

ABSTRACT

Title of dissertation: LABOR, DELIVERY, AND NEONATAL OUTCOMES
ASSOCIATED WITH PLACENTAL ABRUPTION

Katheryne Leah Downes, Doctor of Philosophy, 2015

Dissertation directed by: Associate Professor Edmond Shenassa
Department of Family Science

Placental abruption, the premature detachment of the placenta, before birth and after 20 weeks gestation, occurs in 0.6% -1% of all pregnancies in the United States. Little is known about the duration of labor or the risk of neonatal morbidities attributed to abruption. This study examined labor duration, delivery mode, and neonatal outcomes associated with placental abruption among singleton pregnancies in the Consortium on Safe Labor study (n=223,252), a retrospective, observational study of deliveries from 2002-2008 in 19 U.S. hospitals. Models were fit using generalized estimating equations controlling for maternal age, race, pre-pregnancy BMI, insurance, history of cesarean, marital status, and study site (cervical dilation, birthweight, and gestational age were also included for labor and delivery analyses). Labor duration was modeled for each of the three stages and calculated separately by parity (nulliparous or multiparous) and labor type (induced or spontaneous).

Abruption was associated with elevated risk of cesarean delivery among both nulliparous (RR=1.67, 99% CI: 1.54, 1.80) and multiparous women (RR=1.49, 99% CI:

1.38, 1.59). Abruption was not associated with differences in stage 1 or stage 2 labor in any group, but was associated with a shorter duration of stage 3 labor among multiparous women with spontaneous labor ((exp) $\beta = 0.9$, 99% CI: 0.8, 0.9) that was not clinically meaningful (1 minute). Abruption was associated with elevated risk of neonatal interventions including newborn resuscitation (RR=1.54, 99% CI: 1.48, 1.61) and longer Neonatal Intensive Care Unit Length of Stay (NICU LOS) (IRR=1.98, 99% CI: 1.83, 2.14), as well as morbidities and mortality including respiratory distress syndrome (RR=7.40, 99% CI: 6.77, 8.04), apnea (RR=6.63, 99% CI: 5.86, 7.40), asphyxia (RR=8.96, 99% CI: 6.06, 11.85) and perinatal death (RR=7.29, 99% CI: 5.87, 8.70). With the exception of NICU LOS among term and non-low birthweight neonates, all associations remained significant regardless of the timing of abruption, gestational age, birthweight, or delivery mode.

Contrary to prior studies, abruption was not associated with shorter duration of labor. Abruption was associated with increased morbidity among surviving neonates, which adds to the burgeoning literature highlighting the importance of placental functioning on health during infancy.

LABOR, DELIVERY, AND NEONATAL OUTCOMES ASSOCIATED WITH
PLACENTAL ABRUPTION

by

Katheryne Leah Downes

Dissertation submitted to the Faculty of the Graduate School of the
University of Maryland, College Park in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy
2015

Advisory Committee:

Professor Edmond Shenassa, Chair
Dr. Katherine Grantz
Professor Stephanie Grutzmacher
Professor Marian Moser-Jones
Professor Faika Zanjani

©Copyright by
Katheryne Leah Downes
2015

Acknowledgements

I would like to thank all the individuals who supported, encouraged, and inspired me during this process. I would like to thank my dissertation chair, Dr. Edmond Shenassa, for his unwavering faith in my capabilities and for working with me to forge new pathways in training. I would also like to thank Dr. Katherine Grantz, for opening a door to collaborate with NICHD, helping me to stay passionate about both science and learning, and providing a valuable clinical perspective. Dr. Stephanie Grutzmacher and Dr. Marian Moser Jones, for their endless encouragement and thoughtful critique in writing. Dr. Faika Zanjani, for her insightful epidemiologic critiques and support throughout the endeavor. Finally, I would like to thank my grandmother, Betty James, and my mother, Diana James, for their love and support, through the highs and lows of the last three years because without the two of you, none of this would have been possible.

Table of Contents

List of Tables	v
List of Abbreviations	vi
Chapter 1: Introduction	1
Overview	1
Placental Development and Functioning.....	3
Classification of Abruption	5
Risk Pathways for Abruption	7
Abruption Outcomes	12
Chapter 2: Methods	18
Electronic Medical Records and Variable Coding	18
Consortium on Safe Labor Study	18
Inclusion Criteria.....	21
Abruption Identification	21
Covariates:.....	21
Missing Data	23
Analytic Plan	24
Sensitivity Analysis: Timing of Abruption Relative to Labor	26
Sensitivity Analysis: Independent Effect of Abruption	27
Chapter 3: Results.....	28
Labor and Delivery Outcomes	30
Sensitivity Analysis: Timing of Abruption	32
Neonatal Outcomes	35
Sensitivity Analysis: Timing of Abruption	37
Sensitivity Analysis: Direct effects of abruption	39
Gestational Age	39
Birthweight	42
Delivery Mode.....	45
Chapter 4: Discussion	48
Incidence of Abruption.....	48

Mode of Delivery	49
Duration of Labor.....	51
Newborn Resuscitation, NICU LOS, and Neonatal Outcomes.....	53
Strengths.....	59
Limitations	59
Clinical Implications	60
Future Directions for Research	62
Summary and Conclusions.....	64
APPENDIX A	66
Appendix A.1 Original Coding of Variables Included in Current Study.....	66
Appendix A.2 Summary Table of Study Variables.....	69
APPENDIX B	71
Appendix B.1 Original and imputed overall pregnancy characteristics (n=223,252)..	71
APPENDIX C	72
Appendix C.3s Maternal, Pregnancy, and neonatal characteristics according to timing of placental abruption.....	72
Appendix C.6s Maternal, pregnancy, and neonatal characteristics according to abruption status among term and preterm deliveries	73
Appendix C.8s Maternal, pregnancy, and neonatal characteristics according to abruption status among neonates without and with low birthweight	74
Appendix C.10s Maternal, pregnancy, and neonatal characteristics according to abruption status among vaginal and cesarean deliveries.....	75
Glossary	76
References	83

List of Tables

Table 1 Maternal, pregnancy, and neonatal sample characteristics according to placental abruption exposure.....	34
Table 2 Labor and delivery outcomes according to placental abruption status among nulliparous and multiparous women.....	36
Table 3 Labor and delivery outcomes according to timing of placental abruption among nulliparous and multiparous women.....	38
Table 4 Analyses of neonatal outcome characteristics according to placental abruption status.....	41
Table 5 Analyses of neonatal outcomes according to timing of placental abruption.....	43
Table 6 Analyses of neonatal outcomes according to abruption status among term and preterm deliveries.....	45
Table 7 Gestational age bias-corrected risk estimates for neonatal outcomes in the preterm birth-to-outcome pathway.....	46
Table 8 Analyses of neonatal outcomes according to abruption status among neonates without and with low birthweight.....	48
Table 9 Birthweight bias-corrected risk estimates for neonatal outcomes in the low birthweight-to-outcome pathway.....	49
Table 10 Analyses of neonatal outcomes according to abruption status among vaginal and cesarean deliveries.....	51
Table 11 Delivery mode bias-corrected risk estimates for neonatal outcomes in the cesarean-to-outcome pathway.....	52

List of Abbreviations

ACOG	American College of Obstetricians and Gynecologists
BMI	Body Mass Index
CSL	Consortium on Safe Labor
DCC	Data Coordinating Center
DIC	Disseminated Intravascular Coagulopathy
EMR	Electronic Medical Record
GEE	Generalized Estimating Equations
hCG	Human Chorionic Gonadotropin
HIE	Hypoxic-Ischemic Encephalopathy
HITECH	Health Information Technology for Economic and Clinical Health
ICD-9	International Classification of Disease- 9 th Edition
IRB	Institutional Review Board
LOS	Length of Stay
NICHD	National Institute of Child Health and Human Development
NICU	Neonatal Intensive Care Unit
NRFHT	Non-Reassuring Fetal Heart Tracing
OHSR	Office of Human Subjects Research
PIH	Pregnancy-Induced Hypertension
PROM	Premature Rupture of Membranes
RDS	Respiratory Distress Syndrome
SIDS	Sudden Infant Death Syndrome

Chapter 1: Introduction

Overview

Placental abruption, the premature detachment of the placenta from the uterine wall, before birth and after 20 weeks gestation, occurs in 0.6% -1% of all pregnancies in the United States.^{1,2} It typically presents with maternal symptoms of vaginal bleeding, abdominal pain and contractions and can result in abnormal fetal heart rate tracings.² In severe cases it can rapidly progress to significant maternal blood loss, fetal hypoxia and fetal death, and necessitate emergent cesarean delivery.^{3,4} Much of the scientific literature has focused on maternal outcomes, but relatively little is known about labor and delivery outcomes such as duration of labor and mode of delivery associated with abruption.

The disorder is characterized by placental dysfunction which, with progression, can lead to a decrease in the surface area available for oxygen exchange and nutrient supply.^{5,6} This process can lead to an elevated risk of low birthweight, prematurity, low Apgar scores and perinatal mortality.^{1,3,7} It remains uncertain whether abruption also increases the risk of other adverse neonatal outcomes associated with hypoxia and prematurity such as asphyxia, hypoxic-ischemic encephalopathy (HIE), respiratory distress syndrome and apnea.⁸⁻¹¹

Lastly, for neonates who initially survive the delivery, little is known about the need for and extent of medical interventions utilized, such as admission to neonatal intensive care unit (NICU), length of NICU stay as well as the need for newborn resuscitation.

This study investigated labor, delivery, and neonatal outcomes associated with placental abruption. Specifically, I

- 1) Determined whether the duration of labor and the mode of delivery are different among women with placental abruption compared to women without abruption.
- 2) Determined whether neonatal admission to NICU, duration of stay in the NICU, and use of newborn resuscitation are different among women with placental abruption compared to women without abruption.
- 3) Determined whether the risk of neonatal outcomes associated with hypoxia and prematurity are different among women with placental abruption compared to women without abruption.

