGURE

Table 13: Number and Rate per 1,000 In-Hospital Births of Reported Birth Trauma in the United States, 2003 by Type of Birth Trauma

Type of Birth Trauma (ICD-9 code(s))	Un-weighted N	Weighted Estimate	Std Dev of Weighted Estimate	*Weighted Rate per 1,000 Births
All Birth Trauma (767.0-767.9)	44,658	111,989	3,227	28.56
Injuries to the Scalp (767.1)	22,764	78,644	2,487	20.06
Other Injuries to the Skeleton (767.3)	9,525	14,499	1,160	3.70
Fracture of the Clavicle (767.2)	6,353	9,545	300.10	2.43
Other Specified Birth Trauma (767.8)	3,994	6,136	289.94	1.56
Injury to the Brachial Plexus (767.6)	3,302	5,021	143.06	1.28
Subdural and Cerebral Hemorrhage (767.0)	1,064	1,599	77.49	0.41
Facial Nerve Injury (767.5)	661	1,014	50.69	0.26
Birth Trauma, unspecified (767.9)	218	339	32.25	0.09
Other Cranial and Peripheral Nerve Injuries (767.7)	124	192	18.39	0.05
Injury to the Spine and Spinal Cord (767.4)	10	15	4.79	0.00
Total Number of Births	890,582	3,920,787	61,581	

* Birth Trauma Rate per 1,000 in-hospital births
Std Dev=Standard Deviation

Table 14: Univariate Analysis of Infants Diagnosed with Birth Trauma by Demographic Variables (weighted), KID 2003

Demographic Variables	N_{WE}	N_{BT}	*Rate per 1,000	OR	(95% CI)	p-value	Percent Missing
Infant Gender						<0.001	0.6%
Female	1,900,219	47,439	24.97	1.00	(Ref)		
Male	1,997,286	63,996	32.04	1.29	(1.25-1.34)		
Race						<0.001	28.4%
White	1,486,381	41,877	28.17	1.00	(Ref)		
Hispanic	665,940	19,240	28.89	1.03	(0.93-1.14)		
Black	354,448	8,888	25.08	0.89	(0.81-0.98)		
Other	169,286	4,736	27.98	0.99	(0.88-1.12)		
Asian or Pacific Islander	118,592	4,692	39.56	1.42	(1.25-1.62)		
Native American	13,178	249	18.90	0.67	(0.48-0.92)		
Location of the Patient						<0.001	0.3%
Large Metropolitan	2,279,144	71,524	31.38	1.00	(Ref)		
Small Metropolitan	1,070,318	26,750	24.99	0.79	(0.71-0.88)		
Micropolitan	347,542	8,778	25.30	0.80	(0.71-0.90)		
Non-Core	210,552	4,571	21.71	0.69	(0.59-0.79)		
Median Household Income for Patient's Zip Code						<0.001	1.6%
$60,000+	931,933	29,185	31.32	1.00	(Ref)		
$45,000-59,999	989,247	29,366	29.69	0.95	(0.88-1.02)		
$36,000-44,999	977,151	26,550	27.17	0.86	(0.79-0.94)		
$1-35,999	958,347	24,978	26.06	0.83	(0.75-0.92)		
Payer Information						<0.001	0.1%
Private (including HMO)	2,092,341	60,531	28.93	1.00	(Ref)		
Medicaid	1,515,240	43,123	28.46	0.98	(0.92-1.05)		
Self-pay	187,648	5,074	27.04	0.93	(0.83-1.05)		
Other	109,885	2,853	25.96	0.90	(0.72-1.12)		
No Charge	5,521	210	38.04	1.33	(0.88-2.00)		
Medicare	4,917	100	20.33	0.70	(0.49-0.995)		

* Birth Trauma Rate per 1,000 in-hospital births
N_{WE} =Weighted estimate of the total number births by stratum
N_{BT}=Weighted estimate of the number of infants with reported birth trauma
OR=Odds Ratio
CI=Confidence Interval

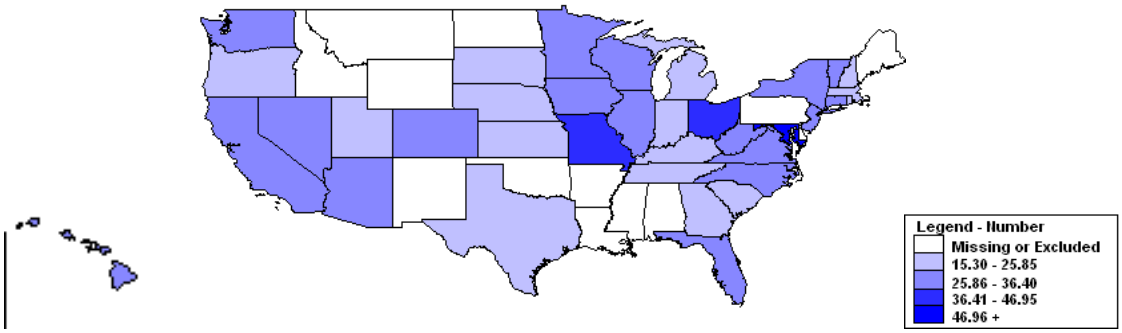

Figure 3. Rates of reported birth trauma per 1,000 in-hospital births by state, KID 2003

Table 15: Univariate Analyses of Birth Trauma by Hospital Variables (weighted), KID 2003

Hospital Variables	N_{WE}	N_{BT}	* Rate per 1,000	OR	(95% CI)	p-value	Percent Missing
Region of Hospital						<0.001	0.0%
South	1,446,837	39,283	27.15	1.00	(Ref)		
West	929,069	29,315	31.55	1.17	(1.02-1.33)		
Midwest	870,745	24,924	28.62	1.06	(0.92-1.21)		
Northeast	674,136	18,468	27.40	1.01	(0.87-1.17)		
Hospital Bed Size						<0.001	0.6%
Large	2,463,598	69,758	28.32	1.00	(Ref)		
Medium	1,031,358	30,418	29.49	1.04	(0.93-1.17)		
Small	400,879	11,296	28.18	1.00	(0.86-1.15)		
Location of Hospital						<0.001	0.6%
Rural	524,470	12,315	23.48	1.00	(Ref)		
Urban	3,371,364	99,157	29.41	1.26	(1.12-1.42)		
Teaching Status of Hospital						0.002	0.6%
Non-teaching	2,190,842	58,352	26.64	1.00	(Ref)		
Teaching	1,704,992	53,120	31.16	1.18	(1.06-1.30)		
Location & Teaching Status of Hospital						<0.001	0.6%
Rural	524,470	12,315	23.48	1.00	(Ref)		
Urban Non-teaching	1,711,037	47,273	27.63	1.18	(1.05-1.33)		
Urban Teaching	1,660,328	51,884	31.25	1.34	(1.17-1.54)		

* Birth Trauma Rate per 1,000 in-hospital births
N_{WE} =Weighted estimate of the total number births by stratum
N_{BT}=Weighted estimate of the number of infants with reported birth trauma
OR=Odds Ratio
CI=Confidence Interval

Table 16: Univariate Analyses of Complications of Labor and Delivery by Birth Trauma Type (weighted), KID 2003

	All Birth Trauma		Injuries to Scalp		Fracture of Clavicle		Other Injuries to Skeleton		Facial Nerve Injury		Injury to Brachial Plexus		Other Specified Birth Trauma	
Complications of Labor and Delivery	**OR**	**(95% CI)**	**OR**	**(95% CI)**	**OR**	**(95% CI)**	**OR**	**(95% CI)**	**OR**	**(95% CI)**	**OR**	**(95% CI)**	**OR**	**(95% CI)**
Complications of Labor and Delivery (ICD9 763.0-763.9)	7.93	(7.12-8.83)	7.00	(6.19-7.92)	6.14	(5.34-7.05)	6.02	(5.03-7.20)	9.65	(7.22-12.90)	24.48	(21.39-28.02)	8.98	(7.52-10.72)
Breech Delivery and Extraction (763.0)	1.35	(1.07-1.70)	0.17	(0.09-0.32)	0.78	(0.32-1.92)	3.30	(2.18-4.99)	3.06	(0.76-12.40)	1.23	(0.45-3.31)	11.95	(8.68-16.46)
Other Malpresentation, malposition, and disproportion (763.1)	13.74	(11.97-15.77)	5.26	(4.31-6.42)	25.31	(21.56-29.72)	9.21	(7.46-11.39)	8.21	(4.47-15.06)	128.78	(112.08-147.96)	9.42	(6.89-12.88)
Forceps Delivery (763.2)	16.34	(12.90-20.70)	14.77	(11.15-19.57)	4.72	(2.97-7.49)	9.23	(6.45-13.21)	76.07	(52.99-109.21)	10.70	(7.10-16.13)	34.50	(25.54-46.59)
Delivery by Vacuum Extractor (763.3)	20.91	(17.67-24.74)	25.42	(21.38-30.21)	5.15	(3.87-6.83)	9.81	(7.67-12.55)	4.76	(2.25-10.07)	6.03	(4.27-8.52)	5.17	(3.63-7.37)
Cesarean Delivery (763.4)	3.74	(2.08-6.72)	3.03	(1.66-5.52)	*		3.08	(1.21-7.85)	5.17	(0.80-33.64)	*		22.98	(10.97-48.14)
Maternal Anesthesia and Analgesia (763.5)	2.02	(1.39-2.95)	1.83	(1.04-3.24)	2.50	(1.05-5.92)	2.23	(0.98-5.04)	*		3.01	(1.04-8.70)	1.27	(0.31-5.17)
Precipitate Delivery (763.6)	2.22	(1.34-3.68)	1.83	(0.87-3.87)	1.88	(0.61-5.82)	2.35	(0.70-7.85)	*		2.94	(0.93-9.24)	8.97	(4.73-17.00)
Abnormal Uterine Contractions (763.7)	4.09	(2.75-6.08)	4.72	(3.00-7.43)	*		1.89	(0.57-6.21)	*		13.26	(5.75-30.61)	*	
Other Specified Complications of Labor and Delivery (763.8-763.84, 763.9)	3.16	(2.73-3.66)	3.34	(2.78-4.03)	1.03	(0.74-1.44)	3.60	(2.64-4.90)	2.53	(1.22-5.26)	2.01	(1.31-3.09)	3.82	(2.87-5.08)
Unspecified Complication of Labor and Delivery (763.9)	2.11	(0.88-5.08)	0.78	(0.19-3.17)	*		1.89	(0.27-13.33)	*		22.54	(6.59-77.12)	5.36	(0.72-39.88)