Placental Development and Functioning

During pregnancy, the placenta supports the growing fetus through provision of nutrition, immune and endocrine regulation, gas exchange and elimination of waste products. The cells that will develop into the placenta, called trophoblasts, form only a few (4-5) days after fertilization of the egg and begin to produce human chorionic gonadotropin (hCG).¹²⁻¹⁷ HCG triggers endometrial changes which allow the fertilized egg to implant and also initiates a complex chemical signaling interaction that culminates in the developing placenta attaching to the lining of the uterus. Initially high levels of hCG released during the creation of the placenta result in the formation of shallow, surface-level attachments to the lining of the uterus. After the first two weeks of gestation, the hormone levels begin to decline and this triggers the placenta to transition to developing deeper attachments to the uterine lining, resulting in a firm connection to the maternal blood supply.¹² By 18-20 weeks of gestation, the placenta (now a pancake-shaped organ), has grown to its full length of approximately 22 cm (8.5 inches) in diameter, but the width will continue to expand approximately 1 mm per week during the pregnancy. At birth, the placenta weighs roughly 470 g (1 pound) and is between 2.0-2.5 cm (1- 1.5 inches) thick.^{13,14,18,19} It is worth noting that although the actual placenta itself is only 22 cm in diameter at term, the end-to-end surface area created by the finger-like projections extending from the placenta (microvilli) is estimated to be nearly 200 miles long.²⁰

The placenta detaches after birth, during what is termed the third stage of labor.²¹ Detachment typically results from the shearing forces that occur as labor contractions continue and the uterus begins to shrink following delivery. Separation can also occur

when contractions cause vascular rupture within the placenta-uterine attachment site; the pooling blood causes increasing pressure between the maternal and fetal interface and forces the placenta to detach from the uterine wall.²¹

Pathologic partial or complete placental separation from the uterine wall can also occur. Prior to 20 weeks gestation, placental separation is considered either a miscarriage or a threatened miscarriage (i.e., vaginal bleeding, but no pregnancy loss) because the fetus has not yet reached the point of viability. The incidence of placental separation occurring prior to 20 weeks gestation is unknown. Many very early miscarriages are missed entirely (mistaken for monthly menstruation) and among those that are documented, it is often unclear whether it resulted from an abnormal pregnancy or placental separation.²² However, early (<20 weeks gestation) vaginal bleeding during pregnancy is associated with a 1.6 fold increased risk of abruption; this risk nearly doubles if there is bleeding during both the first and second trimesters.²³ It is possible that some of the cases of early vaginal bleeding were abruptions that began very early in pregnancy. However, the diagnosis of abruption in this particular study was classified at the time of delivery so it is difficult to determine whether these are early abruptions that bleed throughout pregnancy or if the early bleeding serves as a warning of increased risk for an abruption occurring later in pregnancy.

Placental separation after 20 weeks of gestation and prior to the third stage of labor, termed 'placental abruption,' is the focus of the current study and occurs in 0.6% - 1% of all pregnancies in the United States.^{1,2}

Classification of Abruption

Cases of abruption can be classified as Grade I (mild) when a woman presents with minimal bleeding and uterine irritation, normal blood pressure and no fetal distress or evidence of maternal shock.^{24,25} This diagnosis is typically based on the finding of a small placental clot at the time of delivery. Women are classified with Grade II (intermediate) abruption when presenting with greater vaginal bleeding, uterine hypertonicity, increased maternal heart rate and fetal distress, but no evidence of maternal shock.²⁵ The vast majority of abruption cases are considered either mild (40%) or intermediate (45%) in severity. Grade III (severe) abruption occurs in 15% of all cases and typically presents with significant bleeding, constant contraction of the uterus (tetanic uterus), evidence of either maternal shock or coagulation defect (thrombocytopenia or hypofibrinogenemia), and fetal death.^{24,25} It is important to remember that an abruption may initially present with a small separation, but can rapidly progress to greater separation and maternal-fetal decline.

Although it is not explicitly addressed in the severity classification described above, the degree of placental separation is certainly a major factor in the clinical presentation. The placenta may partially separate from the uterine wall or it may detach completely, but separation of more than 50% of the placental area is associated with a high risk of fetal death and significant maternal morbidity.²⁴ Total separation is associated with the worst prognosis for both mother and neonate, but this most severe form occurs in only 7% of abruption cases and only 0.2% of all pregnancies.^{26,27} Although infrequently reported, estimates of the distribution of cases by degree of separation suggest that the majority (54%) have less than a 25% separation, the remainder

are evenly divided with 16% having between 25-50% separation, 13% having between 50-74% separation and 17% having more than 75% separation.^{7,28}

The diagnosis of the abruption relative to the duration of pregnancy is also an important distinction in case classification. Abruption more frequently occurs earlier in gestation, with a peak of about 9/100 births between 24-26 weeks gestation and then steadily declines with each successive week. By 32 weeks, only 5/100 births are affected and by 36 weeks only 1/100 births have an abruption.²⁹ In a Finnish study, more than half (59%) of women with abruption delivered preterm.²⁶ Abruption occurring preterm may more frequently be the result of acute, inflammatory processes (e.g. trauma, infections, premature rupture of membranes), whereas abruption occurring at term is thought to be a mixture of both acute and chronic processes (e.g. vascular dysfunction associated with conditions like diabetes and smoking).³⁰

Diagnosis of abruption relative to the onset of labor is another important distinction. Between 50-75% of cases occur prior to the onset of labor (anteartum), with roughly 25-50% occurring during labor (intrapartum).^{26,31} Only one previous study has reported outcomes separately for anteartum and intrapartum abruption and in that instance, both emergency cesarean and admission to the NICU were higher among cases of abruption that occurred anteartum.³² It is reasonable to suspect that intrapartum abruption may involve more of a mechanical/traumatic force as the uterus is actively contracting, but the other previously described chronic and acute risk factors may increase the vulnerability of the placenta to these forces. The lack of literature on this particular topic may be due to the difficulty in distinguishing the timing of the abruption. Anteartum abruption is more easily distinguished because the abruption occurs prior to

the onset of labor, but cases that are identified during labor could potentially be misclassified. It is possible that these abruptions began earlier in pregnancy, but were not detected until the onset of labor. It would seem reasonable that a woman experiencing an antepartum abruption that subsequently resolves may also experience an intrapartum abruption in the same pregnancy

Lastly, there is evidence to suggest that abruption occurring in the first pregnancy may have a different risk pattern compared to abruptions that occur for the first time in subsequent pregnancies.³³ Specifically, when stratified by parity, smoking duration, and presence of placental infarcts have been associated with increased risk of abruption in second pregnancy but not the first pregnancy.³³ However, this study grouped together women with a history of abruption as well as those without a history of abruption in the second pregnancy group. The established differences in risk between women with a history of abruption versus those without make the interpretation of these findings difficult.

Risk Pathways for Abruption

Although there are a variety of risk pathways, cases can initially be separated into acute versus chronic cases. Maternal abdominal trauma resulting from a fall, car accident (seatbelt worn incorrectly across the abdomen or sudden deceleration), or physical abuse can lead to an acute antepartum abruption. The elastic tissue within the uterus can undergo slight changes in shape to absorb a blow or a sudden change in pressure, but the placenta has no such elasticity and therefore undergoes a shearing force in such circumstances.²⁴ Maternal trauma from car accidents is estimated to account for 1-2% of

all severe abruptions; however, it is noteworthy that abruption occurs in 40-50% of all life-threatening maternal traumatic injuries.³⁴

Acute abruption can also occur in the postpartum period in the context of multiple gestation pregnancies. Delivery of the first neonate leads to a rapid loss of fluid and sudden decompression of the uterus, which generates a shearing force on the placenta (similar to the natural detachment during third stage of labor) causing it to detach from the uterus before all of the neonates have been delivered.²⁴ However, there are also documented differences in risk factor profiles for singleton versus twin gestation cases of abruption.³⁵ One study found that chronic hypertension and pregnancy-induced hypertension are risk factors for abruption in singleton pregnancies, but not twin pregnancies.³⁵ The explanation for why the same risk factors would have a different impact depending on the number of fetuses being carried is not currently known, but it may be that the increased placental area that occurs in multiple gestations somehow better compensates for oxygen/nutrient deprivation. Altogether, multiple gestation is associated with a 1.5-3.0 fold elevated risk of abruption compared to singleton pregnancies.²⁴

Similarly, premature rupture of membranes (PROM) (associated with a 1.8-5.1 fold increased risk of abruption) can also result in a sudden, dramatic decrease in amniotic fluid and decompression of the uterus which can generate the same shearing force.^{24,36} Abruption can take place in up to 50% of PROM cases that occur prior to 20 weeks gestation and up to 44% of PROM cases that occur between 20-24 weeks pregnancy.³⁷ Lastly, use of cocaine and other central nervous system stimulants during pregnancy is associated with 5.0-10.0 fold elevated risk as they can result in a

combination of sudden increased blood pressure and constriction of the blood vessels in the placenta, which can lead to a large, acute abruption.²⁴

Chronic cases of abruption are largely attributed to processes that interrupt or weaken the vascular attachment between the placenta and the uterine wall. Women with certain genetic conditions that affect coagulation tend to have higher incidence of abruption.^{24,38-40} Specifically, women with either inadequate levels of the clotting factor fibrinogen (hypofibrinogenemia) or dysfunctional fibrinogen (dysfibrinogenemia) are predisposed to abruption.^{40,41} Among these women, even a small placental separation can lead to prolonged bleeding under the placenta and the force exerted by the pooling blood pushes the placenta off of the uterine surface. Hypofibrinogenemia is a rare disorder, but an estimated 8%-15% of Caucasian women are carriers of a thrombophilia gene.^{39,42} On the opposite end of the spectrum, women who have disorders in which their blood clots too easily (thrombophilias) are also predisposed to abruption. It has been hypothesized that thrombophilia can lead to clots forming in the placenta, blocking blood flow and causing tissue damage, which weakens the placental attachment to the uterine wall.^{24,38} It has been suggested that undiagnosed or, as of yet, undiscovered genetic markers may be responsible for a large percentage of placental abruption cases with no known risk factors.²⁴

Advanced maternal age (>35 years) and increasing parity have also been documented as risk factors for abruption (1.1-3.7 fold increased risk), but as they are inherently intertwined, it is unclear whether both independently increase risk. Studies of these two factors have frequently yielded conflicting results, with some finding significant risk with parity, but not advanced maternal age and others finding the opposite

and still more finding no significant association with either factor.²⁴ The explanation for *why* there is elevated risk in this setting has not been established in the literature, but given the nature of the other risk factors, it is reasonable to suspect compromised uterine vasculature.⁴³

Preexisting chronic hypertension (1.8-5.1 fold increased risk), pregnancy-induced hypertension (PIH) (2.5 fold increased risk) and preeclampsia (0.4-4.5 fold increased risk) have all been associated with increased risk of abruption, but the exact nature of this association has not been established.^{24,44} It may be that underlying systemic vascular disease is responsible for all of these conditions. However, it has also been suggested that PIH and preeclampsia may be manifestations of chronic placental disease or earlier dysfunction at the time of trophoblast invasion of the uterine lining, which may then increase risk of abruption.^{24,44-46} Both maternal and paternal smoking are also associated with abruption (with an additive risk if both parents smoke), likely due to the chronic hypoxia and vasoconstriction which lead to tissue damage and weaken the attachment site.^{26,45} There also appears to be a synergistic interaction between hypertensive disorders and smoking for risk of abruption: non-smokers with chronic hypertension had a 2.29 fold increased risk of abruption, smokers who were normotensive had a 1.96 fold increased risk, but smokers with chronic hypertension had a 4.66 fold increased risk.³⁵