* a cell in the two by two table contained a zero
OR=Odds Ratio
CI=Confidence Interval

Table 17: Rate and Odds Ratio of Specific Neonatal Diagnoses in Birth Trauma Cases (weighted), KID 2003

Neonatal Diagnoses	N_{EW}	N_{BT}	* Rate per 1,000	OR	(95% CI)	p-value	Percent Missing
Birth Weight						<0.001	78.1%
Low (<2500 g)	76,990	1,300	16.89	0.54	(0.47-0.62)		
Normal (2500-3999 g)	702,695	21,534	30.65	1.00	(Ref)		
High (≥4000 g)	78,952	3,710	46.99	1.56	(1.41-1.72)		
†Short Gestation; Low Birth Weight; and Fetal Growth Retardation						<0.001	0.0%
Yes	448,673	10,486	23.37	0.80	(0.72-0.88)		
No	3,472,114	101,504	29.23	1.00	(Ref)		
†Intrauterine Hypoxia and Birth Asphyxia						<0.001	0.0%
Yes	18,752	1,201	64.05	2.35	(2.14-2.58)		
No	3,902,035	110,789	28.39	1.00	(Ref)		

*Birth Trauma Rate per 1,000 in-hospital births
†Category from Clinical Classification Software
N_{WE} =Weighted estimate of the total number births by stratum
N_{BT}=Weighted estimate of the number of infants with reported birth trauma
OR=Odds Ratio
CI=Confidence Interval
g=grams

Table 18: Rate and Odds Ratio of Severity Indicators in Birth Trauma Cases (weighted), KID 2003

Severity Indicators	N_{EW}	N_{BT}	* Rate per 1,000	OR	(95% CI)	p-value	Percent Missing
In-Hospital Birth Type						<0.001	0.0%
Complicated birth	2,939,665	60,657	61.82	3.71	(3.49-3.94)		
Uncomplicated birth	981,122	51,332	17.46	1.00	(Ref)		
Length of Stay (days)						<0.001	0.0%
0	50,024	801	16.01	0.50	(0.43-0.57)		
1	695,598	15,750	22.64	0.71	(0.66-0.76)		
2	2,010,960	63,801	31.73	1.00	(Ref)		
3	641,915	15,665	24.40	0.76	(0.72-0.81)		
4	247,479	6,985	28.23	0.89	(0.82-0.96)		
5+	274,811	8,988	32.71	1.03	(0.97-1.10)		
Number of Diagnoses						<0.001	0.0%
1	1,577,566	0	0.00	†			
2	1,182,679	29,221	24.71	1.00	(Ref)		
3	562,739	34,060	60.53	2.54	(2.36-2.74)		
4	252,729	22,292	88.21	3.82	(3.52-4.15)		
5	122,926	11,602	94.38	4.11	(3.76-4.51)		
6+	222,149	14,813	66.68	2.82	(2.56-3.11)		
Number of Procedures						<0.001	0.0%
0	1,929,510	49,731	25.77	1.00	(Ref)		
1	1,418,424	43,101	30.39	1.19	(1.11-1.26)		
2	403,266	13,446	33.34	1.30	(1.17-1.45)		
3+	169,587	5,712	33.68	1.32	(1.19-1.46)		
Total Charges						<0.001	3.3%
$0-1,093	949,224	22,433	23.63	1.00	(Ref)		
$1,094-1,602	948,272	26,352	27.79	1.18	(1.08-1.29)		
$1,603-2,584	946,681	28,040	29.62	1.26	(1.14-1.39)		
$2,585+	947,877	32,077	33.84	1.45	(1.30-1.61)		
All Patient Refined DRG: Severity of Illness Subclass						<0.001	0.0%
No Class Specified	1,932	74	21.41	0.81	(0.54-1.23)		
‡Minor Loss of Function	833,576	84,012	26.17	1.00	(Ref)		
Moderate Loss of Function	35,201	20,426	39.02	1.51	(1.44-1.58)		
Major Loss of Function	12,463	6,699	43.64	1.70	(1.61-1.79)		
Extreme Loss of Function	7,410	779	26.13	1.00	(0.89-1.12)		
All Patient Refined DRG: Risk of Mortality Subclass						<0.001	0.0%
No Class Specified	1,932	74	21.41	0.75	(0.49-1.13)		
Minor Likelihood of Dying	517,929	109,000	28.45	1.00	(Ref)		
Moderate Likelihood of Dying	250,548	1,823	34.16	1.21	(1.11-1.31)		
Major Likelihood of Dying	100,353	801	42.74	1.52	(1.36-1.71)		
Extreme Likelihood of Dying	19,820	292	21.81	0.76	(0.54-1.07)		
Died During Hospitalization						<0.001	0.0%
Did Not Die During Hospitalization	3,907,761	111,752	28.60	1.00	(Ref)		
Died During Hospitalization	12,306	210	17.07	0.59	(0.49-0.70)		

*Birth Trauma Rate per 1,000 in-hospital births
†A cell in the two by two table contained a zero (a cell)
‡includes cases with no co-morbidity or complications
N_{WE} =Weighted estimate of the total number births by stratum
N_{BT}=Weighted estimate of the number of infants with reported birth trauma
OR=Odds Ratio
CI=Confidence Interval

7.0 OVERALL DISCUSSION

7.1 SUMMARY OF FINDINGS

Through three individual research questions and papers, this dissertation examined the association of injury during pregnancy and nervous system birth defects, applied an underutilized method of exposure misclassification analyses to better quantify injury's role in nervous system birth defects, and determined a national rate estimate of birth trauma. In summary, it was determined through the first two papers that among a study population of live born infants with a non-chromosomal birth defect in the Texas Birth Defects Registry 1999-2003, there was a significant association between injury during pregnancy and nervous system birth defects for breech presentation infants and no association between injury during pregnancy and nervous system birth defects among normal presentation infants and among the entire study population, even when accounting for exposure misclassification. The third paper determined that the national rate of birth trauma is higher than a majority of previously published literature with 29 per 1,000 in-hospital births being diagnosed with birth trauma in the United States in 2003. Although each paper addressed different gaps and/or weaknesses in the literature, together the papers highlighted injury's role during the perinatal period for maternal and child health.

7.2 PUBLIC HEALTH SIGNIFICANCE

This dissertation work is important both in the context of injury research and maternal and child health by taking some of the first steps toward exploring injury's role in nervous system birth defects and injury in the form of birth trauma. Beyond findings in case studies and series, injury during pregnancy has never been considered as a causal or contributing factor for birth defects. The first paper of this dissertation tested the association between injury during pregnancy and nervous system birth defects through a case-control study. This study attempted to explain one of the many unknown causes of birth defects.

This paper is of public health significance due to the infant and often life long morbidity and mortality associated with birth defects and the fact that 65-70% of birth defects are due to unknown causes. Since injury during pregnancy was identified as a significant risk factor for nervous system birth defects among breech presentation infants, ways to prevent injury during pregnancy and subsequent nervous system birth defects among this specific population should be further explored to help reduce the public health burden of birth defects. Beyond nervous system birth defects, the literature has shown that injury during pregnancy is also associated with a myriad of adverse maternal, fetal, and child outcomes. Therefore, through injury mechanisms including direct injury, reproductive organ injury, iatrogenic effects, hypoxia or ischemia, and stress, injury during pregnancy should continue to be researched as a risk factor for nervous system birth defects as well as other unexplored adverse maternal, fetal, and child outcomes.

The third paper in this dissertation identified birth trauma as a more common form of injury than was previously thought. This is of public health significance because birth trauma increases infant morbidity and mortality. Therefore, if birth trauma is occurring more frequently

than previously estimated, ways to prevent or lessen the effects of birth trauma should be explored and implemented by public health professionals.

This dissertation also highlights the need for better injury surveillance systems, injury data collection, and further research considering injury during pregnancy and birth trauma as a risk factor for adverse maternal, fetal, and child outcomes. If a national or even several state based injury surveillance systems were put into place, studies on the effects of injury for various outcomes, including maternal and child health related outcomes, could be better explored. Additionally, studies looking at injury timing, severity, and specific mechanisms could be conducted to help tease out associations between outcomes and the specific types, severities, and timings of injury. This improved data collection from what is currently available (in most cases) would aid injury and maternal and child health researchers to identify risk factors for adverse maternal and child health outcomes and suggest ways to prevent or lessen the burden of these outcomes.

7.3 STRENGTHS AND WEAKNESSES

Each of the three research papers presented in this dissertation had its own strengths and weaknesses. These strengths and weaknesses were discussed in their respective discussion sections; however there were some common strengths and weaknesses related to researching injury during the perinatal period that were identified.

One strength of this dissertation was the availability of databases for secondary data analyses. Specifically, the availability of the Texas Birth Defects Registry (TBDR) and the HCUP Kids Inpatient Database (KID) to researchers and students made this work possible.

Performing a prospective study to solely examine the research questions explored in this dissertation would not have been feasible due to time and funding constraints. Another common strength of this dissertation was the availability of sophisticated statistical analyses to deal with unique qualities and analytical needs of the data. For instance, the SAS macro sensmac was used to determine the odds ratio and 95% confidence interval of the association between injury during pregnancy and nervous system birth defects. This provided a more precise testing of the association while taking into account the limitation of exposure misclassification in the data. Another example of sophisticated statistical analyses was the use of the new SAS procedures PROC SURVEYLOGISTIC and PROC SURVEYFREQ. These procedure statements allowed for the analysis of KID for the birth trauma paper while taking into account the complex sampling of the KID data.