Both smoking and gestational diabetes also alter the production and availability of prostaglandins that are manufactured within the umbilical vessels. These prostaglandins serve both as vasodilators and clotting inhibitors, so a decline in production could potentially increase the risk of clot formation and placental infarcts, resulting in placental damage.²⁰ Alcohol consumption can also cause disruption to the rather delicate maternal-

fetal hormonal balance and vasoconstriction in both the umbilical cord and placenta which can lead to an abruption.^{47,48} Infection of the fetal membranes (chorioamnionitis) may cause inflammation and disruption of the placental attachment site, which increases risk of abruption.⁴⁹

Lastly, a history of abruption is associated with as much as a 20-30 fold increased risk of abruption in a subsequent pregnancy, but it is likely that this phenomenon is simply capturing underlying, unknown risk factors in the previous pregnancy that are continuing to be present in subsequent pregnancies.²⁴ Recurrence risk after first episode ranges from 6-17% and increases to 25% if there have been two episodes.²⁷

Nutritional deficiencies during pregnancy can lead to poor placental development, which may explain why a lower pre-pregnancy body mass index (BMI) and inadequate weight gain during pregnancy have been associated with a 0.9-2.0 fold increased risk of abruption.^{50,51} Similarly, the association between both single marital status and Medicaid use with the risk of abruption is thought to largely be a reflection of access to resources. Lack of adequate nutrition and prenatal care can result in poor management of various conditions, such as hypertension and diabetes, that are associated with elevated risk of abruption.⁵²

Abruption also occurs more frequently among African-American women. However, there is a particular pattern where, compared to white women, there is a greater risk of abruption in term pregnancies, but not preterm pregnancies. This suggests that the association may be attributed to chronic risk factors more prevalent among African-American women (hypertension, diabetes, etc).⁵³

Overall, there have been increases in the incidence of abruption over the last few decades in the U.S., with notable differences between black and white women. For black women, the incidence increased from 0.76% from 1979-1981 to 1.43% from 1999-2001. Although the overall percentage is still low, this change in incidence represents a 92% increase.²⁴ The incidence among white women increased only 15%, from 0.82% during 1979-1981 to 0.94% in 1999-2001.²⁴ In contrast to the U.S., Scandinavian countries have reported decreasing incidence of abruption. In Finland, the incidence has gone from 0.49% in 1980 to 0.34% in 2005.^{1,54} It is possible that the increasing rate of abruption in the U.S. is due to changes in the risk profile of women giving birth in this country. Factors associated with abruption have increased over this same period of time including: anemia during pregnancy, gestational diabetes, and gestational hypertension, as well as behavioral risk factors such as smoking and drug use during pregnancy.^{52,55} There is also some evidence to suggest that the true incidence of abruption may be much higher than currently reported as subclinical cases are not always detected. A large study of 7,038 pregnancies identifying cases through pathological examination found an abruption incidence of 3.8%, which is considerably higher than the typically presented 1%.²⁹ It is unknown whether these subclinical cases are also associated with poorer neonatal outcomes.

Abruption Outcomes

The immediate consequences of the placenta's detachment from the uterine wall are blood loss and reduction in oxygen and nutrient availability to the fetus, the severity of which depends on the amount, duration and timing of separation.²⁴

The majority (70-80%) of pregnancies with an abruption will present with vaginal bleeding to some extent, but the amount of blood loss does not necessarily correlate to the degree of placental separation.^{26,56,57} Abdominal pain (27.8%) and uterine hypertonia (26.1%) are other frequent maternal symptoms.⁵⁶ In terms of the fetus, the majority of abruption cases (64.8%) present with non-reassuring fetal heart tracing (NRFHT), but more severe cases may present with fetal death.^{56,58,59}

The main maternal outcome of concern is blood loss, which can be significant and can rapidly progress to disseminated intravascular coagulopathy (DIC). This aggressive coagulation response can lead to extensive, system-wide clot formation as the maternal body attempts to control the uterine bleeding.²⁹ Clots travel to the organs and block blood flow, which leads to organ damage and multi-system organ failure. As this coagulation response continues, the clotting factors in the bloodstream are exhausted (this condition is also called 'consumptive coagulopathy' for this reason), and massive blood loss and hemorrhagic shock can occur.²⁹ Approximately 15% of women with abruptions will require a blood transfusion and 7-10% will develop a coagulation disorder. However, only 6% will experience DIC and only 2.9% will experience hemorrhagic shock.^{4,27,56,60} Post-partum hemorrhage also complicates roughly 12% of abruption cases.⁵⁶ In cases where bleeding cannot be controlled, emergency hysterectomy may be necessary (0.4% of all cases).⁴

Uterine bleeding and coagulation factors released in response to the bleeding can both cause the uterus to contract.²⁷ Abruption typically presents with high-frequency, low-amplitude contractions but it can progress into labor contractions or, alternatively, can cause the uterus to be in a constant contracted state (tetanic uterus).²⁹ These

contractions can also exacerbate the abruption by causing more of the placenta to shear off, which will lead to more bleeding, pushing the placenta further off the uterine surface and irritating more uterine tissue, generating a self-perpetuating cycle.

Given the partial separation of the placenta and the uterine contractions that are typically present in abruption, it is generally thought that labor (especially the third stage) progresses more rapidly than usual, but the duration of each stage of labor has not been documented. Two studies found a significant association with abruption and a total labor duration less than 3 hours (precipitous labor); in one case, there was more than 30 fold increased risk.^{61,62} However, these studies were based on small numbers (n=99 each) of precipitous labor subjects, with very few cases of abruption within these groups (n=10 and n=6), and did not control for important confounding factors such as maternal age and parity (or did not control for any variables at all).^{61,62} An elevated incidence of precipitous labor is of concern because this phenomenon is linked to a higher risk of uterine rupture, post-partum hemorrhage, retained placenta, need for transfusion and prolonged hospital stay for the mother.⁶¹

Abruption is also associated with a considerably higher rate of cesarean delivery (ranging from 67.7% to over 90%), but most of these reports have been in countries where medical practice and the demographics of the women giving birth are different from those in the U.S.^{4,26,56,58-60,63} Cesarean delivery is associated with the typical short term risks associated with all major surgeries (blood loss, infection, damage to surrounding structures, etc), but it is also associated with increased risks in subsequent pregnancies including placental disorders (abruption, previa, and accreta) and need for

hysterectomy.⁶⁴ Previous cesarean delivery also increases risks of preterm birth, small for gestational age, low birthweight, and stillbirth for the neonate.^{65,66}

Placental abruption has much more frequent and severe consequences for the fetus because, in addition to the acute blood loss, separation of the placenta restricts or removes the fetal oxygen and nutrient supply. On average, these neonates are born 3-4 weeks earlier and weigh 200-500 grams less than in pregnancies without abruption.⁶⁷ Specifically, between 40% -59.4% are born prior to 37 weeks gestation and 8.1% - 65.1% are born growth restricted (low birthweight).^{4,7,26,31,59,60,68} Many of these preterm births are attributed to spontaneous preterm labor rather than a medically indicated preterm birth and it has been suggested that some idiopathic preterm births might actually be due to undetected placental abruption.⁷ A separation of even one fourth of the placenta is associated with a 5.5 fold increased risk of preterm birth.⁷ In the past, it was assumed that the association between abruption and low birthweight was mostly due to the large percentage of neonates born prematurely. However, after adjustment for gestational age as well as other confounding factors, abruption still associated with a 4.6 fold increased risk of low birthweight.⁷

The few studies that have examined morbidities associated with prematurity and hypoxia report elevated risk of intraventricular hemorrhage (17.5%-72%), respiratory distress syndrome (40%), and birth asphyxia (47.5%).^{1,58,59,67} There is also often a greater need for medical intervention: assisted ventilation is required in 30% of cases and 20% are admitted to the neonatal intensive care unit, with an average length of stay of 8.4 days.^{1,31,59,60,69,70} In an Iranian study of risk factors necessitating resuscitation, 25.9% of abruption cases required basic resuscitation and 18.5% required advanced resuscitation.⁷¹

However, these studies had small numbers of abruption cases (ranging from n= 27 to n=103), were conducted among non-U.S. populations (United Kingdom, Iran, Finland, Thailand and Italy), and typically examined only one or two of the outcomes discussed above. The small numbers of abruption cases reported in these studies make it difficult to evaluate the accuracy of these neonatal morbidity estimates. Furthermore, given the differences in obstetric populations and medical practices in these countries compared to the U.S., the generalizability of the estimates to a U.S. population may also be questionable.^{1,31,59,60,69,70} Neonates with respiratory distress syndrome (RDS) have an elevated risk of long-term complications that are due to the associated treatment, including damage to the lungs and brain from too much oxygen or pressure from mechanical ventilation.⁷² Perinatal asphyxia has been found to be associated with a range of poor long term outcomes (dependent on severity of asphyxia) including: hypoxic-ischemic encephalopathy (HIE; brain injury due to oxygen deprivation), cerebral palsy, mental retardation, epilepsy, attention deficit – hyperactivity disorders, schizophrenia, and development of psychotic disorders in adulthood.⁷³

Abruption is also associated with a high risk of perinatal mortality ranging from 6.5%-60% of all cases, much of which occurs prior to birth (stillbirth).^{4,26,31,60,68} This translates to an 8.9 fold increased risk of stillbirth and a 15-19 fold increased risk of death overall compared to pregnancies without abruption.^{7,68} More than half (55%) of perinatal deaths associated with abruption can be attributed to preterm birth, but the increased risk of perinatal mortality remains significant even after adjusting for preterm delivery and growth restriction. In one study, neonates in pregnancies complicated by abruption that

were born at normal weight and full term still had a 25-fold increased risk of mortality compared to neonates in pregnancies without abruption.⁶⁸

Finally, there are also long-term risks associated with abruption. In a study of low birthweight cases of abruption, 11.1% of the neonates born were later diagnosed with cerebral palsy, and increased incidence of sudden infant death syndrome (SIDS) has also been observed.^{1,59} Two of the most frequently reported outcomes of abruption, low birthweight and preterm birth, are also associated with increased risk of disease in adulthood. In particular, hypertension, type II diabetes and coronary artery disease have been associated with growth restriction during pregnancy^{74,75} Chronic lung and kidney disease, hypertension, and cardiovascular disease, as well as general increased risk of mortality in childhood and young adulthood are all associated with preterm birth.⁷⁶⁻⁷⁹

In conclusion, placental abruption is a major risk factor for preterm birth, low birthweight and perinatal mortality. However, labor and delivery characteristics as well as many important neonatal outcomes have remained understudied. Examining these other outcomes will add to our knowledge of abruption specifically, but it may also potentially expand our general understanding of how placental dysfunction and disease occur and the consequences thereof. This is an area of growing public health importance due to the immediate neonatal morbidity and mortality, as well as the associated long-term disease risks in adulthood.