Common weaknesses throughout the dissertation include the limited availability of data, lacking detailed injury information, and no long term follow-up of cases. There is limited data available that contains both the exposure and outcomes of interest for this dissertation's research questions. Therefore, even though there were known limitations in the databases, they were used and allowed for some of the first explorations into the paper topics. Specifically, it was known that exposure misclassification of injury during pregnancy in the TBDR was a limitation, but this was also one of the only databases that contained both the exposure and outcome of interest. The lacking detail in the injury information, especially in the TBDR, did not allow for further exploration into how the timing, severity, and various mechanisms of injury affected the outcomes of interest. Finally, neither the TBDR nor the KID performed long term follow-up. Therefore, other milder or later developing adverse maternal and child outcomes could not be explored in this dissertation. Regardless of these weaknesses, this dissertation took some of the

first steps toward researching the role of injury in nervous system birth defects and injury in the form of birth trauma, both of which contribute significant to infant morbidity and mortality and are therefore important to research.

7.4 FUTURE RESEARCH

Injury research during the perinatal period is limited due to the availability of data, quality of data, funding, and traditional ideals of injury being a chance occurrence. The research conducted in this dissertation took some of the first steps toward determining if injury during pregnancy was associated with nervous system birth defects and determining a national rate estimate of birth trauma in the United States, as well as using sophisticated exposure misclassification analyses. There are several more steps to take in many different directions in order for injury's role in the perinatal period to be thoroughly researched. To build on the work done in this dissertation, other databases could be linked in order to repeat the analyses performed and to build on the idea that timing of injury, severity of injury, and mechanism of injury are important factors for the outcomes of interest (since these factors were not able to be assessed in this dissertation).

Ideally, if prospective large scale studies (such as the National Children's Study) would incorporate exposure questions on maternal injury during pregnancy, include birth trauma information, and capture timing, severity, mechanism, and other detailed injury information; several of the weaknesses identified in the literature and in the present work could be addressed. In general, prospective studies of injury during pregnancy and labor and delivery would be time consuming, costly to conduct, and an adequate sample size may be difficult to obtain. Therefore,

performing nested studies within large prospective studies maybe the best solution to getting the information necessary to conduct specific injury studies, without wasting valuable research funding and time.

7.5 CONCLUSIONS

Rees and Harding point out that "only in the last few decades have we come to understand just how significantly our life outside the uterus is determined by our 40 or so weeks with in it."[63] This dissertation took several steps toward researching injury during the perinatal period as it relates to nervous system birth defects, re-testing an association that was known to be affected by exposure misclassification, and determining the burden of birth trauma in the United States. Nevertheless, there is still much research to be done to determine how and all the ways that injury during pregnancy and labor and delivery affect the health of the pregnant woman, fetus, neonate, and child.

APPENDIX A. Paper One Appendices

A.1 SIX-DIGIT CODES FOR REPORTABLE CONGENITAL ANOMALIES OF THE NERVOUS SYSTEM

The following codes are based on the British Pediatric Association (BPA) Classification of Diseases (1979) and the World Health Organization's International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) (1979).

742 Other Congenital Anomalies of Nervous System

742.0 Encephalocele-

742.000	Occipital encephalocele
	Occipital meningocele
	Posterior encephalocele
	Occipitocervical encephalocele
742.080	Other encephalocele of specified site (includes midline defects)
	Sphenoid encephalocele
742.085	Frontal encephalocele
	Frontonasal encephalocele
742.086	Parietal encephalocele
742.090	Unspecified encephalocele

742.1 Microcephalus

742.100	Microcephalus
	Small head

742.2 Reduction deformities of brain

742.200	Anomalies of cerebrum
	Anomalies of frontal lobes
	Anomalies of cortex (brain)
	Excludes: Cortical atrophy (Use 742.480)

742.210 Anomalies of corpus callosum
Hypoplasia of septum pellucidum
742.220 Anomalies of hypothalamus
742.230 Anomalies of cerebellum
Anomalies of inferior vermis
Cerebellar atrophy
Posterior fossa cyst (not associated with Dandy-Walker malformation)
Vermian atrophy
742.240 Agyria and lissencephaly
742.250 Microgyria, polymicrogyria
742.260 Holoprosencephaly
Fused thalami
742.270 Arrhinencephaly
Absent olfactory nerve
Hypoplastic olfactory nerve
742.280 Other specified reduction defect of brain
Includes: Colpocephaly
Pachygyria
Schizencephaly
Pontine hypoplasia
Hypoplastic thalamus
Reduction defect of brainstem
Hypoplastic brainstem
Small brainstem
742.290 Unspecified reduction defect of brain

742.3 Congenital hydrocephalus

Excludes: Hydrocephalus with any condition in 741.9 (Use 741.0)

742.300 Anomalies of aqueduct of Sylvius
Includes: Aqueductal stenosis
742.310 Atresia of foramina of Magendie and Luschka
Dandy-Walker syndrome 1
Special instructions:
1 *If a diagnosis of Dandy-Walker syndrome is made, do not list and code the hypoplasia/aplasia of the cerebellar vermis or the dilated fourth ventricle separately.*
742.320 Hydranencephaly
742.380 Other specified hydrocephaly
Includes: Communicating hydrocephaly
Enlarged cisterna magna
Non-communicating hydrocephaly
742.390 Unspecified hydrocephaly, NOS
Enlarged ventricles
Ventriculomegaly
Dilation ventricles

742.4 Other specified anomalies of brain

742.400 Enlarged brain and/or head
Megalencephaly 1
Macrocephaly 1
Special instructions:
1 *Never code in the presence of hydrocephaly.*

742.410 Porencephaly
Includes: Porencephalic cysts 1
Special instructions:
1 *Never code if secondary to intraventricular hemorrhage.*

742.420 Cerebral cysts
Subependymal cyst
Periventricular cyst
Intracranial cyst
Corpus callosum cyst
Ependymal cysts
Glioependymal cysts

742.480 Other specified anomalies of brain
Includes: Cortical atrophy
Cranial nerve defects
Anomalies of brainstem
Cerebral atrophy
Arnold-Chiari malformation without spina bifida
Cortical dysplasia (cerebral)
Excludes: Reduction defect of brainstem (Use 742.280)

742.485 Ventricular cysts
Choroid plexus cyst 1
Excludes: Arachnoid cysts
Special instructions:
1 *Code only if there are multiple cysts that were diagnosed postnatally.*

742.486 Small brain

742.5 Other specified anomalies of spinal cord

742.500 Amyelia

742.510 Hypoplasia and dysplasia of spinal cord
Atelomyelia
Myelodysplasia

742.520 Diastematomyelia

742.530 Other cauda equina anomalies

742.540 Hydromyelia
Hydrorachis
Syringohydromyelia
Syringomyelia

742.580 Other specified anomalies of spinal cord and membranes
Includes: Congenital tethered cord

742.8 Other specified anomalies of nervous system

Excludes: Congenital oculofacial paralysis
Moebius syndrome (Use 352.600)

742.800 Jaw-winking syndrome
Marcus Gunn syndrome

742.810 Familial dysautonomia
Riley-Day syndrome

742.880 Other specified anomalies of nervous system
Septo-optic dysplasia
Walker-Warburg syndrome

742.9 Unspecified anomalies of brain, spinal cord and nervous systems

742.900 Brain, unspecified anomalies

742.910 Spinal cord, unspecified anomalies

742.990 Nervous system, unspecified anomalies

A.2 EXPOSURE VARIABLES BY INJURY DURING PREGNANCY STATUS

Table 19: Exposure Variables by Injury During Pregnancy Status, Texas Birth Defects Registry 1999-2003

			Injury During Pregnancy				Missing
Exposure Variables	**N**	**%**	**Yes**	**%**	**No**	**%**	**N**
Prenatal Care During Pregnancy							23,526
No	2,725	7.52	9	3.90	2,716	7.55	
Yes	33,499	92.48	222	96.10	33,277	92.45	
Alcohol During Pregnancy							0
No	56,422	94.43	279	88.57	56,143	94.46	
Yes	3,328	5.57	36	11.43	3,292	5.54	
Tobacco During Pregnancy							0
No	53,720	89.91	244	77.46	53,476	89.97	
Yes	6,030	10.09	71	22.54	5,959	10.03	
Any Diabetes During Pregnancy							0
No	54,979	92.02	292	92.70	54,687	92.01	
Yes	4,771	7.98	23	7.30	4,748	7.99	
Any Bleeding During Pregnancy							0
No	58,586	98.05	301	95.56	58,285	98.07	
Yes	1,164	1.95	14	4.44	1,150	1.93	
Hypertension During Pregnancy							0
No	57,713	96.59	304	96.51	57,409	96.59	
Yes	2,037	3.41	11	3.49	2,026	3.41	
Epilepsy/Seizures During Pregnancy							0
No	59,537	99.64	313	99.37	59,224	99.64	
Yes	213	0.36	2	0.63	211	0.36	
Family History of Birth Defect Any Relative							0
No	53,428	89.42	271	86.03	53,157	89.44	
Yes	6,322	10.58	44	13.97	6,278	10.56	
Parent with a Birth Defect							0
No	57,315	95.92	297	94.29	57,018	95.93	
Yes	2,435	4.08	18	5.71	2,417	4.07	

A.3 INFANT AND PREGNANCY VARIABLES BY INJURY DURING PREGNANCY STATUS

Table 20: Infant and Pregnancy Variables by Injury During Pregnancy Status, Texas Birth Defects Registry 1999-2003