Chapter 2: Methods

Electronic Medical Records and Variable Coding

The U.S. began to shift towards adoption of electronic medical records (EMR) over the last two decades- partly as a consequence of The Health Information Technology for Economic and Clinical Health (HITECH) Act which was part of the American Recovery and Reinvestment Act of 2009.⁸⁰ The legislation served as both a support and incentive program for organizations to design and implement an EMR system and transition existing records over to this system. Converting from paper to electronic records offered a number of benefits to the medical and public health communities as well as to individual patients. It allows for improved accuracy and centralization of records, faster transfer of information between providers, easier tracking of public health initiatives such as vaccination and it creates large, automated databases of health information that can help guide insurance, medical and public health practices by basing decisions on actual information.⁸⁰

Consortium on Safe Labor Study

This study utilized data from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Consortium on Safe Labor (CSL) study. This retrospective, observational study was originally conducted to gather extensive information on contemporary labor patterns and explore practices surrounding use of cesarean delivery in the U.S. As stated in the protocol, the primary purposes of the original study were: “(1) to describe contemporary labor progression in the U.S.

population; and (2) to determine when is more appropriate time to perform cesarean delivery in women with labor protraction and arrest.”⁸¹ The study concept and protocol were developed by scientists at NICHD and a request for site proposals was released. The original sample size calculation called for approximately 200,000 deliveries to have adequate power to evaluate differences in perinatal outcomes based on the duration of non-progressing labor during the active phase.⁸¹

A total of 12 clinical centers containing 19 hospitals (some clinical centers included more than one hospital) were ultimately selected based on availability of existing EMR data and representation of 9 out of the 12 American College of Obstetricians and Gynecologists (ACOG) districts in the U.S. Both public and private institutions were included and there were no race or ethnic exclusion criteria. All participating sites were required to obtain Institutional Review Board (IRB) approval at their institution prior to submitting data to the central data coordinating center (DCC) for the study. Since all sites would be reviewing existing EMR data at their location, the original NICHD study protocol recommended that all sites apply for their IRB using the minimal risk, expedited review category with a waiver of informed consent from the individual patients.⁸¹ Individually identifiable patient information was removed from the EMR data and each maternal-neonatal delivery instance was assigned a random database identifier to be used for the time frame of the study prior to transfer to the central DCC. Once the final, cumulative data file including all site data was completed, all sites were instructed to destroy any linking files.⁸¹ IRB approval was also obtained at the DCC and at NICHD; since the study represented a retrospective review of electronic medical

records and only deidentified data was sent to NICHD, it was classified as exempt by the Office of Human Subjects Research (OHSR) at the National Institutes of Health.

Most EMRs are completed using a variety of checkboxes and dropdown menu selections, with occasional free text areas. The current study utilized a large database of EMRs compiled as part of the original CSL study. The original coding of the variables selected for the current study is presented in Appendix A.1. It was anticipated that there may be some variation in terms of what details are captured in the EMR systems at each location, but each participating site was required to have the following available in their EMR data: maternal demographics, reproductive history, medical history, prenatal history of current pregnancy, labor admission assessment, labor progression, labor and delivery summary, maternal postpartum condition, and newborn information.⁸¹

Each participating site was first required to create a site-specific data dictionary detailing the common and unique elements of their data as well as detailed information about the formatting of all variables, which was then sent to the DCC. A common data dictionary based on all of the site-specific data dictionaries was created at the DCC and was used as the template for data extraction and the main dataset.⁸¹ Then, each participating site was expected to extract their EMR data, de-identify all of the entries, and then transfer these records securely to the DCC for processing and combining with all of the other site data. Once received at the central site, error and consistency checks were performed and records were verified, with any identified errors being resolved in collaboration with the sites.⁸¹

Although this study captured 9 out of the 12 ACOG districts, it is not considered a representative sample of women giving birth in the US. However, it is the largest existing

US study to include detailed labor, delivery, and neonatal records. In total, retrospective EMR data on 228,668 deliveries occurring from 2002-2008 were collected for the study, with 9.5% of women contributing more than one birth during the specified time period. The specific number of records contributed by each site was based on the total number of deliveries occurring each year during the study review time frame. All deliveries occurring at 23 weeks of gestation or later with the required EMR data were included in the original study.^{81,82}

Inclusion Criteria

This study was limited to singleton pregnancies as multiple gestation pregnancies are likely to have a different risk profile for abruption.³⁵

Abruption Identification

Placental abruption was parameterized based on the presence of any of the following four variables abstracted from patient medical records: 1) prenatal history of antepartum abruption, 2) labor and delivery record of intrapartum abruption, 3) cesarean indication for abruption, and 4) International Classification of Disease- 9th edition (ICD-9) discharge codes for abruption as assigned by the physician and/or medical coder reviewing the chart.

Covariates:

For duration of labor and mode of delivery outcomes, the following covariates were selected due to their established biological association with both abruption and the outcomes: maternal age, cervical dilation at first examination, gestational age, birthweight, pre-pregnancy body mass index (BMI) and history of cesarean delivery.^{1,8,50,51,82} Race, insurance status, and marital status were selected as additional

covariates to adjust for socio-demographic characteristics of the subjects. Finally, study site was included as a covariate to adjust for possible geographic or site-specific variation. Duration of labor was modeled separately by parity (nulliparous vs. multiparous) and by type of labor (induced vs. spontaneous) because both of these factors are associated with significantly different labor patterns and because separate estimates have greater clinical utility.^{8,83}

For neonatal outcomes and utilization of medical intervention, the following covariates were selected due to their established biological association with both abruption and the outcomes: maternal age, parity and pre-pregnancy BMI.^{8,24,50,51,56,82} Race, insurance status, and marital status were selected as additional covariates to adjust for socio-demographic characteristics of the subjects. Unfortunately, more accurate measures of socioeconomic status, such as maternal education and income level, were not available for analysis in this dataset. Finally, study site was included as a covariate to adjust for possible geographic or site-specific variation.

Gestational age, birthweight, and delivery mode are important risk factors for many poor neonatal outcomes; however, it is likely that these variables are on the causal pathway and serve as intermediates between abruption and the specified neonatal outcomes. Controlling for these types of variables can lead to inaccurate risk estimates if there is unmeasured confounding between the intermediate and the outcome, creating what is otherwise known as collider bias.⁸⁴ In the context of the current study, there is a strong likelihood that this phenomenon would occur as there is missing information for the potential confounding factors (such as occurrence of chorioamnionitis) in the current pregnancy. However, the aim of the current study is to estimate the risk of neonatal

outcomes associated with abruption regardless of pathways involved, not to estimate the risks independent of preterm birth, low birthweight, and delivery mode. In such cases, it is best to not include the intermediate variables (i.e., gestational age, birthweight, and delivery mode) in the regression model.⁸⁴

Nevertheless, it is acknowledged that understanding the direct effect attributed to abruption independent of preterm birth, low birthweight, and delivery mode would also be informative and to that end, a sensitivity analysis was conducted (see the below section for detail).

Missing Data

There are two types of missing data in the CSL study: missing by individual and missing by hospital. Missing by individual means that the hospital was reporting that particular variable, but was missing the information in the individual patient's EMR; whereas, missing by hospital means that the site did not report that variable for any of the patients at that site. For the purposes of this study, individually missing information from the covariates was completed using multiple imputation techniques. Although there does not appear to be a rule of thumb for acceptable percentages of missing data, for the purposes of this study, if an individual patient was missing more than 50% of the covariates, they were dropped from the analysis. None of the covariates selected for this study had information missing by hospital site.

Multiple imputation of missing covariates was performed using PROC FCS (Fully Conditional Specification), which is recommended when the missing data pattern is arbitrary and both continuous and categorical variables are being imputed in the same model. Next, PROC MIANALYZE was used to conduct all remaining regression

analyses.⁸⁵ In instances of repeated observations/longitudinal designs, missing data were imputed with the dataset in the wide format (one person per row) to account for the correlation between observations within person; remaining analysis were performed with the dataset converted to the long format (one observation per row). However, in the current study, only a small percentage of the women had more than one pregnancy captured in the data and the percentage of missing data for most variables was also quite small. The initial steps in multiple imputation require a certain amount of existing data to begin calculations and with only 10% of the women having more than one pregnancy, the total percentage of missing data (90%) was too high to impute values for the subsequent pregnancies.⁸⁵ Therefore, the repeated measures structure was ignored during the imputation phase, but was accounted for in the analytic phase.

For the outcome variables, only NICU LOS and neonatal apnea have missing information: sites 4 and 8 did not report NICU LOS and site 6 did not report neonatal apnea for any of their patients. These sites were dropped from the regression analysis of their respective missing variables (and this detail was documented in associated tables). Otherwise, the sites were retained for all other outcome analyses. Multiple imputation was not performed for outcome variables.

Analytic Plan

Descriptive statistics were reported for demographic characteristics as well as all outcome variables. Since approximately 10% of the women included in the study had more than one birth recorded during the study period, the statistical assumption of independent observations is violated within this data and standard regression models would not be appropriate. Generalized estimating equation (GEE) models were fit to

estimate the risk of the outcomes of interest, while accounting for these instances of repeated observations. An exchangeable within-subject correlation structure was specified.⁸⁶

Continuous variables (i.e., duration of labor, length of NICU stay) were fit with a generalized linear model and dichotomous variables were fit using the modified Poisson approach with a robust error variance estimator.⁸⁷ Distributions of the duration of labor and NICU length of stay variables were assessed for normality prior to modeling. Duration of stage 1 labor was approximately normal, but the distributions of stage 2 and stage 3 labor durations required a log transformation to achieve normality. The distribution of NICU length of stay was fit with a negative binomial model, which is appropriate for over-dispersed count data.^{88,89}

The modified Poisson approach was selected for the dichotomous variables because estimating relative risk using the traditional log-binomial models has been found to result in both inaccurately narrow confidence intervals as well as problems with model convergence.^{87,90} The primary purpose of the study is to estimate risk of outcomes associated with abruption rather than contribution of covariates; therefore, only saturated models (containing all covariates) were fit. See Appendix A.2 for a summarized listing of independent and dependent variables and covariates for the specified models. Hypoxic-ischemic encephalopathy was ultimately excluded from analysis after determining that there were too few cases for the regression models to converge.

Beta coefficients and confidence intervals were estimated for continuous variables and relative risk and confidence intervals were estimated for all dichotomous outcomes. Stage 2 and stage 3 labor duration betas and confidence intervals were back-transformed

using the delta method to obtain estimates based on the original variable scaling.^{91,92}

Since multiple outcomes are being evaluated in this study and there is increased risk of Type I errors, the 99% confidence interval were computed and a p-value <0.01 was used as the cut-off for determining statistical significance.

Sensitivity Analysis: Timing of Abruption Relative to Labor

In Chapter 1 of this document it was noted that the nature of an abruption (and possibly the associated consequences) might vary depending on whether it occurs before labor (anteartum) or during labor (intrapartum). Therefore, a sensitivity analysis was conducted replicating the previously described regression models, but utilizing the anteartum and intrapartum abruption variables only, rather than the combined “any abruption” variable. The main analyses did not take this approach because the focus was on estimating the overall risk of the specified outcomes regardless of timing. The timing of abruption relative to onset of labor was also not reported by five of the participating sites. Therefore, this sensitivity analysis distinguishing anteartum and intrapartum abruption was performed on the reduced sample from the seven remaining sites. This analysis still yielded a sample of 145,212 and the additional information will contribute to our understanding of the role of the timing of abruption relative to the onset of labor.

To perform this analysis, risk estimates were generated separately for anteartum only (excluding women who were also documented as having an intrapartum abruption), intrapartum only (excluding women who also had anteartum abruption), and for cases in which both anteartum and intrapartum abruption occurred. These estimates (and the generated confidence intervals) were compared to the no abruption group, as well as the main study results. A change in the direction of association with the specified outcomes,

or a large change in magnitude of association when comparing these estimates would provide evidence that the timing of the abruption relative to labor might be an important variable to consider when evaluating labor, delivery and neonatal outcomes in future studies.

Sensitivity Analysis: Independent Effect of Abruption

In order to estimate the effect of abruption independent of preterm birth, low birthweight, and delivery mode, an analysis was conducted utilizing one of the accepted techniques for handling potential collider bias called ‘conditioning on an intermediate with sensitivity analysis.’⁸⁴ This approach assessed the potential impact of unmeasured confounding and yielded a range of risk estimates for individuals with low birthweight, preterm birth, and cesarean delivery. These estimates were then used to create a ‘bias factor’ which was incorporated into equations to generate corrected overall risk estimates.⁸⁴ Again, the main purpose of this study was to estimate risk of poor outcomes regardless of the particular pathway, but this sensitivity analysis provided additional insight into the relative contribution of low birthweight, preterm birth, and cesarean delivery in these associations.

Analyses were performed using SAS version 9.4. This study received an exemption from the University of Maryland Institutional Review Board.

Chapter 3: Results

Overall, the average maternal age at the time of delivery was 27.6, approximately half of the sample (51.9%) was white, non-Hispanic and the majority of the women were multiparous (60.2%). The average birthweight was 3,242 grams and gestational age at delivery was, on average, 38.3 weeks (Appendix B.1). The incidence of placental abruption was 1.6% (n=3,613 cases). Sample characteristics by abruption group are presented in Table 1. Abruption cases were less likely to be white (46.5%), and more likely to be single (48.8%), multiparous (64.2%), have public insurance (48.5%), and have a history of cesarean delivery (26.3%), compared to women without an abruption. Neonates in pregnancies complicated by abruption weighed an average of approximately 800 grams less and were born nearly a month (3.7 weeks) earlier compared to neonates in pregnancies not complicated by abruption. Sample characteristics for all sensitivity analyses appear in Appendices C.3s – C.10s (Appendix C).

Table 1. Maternal, pregnancy, and neonatal sample characteristics according to placental abruption exposure

	No Abruption (n=219,639)	Abruption (n=3,613)	P value
Maternal Age, years ^a	27.6 ± 6.2	27.6 ± 6.4	0.70
Maternal Race, n (%)			
White	114,109 (52.0)	1,679 (46.5)	<0.001
Black	51,282 (23.4)	1,179 (32.6)	
Hispanic	39,575 (18.0)	580 (16.0)	
Asian	9,310 (4.2)	107 (3.0)	
Multi/Other	5,363 (2.4)	68 (1.9)	
Pre-pregnancy BMI ^a	25.7 ± 6.6	26.0 ± 6.8	0.05
Insurance, n (%)			
Private	136,763 (62.3)	1,800 (49.8)	<0.001
Public	79,158 (36.0)	1,752 (48.5)	
Self-pay/Other	3,718 (1.7)	61 (1.7)	
Marital Status, n (%)			
Single	86,217 (39.3)	1,763 (48.8)	<0.001
Married	133,422 (60.8)	1,850 (51.2)	
Parity, n (%)			
Nulliparous	87,683 (39.9)	1,292 (35.8)	<0.001
Multiparous	131,956 (60.1)	2,321 (64.2)	
History of Cesarean, n (%) ^b			
No	101,172 (76.7)	1,710 (73.7)	<0.001
Yes	30,784 (23.3)	611 (26.3)	
Cervical Dilation at First Exam, cm ^a	3.1 ± 2.1	2.8 ± 2.3	<0.001
Induction of Labor, n (%)			
No	143,450 (65.3)	2,674 (74.0)	<0.001
Yes	76,189 (34.7)	939 (26.0)	
Birthweight, grams ^a	3255 ± 594	2447 ± 949	<0.001
Gestational Age, weeks ^a	38.4 ± 2.3	34.7 ± 4.7	<0.001

^a Data are given as mean ± standard deviation

^b Among multiparous women only

Labor and Delivery Outcomes

Descriptive statistics and adjusted analyses of labor and delivery outcomes are presented in Table 2. Abruptio was associated with an elevated risk of cesarean delivery among both nulliparous (RR= 1.67, 99% CI: 1.54, 1.80) and multiparous (RR=1.49, 99% CI: 1.38, 1.59) women. For vaginal deliveries among nulliparous women, there were no significant differences in stage 1, stage 2, or stage 3 labor durations for either induced or spontaneous labor. For vaginal deliveries among multiparous women, there were no significant differences in stage 1 and stage 2 labor durations for women with either induced or spontaneous labor. There was also no significant difference in stage 3 labor duration for women with induced labor. However, abruptio was associated with a 10% shorter duration of stage 3 labor among multiparous women with spontaneous labor [(exp) β = 0.9, 99% CI: 0.8, 0.9]. With a median duration of labor of 5 minutes for the no abruptio group, this translates to a difference of less than one minute.

Table 2. Labor and delivery outcomes according to placental abruption status among nulliparous and multiparous women

Nulliparous Women					
Labor and delivery outcomes	N	No Abruption	Abruption	β (99% CI) ^a	P value ^a
Delivery Mode, n (%)	88,975				
Vaginal		61,815 (70.5%)	629 (48.7%)		
Cesarean		25,868 (29.5%)	663 (51.3%)	1.67 (1.54, 1.80) ^b	<0.001
Induced Labor ^c					
Stage 1 Labor, hrs	16,192	8.4 (0.0-24.0) ^d	8.9 (0.3-23.0) ^d	-0.5 (-1.6, 0.5) ^e	0.17
Stage 2 Labor, mins	20,368	60 (1-360) ^d	40 (1-258) ^d	0.9 (0.8, 1.1) ^f	0.18
Stage 3 Labor, mins	20,466	5 (1-153) ^d	5 (1-104) ^d	1.0 (0.8, 1.2) ^f	0.97
Spontaneous Labor ^c					
Stage 1 Labor, hrs	28,361	6.8 (0.0-24.0) ^d	8.4 (0.0-23.7) ^d	0.4 (-0.5, 1.2) ^e	0.24
Stage 2 Labor, mins	32,086	58 (1-360) ^d	31 (1-269) ^d	1.0 (0.8, 1.1) ^f	0.05
Stage 3 Labor, mins	33,298	5 (1-161) ^d	5 (1-110) ^d	1.0 (0.9, 1.1) ^f	0.32
Multiparous Women					
Labor and delivery outcomes	N	No Abruption	Abruption	β (99% CI) ^g	P value ^g
Delivery Mode, n (%)	134,277				
Vaginal		97,135 (73.6%)	1,209 (52.1%)		
Cesarean		34,821 (26.4%)	1,112 (47.9%)	1.49 (1.38, 1.59) ^b	<0.001
Induced Labor ^c					
Stage 1 Labor, hrs	25,824	5.9 (0.0-24.0) ^d	7.7 (0.3-23.2) ^d	0.2 (-0.5, 0.9) ^e	0.52
Stage 2 Labor, mins	29,435	18 (1-360) ^d	15 (1-315) ^d	1.1 (0.9, 1.3) ^f	0.10
Stage 3 Labor, mins	31,170	5 (1-178) ^d	5 (1-98) ^d	0.9 (0.8, 1.0) ^f	0.05
Spontaneous Labor ^c					
Stage 1 Labor, hrs	43,122	4.7 (0.0-24.0) ^d	6.6 (0.0-23.6) ^d	0.0 (-0.5, 0.6) ^e	0.89
Stage 2 Labor, mins	48,656	16 (1-360) ^d	14 (1-347) ^d	1.0 (0.9, 1.1) ^f	0.87
Stage 3 Labor, mins	54,609	5 (1-165) ^d	4 (1-175) ^d	0.9 (0.8, 0.9) ^f	<0.001

^a Estimates for nulliparous women adjusted for maternal age, race, pre-pregnancy body mass index, insurance, marital status, cervical dilation at first exam, birthweight, gestational age, and study site;

^b Relative risk of cesarean delivery estimated with modified Poisson model; ^c Among vaginal deliveries;

^d Data are given as median, range; ^e Beta coefficient estimated with generalized linear model. Estimate is interpreted as the average difference in duration of stage 1 labor (in hours) for the abruption group, compared to the no abruption group; ^f Exponential of the beta coefficient estimated with generalized linear model. Estimates can be interpreted as the percentage difference in minutes for the abruption group compared to the no abruption group, where coefficients less than “1” represent a relative decrease and coefficients greater than “1” represent a relative increase; ^g Estimates for multiparous women are adjusted for maternal age, race, pre-pregnancy body mass index, insurance, marital status, cervical dilation at first exam, history of cesarean, birthweight, gestational age, and study site