			Injury During Pregnancy				Missing
Infant and Pregnancy Variables	**N**	**%**	**Yes**	**%**	**No**	**%**	**N**
Birth Year							
1999	10,725	17.95	47	14.92	10,678	17.97	
2000	11,728	19.63	43	13.65	11,685	19.66	
2001	11,759	19.68	67	21.27	11,692	19.67	
2002	12,571	21.04	70	22.22	12,501	21.03	
2003	12,967	21.70	88	27.94	12,879	21.67	
Gender							57
Female	23,698	39.70	120	38.10	23,578	39.71	
Male	35,995	60.30	195	61.90	35,800	60.29	
First Pregnancy							910
No	39,343	66.86	201	63.81	39,142	66.88	
Yes	19,497	33.14	114	36.19	19,383	33.12	
Gestational Age							2,015
<=27 weeks	2,494	4.32	11	3.59	2,483	4.32	
28-32 weeks	3,171	5.49	16	5.23	3,155	5.49	
33-36 weeks	8,070	13.98	53	17.32	8,017	13.96	
>37 weeks	44,000	76.21	226	73.86	43,774	76.22	
Birth Weight							8
<500 grams	552	0.92	1	0.32	551	0.93	
501-1499 grams	3,632	6.08	21	6.67	3,611	6.08	
1500-2499 grams	7,728	12.94	45	14.29	7,683	12.93	
2500-3999 grams	43,210	72.33	229	72.70	42,981	72.33	
>=4000 grams	4,620	7.73	19	6.03	4,601	7.74	
Birth Weight (Low, Normal or High)							3,640
Low (<2500 grams)	11,920	19.95	67	21.27	11,853	19.94	
Normal (2500-3999 grams)	43,210	72.32	229	72.70	42,981	72.32	
High (>=4000 grams)	4,620	7.73	19	6.03	4,601	7.74	
Abnormal Presentation at Delivery							0
No	59,666	99.86	314	99.68	59,352	99.86	
Yes	84	0.14	1	0.32	83	0.14	
Breech Presentation at Delivery							0
No	53,749	89.96	275	87.30	53,474	89.97	
Yes	6,001	10.04	40	12.70	5,961	10.03	
Hydramnios							0
No	58,189	97.39	304	96.51	57,885	97.39	
Yes	1,561	2.61	11	3.49	1,550	2.61	
Umbilical Cord Complications							0

No	51,734	86.58	261	82.86	51,473	86.60	
Yes	8,016	13.42	54	17.14	7,962	13.40	
Head Circumference by Gender at Birth							3,842
<25% of normal values	35,605	63.68	197	67.70	35,408	63.66	
25-50% of normal values	16,501	29.51	74	25.43	16,427	29.54	
>75% of normal values	3,802	6.80	20	6.87	3,782	6.80	
Length of Infant by Gender at Birth							2,558
<25% of normal values	27,048	47.29	148	49.01	26,900	47.28	
25-50% of normal values	18,094	31.64	99	32.78	17,995	31.63	
>75% of normal values	12,050	21.07	55	18.21	11,995	21.08	
Number of Birth Defects							0
1	26,962	45.12	135	42.86	26,827	45.14	
2	12,510	20.94	60	19.05	12,450	20.95	
3	7,175	12.01	44	13.97	7,131	12.00	
4	4,270	7.15	20	6.35	4,250	7.15	
5	2,515	4.21	14	4.44	2,501	4.21	
6	1,551	2.60	8	2.54	1,543	2.60	
7	1,071	1.79	9	2.86	1,062	1.79	
8	814	1.36	9	2.86	805	1.35	
9	578	0.97	1	0.32	577	0.97	
10+	2,304	3.86	15	4.76	2,289	3.85	
Infant Died During First Year of Life							0
No	57,049	95.48	16	5.08	2,685	4.52	
Yes	2,701	4.52	299	94.92	56,750	95.48	
Number of Live Births (including current)							970
One	23,865	39.94	145	46.03	23,720	40.57	
Two	18,344	30.70	95	30.16	18,249	31.21	
Three	10,130	16.95	47	14.92	10,083	17.25	
Four	4,090	6.85	18	5.71	4,072	6.96	
Five or More	2,351	3.93	10	3.17	2,341	4.00	
Number of Pregnancies (including current)			315		58,465		910
One	19,497	32.63	114	36.19	19,383	33.12	
Two	16,544	27.69	79	25.08	16,465	28.13	
Three	11,237	18.81	59	18.73	11,178	19.10	
Four	6,167	10.32	26	8.25	6,141	10.49	
Five	2,907	4.87	29	9.21	2,878	4.92	
Six or more	2,488	4.16	8	2.54	2,480	4.24	

A.4 GEOGRAPHICAL VARIABLES BY INJURY DURING PREGNANCY STATUS

Table 21: Geographical Variables by Injury During Pregnancy Status, Texas Birth Defects Registry 1999-2003

			Injury During Pregnancy			
Geographical Variables	**N**	**%**	**Yes**	**%**	**No**	**%**
County of Residence on Texas Mexico Border						
Non-Border County	52,684	88.17	288	91.43	52,396	88.16
Border County	7,066	11.83	27	8.57	7,039	11.84
Texas Public Health Region Number						
1	2,155	3.61	20	6.35	2,135	3.59
2	1,199	2.01	5	1.59	1,194	2.01
3	19,187	32.11	54	17.14	19,133	32.19
4	2,123	3.55	17	5.40	2,106	3.54
5	1,200	2.01	3	0.95	1,197	2.01
6	11,768	19.70	30	9.52	11,738	19.75
7	5,657	9.47	65	20.63	5,592	9.41
8	5,829	9.76	52	16.51	5,777	9.72
9	1,370	2.29	12	3.81	1,258	2.28
10	1,674	2.80	9	2.86	1,665	2.80
11	7,588	12.70	48	15.24	7,540	12.69