Sensitivity Analysis: Timing of Abruption

To examine whether timing of abruption influenced my findings, I conducted a sensitivity analysis including 175,443 pregnancies with data distinguishing antepartum from intrapartum abruption (Table 3). Abruption was associated with elevated risk of cesarean delivery regardless of timing for both nulliparous and multiparous women, with relative risk ranging from RR=1.32 (99% CI: 1.14, 1.49) for the multiparous women with antepartum abruption to RR=2.20 (99% CI: 1.86, 2.54) for the nulliparous women with both antepartum and intrapartum abruption. Among nulliparous women, there were no significant differences in stage 1 or stage 3 labor duration regardless of timing. However, in contrast to the main results, antepartum abruption was associated with 30% shorter stage 2 labor duration among women with induced labor [(exp) $\beta = 0.7$, 99% CI: 0.5, 0.9]. This estimate translates to a decrease of about 20 minutes in the pregnancies with antepartum abruption, assuming the median duration of 68 minutes for pregnancies without an abruption. Among multiparous women, there were no significant differences in stage 1 or stage 2 labor duration regardless of timing, but women with both antepartum and intrapartum abruption had a 10% shorter duration of stage 3 labor duration among women with spontaneous labor in the antepartum and intrapartum group [(exp) $\beta = 0.90$, 99% CI: 0.8, 0.9]. In sum, this sensitivity analysis suggests that abruption was associated with increased risk of cesarean delivery regardless of whether it occurred before or during labor. However, the relationship between abruption and duration of labor differed based on the timing of the abruption.

Table 3. Labor and delivery outcomes according to timing of placental abruption among nulliparous and multiparous women

		Nulliparous Women						
		Antepartum				Intrapartum		
Labor and delivery outcomes	N	No Abruption	Abruption	β (99% CI) ^a	P value ^a	Abruption	β (99% CI) ^a	P value ^a
Delivery Mode, n	58,170							
Vaginal		40,524 (70.5%)	191 (59.7%)			131 (62.4%)		
Cesarean		16,923 (29.5%)	129 (40.3%)	1.57 (1.28, 1.86)^b	<0.001	79 (37.6%)	1.40 (1.09, 1.71)^b	<0.001
Induced Labor ^c								
Stage 1 Labor, hrs	10,258	9.0 (0.0-24.0) ^d	8.9 (3.4-23.0) ^d	-0.3 (-2.3, 1.8) ^e	0.75	11.0 (0.3-23.0) ^d	-1.5 (-4.3, 1.4)	0.18
Stage 2 Labor, mins	13,984	68 (1-359) ^d	38 (1-230) ^d	0.7 (0.5, 0.9)^f	0.01	36 (5-208) ^d	1.0 (0.7, 1.3)	0.86
Stage 3 Labor, mins	13,950	5 (1-153) ^d	6 (2-70) ^d	1.0 (0.8, 1.5) ^f	0.71	6 (1-104) ^d	1.0 (0.7, 1.5)	0.90
Spontaneous Labor ^c								
Stage 1 Labor, hrs	16,869	8.0 (0-24.0) ^d	10.2 (0-23.7) ^d	0.7 (-0.8, 2.2) ^e	0.22	11.1 (0.4-23.3) ^d	0.6 (-1.2, 2.5)	0.37
Stage 2 Labor, mins	19,393	64 (1-359) ^d	44 (1-269) ^d	1.0 (0.8, 1.2) ^f	0.71	31 (1-240) ^d	1.0 (0.7, 1.3)	0.67
Stage 3 Labor, mins	19,609	5 (1-158) ^d	5 (1-110) ^d	1.0 (0.9, 1.3) ^f	0.55	6 (1-62) ^d	0.9 (0.7, 1.2)	0.36
		Multiparous Women						
		Antepartum				Intrapartum		
Labor and delivery outcomes	N	No Abruption	Abruption	β (99% CI) ^g	P value ^g	Abruption	β (99% CI) ^g	P value ^g
Delivery Mode, n	87,042							
Vaginal		62,612 (73.1%)	409 (63.2%)			213 (50.8%)		
Cesarean		22,995 (26.9%)	238 (36.8%)	1.32 (1.14, 1.49)^b	<0.001	206 (49.2%)	1.57 (1.30, 1.83)^b	<0.001
Induced Labor ^c								
Stage 1 Labor, hrs	17,847	5.8 (0.0-24.0) ^d	8.0 (1.7-23.0) ^d	-0.1 (-1.2, 1.1) ^e	0.88	10.0 (0.3-23.2) ^d	1.1 (-1.0, 3.3)	0.17
Stage 2 Labor, mins	21,269	20 (1-360) ^d	15 (1-186) ^d	1.0 (0.8, 1.3) ^f	0.68	10 (1-137) ^d	0.9 (0.6, 1.2)	0.25
Stage 3 Labor, mins	22,058	5 (1-178) ^d	5 (1-98) ^d	1.0 (0.8, 1.2) ^f	0.98	7 (1-53) ^d	1.0 (0.7, 1.4)	0.90
Spontaneous Labor ^c								
Stage 1 Labor, hrs	25,480	5.8 (0-24.0) ^d	6.5 (0-23.1) ^d	-0.4 (-1.4, 0.5) ^e	0.23	8.3 (0.1-23.6) ^d	1.2 (-0.5, 2.8)	0.08
Stage 2 Labor, mins	29,272	19 (1-360) ^d	17 (1-302) ^d	1.1 (0.9, 1.3) ^f	0.39	12 (1-304) ^d	0.9 (0.7, 1.1)	0.22
Stage 3 Labor, mins	30,677	5 (1-158) ^d	4 (1-88) ^d	0.9 (0.8, 1.0) ^f	0.01	5 (1-87) ^d	0.9 (0.7, 1.0)	0.04

Table 3. Continued

Nulliparous Women					
Labor and delivery outcomes	N	Antepartum & Intrapartum			
		No Abruptio	Abruptio	β (99% CI)^a	P value^a
Delivery Mode, n	58,170				
Vaginal		40,524 (70.5%)	79 (40.9%)		
Cesarean		16,923 (29.5%)	114 (59.1%)	2.20 (1.86, 2.54)^b	<0.001
Induced Labor ^c					
Stage 1 Labor, hrs	10,258	9.0 (0.02-24.0) ^d	4.2 (2.7-16.2) ^d	-2.3 (-5.4, 0.7) ^e	0.05
Stage 2 Labor, mins	13,984	68 (1-359) ^d	81 (20-258) ^d	1.3 (0.7, 2.3) ^f	0.13
Stage 3 Labor, mins	13,950	5 (1-153) ^d	5 (2-16) ^d	1.0 (0.6, 1.7) ^f	0.85
Spontaneous Labor ^c					
Stage 1 Labor, hrs	16,869	8.0 (0-24.0) ^d	9.0 (0.1-23.4) ^d	1.0 (-1.5, 3.4) ^e	0.31
Stage 2 Labor, mins	19,393	64 (1-359) ^d	35 (5-178) ^d	0.9 (0.7, 1.1) ^f	0.15
Stage 3 Labor, mins	19,609	5 (1-158) ^d	4 (1-26) ^d	0.8 (0.7, 1.0) ^f	0.009

Multiparous Women					
Labor and delivery outcomes	N	Antepartum & Intrapartum			
		No Abruptio	Abruptio	β (99% CI)^g	P value^g
Delivery Mode, n	87,042				
Vaginal		62,612 (73.1%)	192 (52.0%)		
Cesarean		22,995 (26.9%)	177 (48.0%)	1.69 (1.40, 1.98)^b	<0.001
Induced Labor ^c					
Stage 1 Labor, hrs	17,847	5.8 (0.02-24.0) ^d	6.8 (1.0-16.0) ^d	0.4 (-0.9, 1.7) ^e	0.42
Stage 2 Labor, mins	21,269	20 (1-360) ^d	25 (4-155) ^d	1.2 (0.8, 1.8) ^f	0.18
Stage 3 Labor, mins	22,058	5 (1-178) ^d	4 (1-26) ^d	1.0 (0.7, 1.3) ^f	0.68
Spontaneous Labor ^c					
Stage 1 Labor, hrs	25,480	5.8 (0-24.0) ^d	7.0 (0-23.3) ^d	0.0 (-1.4, 1.3) ^e	0.99
Stage 2 Labor, mins	29,272	19 (1-360) ^d	17 (1-113) ^d	1.0 (0.8, 1.2) ^f	0.94
Stage 3 Labor, mins	30,677	5 (1-158) ^d	4 (1-23) ^d	0.9 (0.8, 0.9)^f	0.003

^a Estimates adjusted for maternal age, race, pre-pregnancy body mass index, insurance, marital status, cervical dilation at first exam, birthweight, gestational age, and study site; ^b Relative risk of cesarean delivery estimated with modified Poisson model; ^c Among vaginal deliveries; ^d Data are given as median, range; ^e Beta coefficient estimated with generalized linear models. Estimate is interpreted as the average difference in duration of stage 1 labor (in hours) for the abruptio group, compared to the no abruptio group; ^f Exponential of the beta coefficient estimated with generalized linear model. Estimates are interpreted as average labor duration (in minutes), Estimates can be interpreted as the percentage difference in minutes for the abruptio group compared to the no abruptio group where coefficients less than “1” represent a relative decrease and coefficients greater than “1” represent a relative increase; ^g Estimates are adjusted for maternal age, race, pre-pregnancy body mass index, insurance, marital status, cervical dilation at first exam, history of cesarean, birthweight, gestational age, and study site.

Note: Statistically significant findings are bolded.

Neonatal Outcomes

Descriptive statistics and adjusted regression analyses of the neonatal outcomes appear in Table 4. Compared to neonates in pregnancies not complicated by abruption, the neonates in pregnancies complicated by abruption were more likely to need resuscitation in the delivery room (RR=1.54, 99% CI: 1.48, 1.61) and to be admitted to the NICU (RR=3.70, 99% CI: 3.51, 3.89). Among the neonates admitted to the NICU, abruption was also associated with a length of stay nearly twice as long (IRR= 1.98, 99% CI: 1.83-2.14). Abruptio was also associated with elevated risk of respiratory distress syndrome, apnea, asphyxia and perinatal death.

Table 4. Analyses of neonatal outcome characteristics according to placental abruption status

Neonatal outcome	No Abruption (n=219,639)	Abruption (n=3,613)	Relative Risk (99% CI) ^{a, e}
Newborn Resuscitation, n (%)			
No	169,638 (77.2)	2,205 (61.0)	
Yes	50,001 (22.8)	1,408 (39.0)	1.54 (1.48, 1.61)
NICU Admission, n (%)			
No	194,137 (88.4)	1,913 (53.0)	
Yes	25,502 (11.6)	1,700 (47.0)	3.70 (3.51, 3.89)
NICU LOS, days	6 (0-483) ^b	20 (0-365) ^b	1.98 (1.83, 2.14) ^c
Respiratory Distress Syndrome, n (%)			
No	213,211 (97.1)	2,728 (75.5)	
Yes	6,428 (2.9)	885 (24.5)	7.40 (6.77, 8.04)
Apnea, n (%) ^d			
No	194,969 (97.9)	2,981 (85.5)	
Yes	4,202 (2.1)	506 (14.5)	6.63 (5.86, 7.40)
Asphyxia, n (%)			
No	219,126 (99.8)	3,537 (97.9)	
Yes	513 (0.2)	76 (2.1)	8.96 (6.06, 11.85)
Perinatal Death, n (%)			
No	217,852 (99.2)	3,390 (93.8)	
Yes	1,787 (0.8)	223 (6.2)	7.29 (5.87, 8.70)

^a RR estimated with modified Poisson model adjusting for maternal age, race, parity, pre-pregnancy body mass index, insurance, marital status, and study site

^b Data are given as median, range among those admitted to NICU; excludes sites 4 and 8 which did not report NICU LOS

^c Incident rate ratio estimated with negative binomial model

^d Excluding site 6 which did not report neonatal apnea

^e All models were significant at p<0.001

Sensitivity Analysis: Timing of Abruption

Abruption remained associated with elevated risk for all outcomes regardless of timing of the abruption, but the estimated risk varied greatly across the groups (Table 5). The risk of respiratory distress syndrome associated with pregnancies having both antepartum and intrapartum abruption was nearly twice that of the antepartum only group [(RR=9.47, 99% CI: 7.80, 11.14) and (RR=5.28, 99% CI: 4.30, 6.27) respectively]. A similar pattern was apparent for apnea [RR=8.62 (99% CI: 5.97, 11.27) and RR=4.54 (99% CI: 3.25, 5.84) respectively]. In sum, the results of the sensitivity analysis indicated that abruption was associated with poor neonatal outcomes regardless of whether it occurred before or during labor.

Table 5. Analyses of neonatal outcomes according to timing of placental abruption

Neonatal outcome	No Abruption (n=143,054)	Antepartum		Intrapartum		Antepartum & Intrapartum	
		Abruption (n=967)	Relative Risk (99% CI) ^{a, e}	Abruption (n=629)	Relative Risk (99% CI) ^{a, e}	Abruption (n=562)	Relative Risk (99% CI) ^{a, e}
Newborn							
Resuscitation, n (%)							
No	105,916 (74.0)	619 (64.0)		497 (79.0)		190 (33.8)	
Yes	37,138 (26.0)	348 (36.0)	1.29 (1.19, 1.39)	132 (21.0)	1.56 (1.31, 1.81)	372 (66.2)	1.43 (1.34, 1.53)
NICU							
Admission, n (%)							
No	125,988 (88.1)	597 (61.7)		316 (50.2)		268 (47.7)	
Yes	17,066 (11.9)	370 (38.3)	2.73 (2.42, 3.04)	313 (49.8)	3.26 (2.89, 3.62)	294 (52.3)	4.99 (4.45, 5.53)
NICU LOS, days	6 (0-483) ^b	12 (0-148) ^b	1.84 (1.52, 2.15) ^c	22 (0-173) ^b	2.00 (1.68, 2.33) ^c	22 (0-181) ^b	2.12 (1.76, 2.49) ^c
Respiratory Distress Syndrome, n (%)							
No	138,562 (96.9)	790 (81.7)		489 (77.7)		393 (69.9)	
Yes	4,492 (3.1)	177 (18.3)	5.28 (4.30, 6.27)	140 (22.3)	6.38 (5.07, 7.69)	169 (30.1)	9.47 (7.80, 11.14)
Apnea, n (%) ^d							
No	140,407 (98.2)	883 (91.3)		552 (87.8)		501 (89.1)	
Yes	2,647 (1.8)	84 (8.7)	4.54 (3.25, 5.84)	77 (12.2)	5.86 (4.09, 7.63)	61 (10.9)	8.62 (5.97, 11.27)
Asphyxia, n (%)							
No	142,678 (99.7)	951 (98.4)		621 (98.7)		543 (96.6)	
Yes	376 (0.3)	16 (1.6)	6.76 (2.17, 11.35)	8 (1.3)	5.70 (0.62, 10.77)	19 (3.4)	11.49 (4.43, 18.55)
Perinatal Death, n (%)							
No	141,769 (99.1)	936 (96.8)		589 (93.6)		544 (96.8)	
Yes	1,285 (0.9)	31 (3.2)	3.29 (1.60, 4.97)	40 (6.4)	4.95 (2.84, 7.06)	18 (3.2)	5.68 (2.30, 9.06)

^a RR estimated with modified Poisson model adjusting for maternal age, race, parity, pre-pregnancy body mass index, insurance, marital status, and study site

^b Data are given as median, range among those admitted to NICU; excludes sites 4 and 8 which did not report NICU LOS

^c Incident rate ratio estimated with negative binomial model

^d Excluding site 6 which did not report neonatal apnea

^e All comparisons significant to p<0.001

Sensitivity Analysis: Direct Effects of Abruption

To determine whether there is a direct effect attributed to abruption, beyond the risks associated with preterm birth, low birthweight and cesarean delivery, I conditioned on these intermediates with sensitivity analyses.⁸⁴ For each variable, analyses are presented within each stratum and then, sensitivity analyses examining the impact of potential bias within the “risk” group (e.g. preterm/low birthweight/cesarean delivery) are presented.

Gestational Age

Descriptive statistics and adjusted regression analyses of the neonatal outcomes appear in Table 6. With the exception of NICU LOS among term deliveries, the association between abruption and all neonatal outcomes remained significant among both term and preterm birth neonates. The estimated risk of all neonatal outcomes was higher in the term group than the preterm group, but there were no instances of illogical findings among the preterm group (e.g., estimates suggesting a protective effect for abruption). Although there are differences in the magnitude of risk between the term and preterm groups, these findings indicate that abruption has a direct effect on neonatal outcomes not through gestational age. In other words, abruption is associated with an increased risk of poor neonatal outcomes beyond the risk that can be attributed to preterm birth. The bias-adjusted risk estimates for neonatal outcomes among the preterm neonates appear in Table 7. Estimated risk of neonatal outcomes increased to varying levels in all scenarios indicating that unmeasured causes of preterm birth in this sample may result in some underestimation of the risk associated with abruption for poor neonatal outcomes among preterm neonates.

Table 6. Analyses of neonatal outcomes according to abruption status among term and preterm deliveries

Neonatal outcome	Term (n=197,155)			Preterm (n=26,097)		
	No Abruptio	Abruptio	Relative Risk (99% CI) ^{a, e}	No Abruptio	Abruptio	Relative Risk (99% CI) ^{a, e}
Newborn Resuscitation, n (%)						
No	153,091 (78.3)	1,099 (65.1)		16,547 (68.5)	1,106 (57.4)	
Yes	42,377 (21.7)	588 (34.9)	1.34 (1.24, 1.43)	7,624 (31.5)	820 (42.6)	1.30 (1.22, 1.37)
NICU Admission, n (%)						
No	181,878 (93.1)	1,438 (85.2)		12,259 (50.7)	475 (24.7)	
Yes	13,590 (6.9)	249 (14.8)	1.97 (1.67, 2.27)	11,912 (49.3)	1,451 (75.3)	1.51 (1.45, 1.57)
NICU LOS, days	3 (0-280) ^b	4 (0-105) ^b	0.96 (0.74, 1.19) ^c	14 (0-483) ^b	25 (0-365) ^b	1.41 (1.30, 1.51) ^c
Respiratory Distress Syndrome, n (%)						
No	194,247 (99.4)	1,643 (97.4)		18,964 (78.5)	1,085 (56.3)	
Yes	1,221 (0.6)	44 (2.6)	3.45 (2.08, 4.82)	5,207 (21.5)	841 (43.7)	2.00 (1.85, 2.15)
Apnea, n (%) ^d						
No	175,424 (99.5)	1,605 (98.5)		19,545 (85.4)	1,376 (74.1)	
Yes	854 (0.5)	24 (1.5)	2.79 (1.28, 4.31)	3,348 (14.6)	482 (25.9)	1.87 (1.67, 2.07)
Asphyxia, n (%)						
No	195,166 (99.8)	1,667 (98.8)		23,960 (99.1)	1,870 (97.1)	
Yes	302 (0.2)	20 (1.2)	7.52 (2.88, 12.16)	211 (0.9)	56 (2.9)	3.59 (2.18, 5.00)
Perinatal Death, n (%)						
No	194,907 (99.7)	1,654 (98.0)		22,945 (94.9)	1,736 (90.1)	
Yes	561 (0.3)	33 (2.0)	8.07 (4.10, 12.04)	1,226 (5.1)	190 (9.9)	1.99 (1.61, 2.39)

^a RR estimated with modified Poisson model adjusting for maternal age, race, parity, pre-pregnancy body mass index, insurance, marital status, and study site

^b Data are given as median, range among those admitted to NICU; excludes sites 4 and 8 which did not report NICU LOS

^c Incident rate ratio estimated with negative binomial model

^d Excluding site 6 which did not report neonatal apnea

^e All comparisons significant to $p < 0.001$, except NICU LOS in Term Group ($p = 0.63$)

Table 7. Gestational age bias-corrected risk estimates for neonatal outcomes in the preterm birth-to-outcome pathway (n=26,097)

Neonatal outcome	Adjusted RR	$\pi_{11}=0.05, \pi_{01}=0.50$			$\pi_{11}=0.10, \pi_{01}=0.75$			$\pi_{11}=0.15, \pi_{01}=0.80$		
		Odds of Preterm Birth			Odds of Preterm Birth			Odds of Preterm Birth		
		2.0	5.0	10.0	2.0	5.0	10.0	2.0	5.0	10.0
Newborn Resuscitation	1.30	1.85	3.25	5.00	2.06	3.71	5.20	2.03	3.42	4.48
NICU Admission	1.51	2.16	3.77	5.81	2.40	4.31	6.29	2.36	3.97	5.21
NICU LOS	1.41	2.01	3.53	5.42	2.24	4.03	5.64	2.20	3.71	4.86
Respiratory Distress Syndrome	2.00	2.86	5.00	7.69	3.17	5.71	8.00	3.13	5.26	6.90
Apnea	1.87	2.67	4.68	7.19	2.97	5.34	7.48	2.92	4.92	6.45
Asphyxia	3.59	5.13	8.98	13.81	5.70	10.26	14.36	5.61	9.45	12.38
Perinatal Death	1.99	2.84	4.98	7.65	3.16	5.69	7.96	3.11	5.24	6.86

π_{11} = Estimated prevalence of unmeasured causes of preterm birth in the abruption group

π_{01} = Estimate prevalence of unmeasured causes of preterm birth in the non-abruption group

^a Risk estimates are adjusted for unmeasured common causes (confounding) of preterm birth and the specified outcomes. For newborn resuscitation under “2.0” in the first column, the scenario is that 5% of the abruption group and 50% of the non-abruption group have unmeasured common causes (confounding) of preterm birth and newborn resuscitation and that these unmeasured causes result in a 2-fold increase in risk for newborn resuscitation. In this scenario, the original adjusted risk for newborn resuscitation was RR=1.30 and the bias factor yielded a corrected RR=1.85.