A.4.1 Texas Public Health Regions

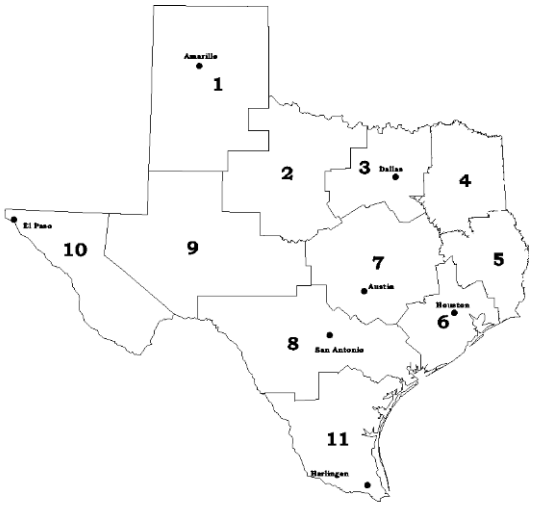

Figure 4. Map of Texas Public Health Regions[158]

A.5 PATERNAL VARIABLES BY INJURY DURING PREGNANCY STATUS

Table 22: Paternal Variables by Injury During Pregnancy Status, Texas Birth Defects Registry 1999-2003

			Injury During Pregnancy				Missing
Paternal Variables	**N**	**%**	**Yes**	**%**	**No**	**%**	**N**
Race							9,407
White	43,901	87.20	201	87.39	43,700	87.20	
Black	4,914	9.76	24	10.43	4,890	9.76	
Asian or Pacific Islander	982	1.95	4	1.74	978	1.95	
Native American	120	0.24	0	0.00	120	0.24	
Central or South American Indian or Asian Indian	426	0.85	1	0.43	425	0.85	
White or Non-White							9,407
White	43,901	87.20	201	87.39	43,700	87.20	
Non-White	6,442	12.80	29	12.61	6,413	12.80	
Hispanic or Non-Hispanic							9,397
Non-Hispanic	27,892	55.39	124	53.91	27,768	55.40	
Hispanic	22,461	44.61	106	46.09	22,355	44.60	
Hispanic Origin							10,612
Non-Hispanic	27,892	46.68	124	55.86	27,768	56.77	
Mexican	19,951	33.39	95	42.79	19,856	40.59	
Puerto Rican	168	0.28	0	0.00	168	0.34	
Cuban	58	0.10	0	0.00	58	0.12	
Central South American	1,069	1.79	3	1.35	1,066	2.18	
Birth Place							10,290
United States	34,743	58.15	192	84.58	34,551	70.18	
Mexico	10,614	17.76	23	10.13	10,591	21.51	
Other	4,103	6.87	12	5.29	4,091	8.31	
High School Education							10,579
Less than High School Education	13,669	27.80	60	26.55	13,609	27.80	
Greater than High School Education	35,502	72.20	166	73.45	35,336	72.20	

APPENDIX B. Paper Three Appendices

ICD-9-CM BIRTH TRAUMA CODES (767)

767.0 Subdural and cerebral hemorrhage
(http://icd9cm.chrisendres.com/index.php?action=child&recordid=7466)

Subdural and cerebral hemorrhage, whether described as due to birth trauma or to intrapartum anoxia or hypoxia
Subdural hematoma (localized)
Tentorial tear
Use additional code to identify cause
Excludes:
intraventricular hemorrhage (772.10-772.14)
subarachnoid hemorrhage (772.2)

767.1 Injuries to scalp
767.11 Epicranial subaponeurotic hemorrhage (massive)
Subgaleal hemorrhage
767.19 Other injuries to scalp
Caput succedaneum
Cephalhematoma
Chignon (from vacuum extraction)

767.2 Fracture of clavicle
767.3 Other injuries to skeleton
Fracture of:
long bones
skull
Excludes:
congenital dislocation of hip (754.30-754.35)
fracture of spine, congenital (767.4)
767.4 Injury to spine and spinal cord
Dislocation of spine or spinal cord due to birth trauma

Fracture of spine or spinal cord due to birth trauma
Laceration of spine or spinal cord due to birth trauma
Rupture of spine or spinal cord due to birth trauma

767.5 Facial nerve injury

Facial palsy

767.6 Injury to brachial plexus

Palsy or paralysis:
- brachial
- Erb (-Duchenne)
- Klumpke (-Déjérine)

767.7 Other cranial and peripheral nerve injuries

Phrenic nerve paralysis

767.8 Other specified birth trauma

Eye damage
Hematoma of:
- liver (subcapsular)
- testes
- vulva

Rupture of:
- liver
- spleen

Scalpel wound
Traumatic glaucoma
Excludes:
- hemorrhage classifiable to 772.0-772.9

767.9 Birth trauma, unspecified

Birth injury NOS

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