Birthweight

Descriptive statistics and adjusted regression analyses are presented in Table 8.

With the exception of NICU LOS among the normal birthweight group, all associations remained significant among both birthweight groups. The model for risk of asphyxia among low birthweight neonates failed to converge due to small sample sizes in some study sites. The risks associated with abruption were more pronounced in the non-low birthweight group, but there were no illogical results (e.g., protective effects) among the low birthweight group. These results again provide evidence that abruption has a direct negative effect on neonatal outcomes not through birthweight. In other words, abruption is associated with an increased risk of poor neonatal outcomes beyond the risk that can be attributed to low birthweight. Bias-adjusted risk estimates for the association between abruption and neonatal outcomes among low birthweight neonates appear in Table 9. Again, estimated risk of neonatal outcomes increased to varying levels in all scenarios indicating that unmeasured causes of low birthweight in this sample may result in underestimation of the risk associated with abruption for poor neonatal outcomes among low birthweight neonates.

Table 8. Analyses of neonatal outcomes according to abruption status among neonates without and with low birthweight

Neonatal Outcome	Non- Low Birthweight (n=204,466)			Low birthweight (n=18,786)		
	No Abruptio	Abruptio	Relative Risk (99% CI) ^{a, e}	No Abruptio	Abruptio	Relative Risk (99% CI) ^{a, e}
Newborn Resuscitation, n (%)						
No	157,853 (78.0)	1,275 (65.1)		11,785 (68.8)	930 (56.2)	
Yes	44,654 (22.0)	684 (34.9)	1.33 (1.24, 1.41)	5,347 (31.2)	724 (43.8)	1.31 (1.23, 1.39)
NICU Admission, n (%)						
No	186,748 (92.2)	1,580 (80.7)		7,389 (43.1)	333 (20.1)	
Yes	15,759 (7.8)	379 (19.4)	2.35 (2.06, 2.64)	9,743 (56.9)	1,321 (79.9)	1.39 (1.34, 1.44)
NICU LOS, days	4 (0-280) ^b	4 (0-105) ^b	1.08 (0.91, 1.26) ^c	18 (0-483) ^b	28 (0-365) ^b	1.32 (1.22, 1.41) ^c
Respiratory Distress Syndrome, n (%)						
No	200,466 (99.0)	1,878 (95.9)		12,745 (74.4)	850 (51.4)	
Yes	2,041 (1.0)	81 (4.1)	3.52 (2.50, 4.55)	4,387 (25.6)	804 (48.6)	1.88 (1.74, 2.02)
Apnea, n (%) ^d						
No	181,901 (99.4)	1,848 (98.0)		13,068 (80.7)	1,133 (70.8)	
Yes	1,083 (0.6)	38 (2.0)	3.19 (1.80, 4.58)	3,119 (19.3)	468 (29.2)	1.61 (1.44, 1.78)
Asphyxia, n (%)						
No	202,159 (99.8)	1,935 (98.8)		16,967 (99.0)	1,602 (96.9)	
Yes	348 (0.2)	24 (1.2)	7.34 (3.22, 11.46)	165 (1.0)	52 (3.1)	-----
Perinatal Death, n (%)						
No	201,913 (99.7)	1,920 (98.0)		15,939 (93.0)	1,470 (88.9)	
Yes	594 (0.3)	39 (2.0)	8.11 (4.42, 11.79)	1,193 (7.0)	184 (11.1)	1.67 (1.33, 2.00)

^a RR estimated with modified Poisson model adjusting for maternal age, race, parity, pre-pregnancy body mass index, insurance, marital status, and study site

^b Data are given as median, range among those admitted to NICU; excludes sites 4 and 8 which did not report NICU LOS

^c Incident rate ratio estimated with negative binomial model

^d Excluding site 6 which did not report neonatal apnea

^e All comparisons significant to p<0.001, except NICU LOS in Normal Birthweight Group (p=0.17)

Table 9. Birthweight bias-corrected risk estimates for neonatal outcomes in the low birthweight-to-outcome pathway (n=18,786)

Variable	$\pi_{11}=0.05, \pi_{01}=0.50$			$\pi_{11}=0.10, \pi_{01}=0.75$			$\pi_{11}=0.15, \pi_{01}=0.80$			
	Odds of Low Birthweight			Odds of Low Birthweight			Odds of Low Birthweight			
	RR	2.0	5.0	10.0	2.0	5.0	10.0	2.0	5.0	10.0
Newborn Resuscitation	1.31	1.87	3.28	5.04	2.08	3.74	5.24	2.05	3.45	4.52
NICU Admission	1.39	1.98	3.47	5.35	2.21	3.97	5.79	2.17	3.66	4.79
NICU LOS	1.32	1.89	3.30	5.08	2.10	3.77	5.28	2.06	3.48	4.55
Respiratory Distress Syndrome	1.88	2.69	4.70	7.23	2.98	5.37	7.52	2.94	4.95	6.48
Apnea	1.61	2.30	4.03	6.19	2.56	4.60	6.44	2.52	4.24	5.55
Asphyxia	----	----	----	----	----	----	----	----	----	----
Perinatal Death	1.67	2.39	4.18	6.42	2.65	4.77	6.68	2.61	4.39	5.76

π_{11} = Estimated prevalence of unmeasured causes of low birthweight in the abruption group

π_{01} = Estimate prevalence of unmeasured causes of low birthweight in the non-abruption group

^a Risk estimates are adjusted for unmeasured common causes (confounding) of low birthweight and the specified outcomes. For newborn resuscitation under “2.0” in the first column, the scenario is that 5% of the abruption group and 50% of the non-abruption group have unmeasured common causes (confounding) of low birthweight and newborn resuscitation and that these unmeasured causes result in a 2-fold increase in risk for newborn resuscitation. In this scenario, the original adjusted risk for newborn resuscitation was RR=1.31 and the bias factor yielded a corrected RR=1.87.

Delivery Mode

Descriptive statistics and adjusted regression analyses are presented in Table 10.

All associations between abruption and the neonatal outcomes remained significant in both the vaginal and cesarean delivery groups, indicating a direct negative effect of abruption not through mode of delivery. There were no illogical findings of protective effects of abruption in either group. In other words, abruption is associated with an increased risk of poor neonatal outcomes beyond the risk that can be attributed to cesarean delivery. Bias-adjusted risk estimates for the association between abruption and neonatal outcomes among neonates delivered via cesarean are presented in Table 11. Risk of neonatal outcomes increased across all scenarios indicating that unmeasured causes of cesarean delivery may result in underestimation of the risk associated with abruption for poor neonatal outcomes among neonates delivered by cesarean.

Table 10. Analyses of neonatal outcomes according to abruption status among vaginal and cesarean deliveries

Neonatal Outcome	Vaginal Delivery (n=160,788)			Cesarean Delivery (n=62,464)		
	No Abruptio	Abruptio	Relative Risk (99% CI) ^{a, e}	No Abruptio	Abruptio	Relative Risk (99% CI) ^{a, e}
Newborn Resuscitation, n (%)						
No	124,874 (78.6)	1,109 (60.3)		44,764 (73.8)	1,096 (61.8)	
Yes	34,076 (21.4)	729 (39.7)	1.44 (1.35, 1.53)	15,925 (26.2)	679 (38.2)	1.47 (1.37, 1.57)
NICU Admission, n (%)						
No	145,023 (91.2)	1,158 (63.0)		49,114 (80.9)	755 (42.5)	
Yes	13,927 (8.8)	680 (37.0)	3.87 (3.55, 4.20)	11,575 (19.1)	1,020 (57.5)	2.66 (2.50, 2.82)
NICU LOS, days	6 (0-483) ^b	19 (0-235) ^b	2.28 (1.99, 2.57) ^c	7 (0-426) ^b	21 (0-365) ^b	1.70 (1.53, 1.86) ^c
Respiratory Distress Syndrome, n (%)						
No	156,048 (98.2)	1,518 (82.6)		57,163 (94.2)	1,210 (68.2)	
Yes	2,902 (1.8)	320 (17.4)	8.33 (7.13, 9.53)	3,526 (5.8)	565 (31.8)	4.76 (4.25, 5.26)
Apnea, n (%) ^d						
No	140,449 (98.5)	1,616 (89.2)		54,520 (96.2)	1,365 (81.4)	
Yes	2,076 (1.5)	195 (10.8)	7.41 (6.00, 8.81)	2,126 (3.8)	311 (18.6)	4.55 (3.87, 5.22)
Asphyxia, n (%)						
No	158,710 (99.9)	1,821 (99.1)		60,416 (99.5)	1,716 (96.7)	
Yes	240 (0.1)	17 (0.9)	5.76 (2.00, 9.51)	273 (0.5)	59 (3.3)	7.40 (4.58, 10.21)
Perinatal Death, n (%)						
No	157,726 (99.2)	1,703 (92.7)		60,126 (99.1)	1,687 (95.0)	
Yes	1,224 (0.8)	135 (7.3)	9.52 (7.14, 11.89)	563 (0.9)	88 (5.0)	5.48 (3.78, 7.18)

^a RR estimated with modified Poisson model adjusting for maternal age, race, parity, pre-pregnancy body mass index, insurance, marital status, and study site

^b Data are given as median, range among those admitted to NICU; excludes sites 4 and 8 which did not report NICU LOS

^c Incident rate ratio estimated with negative binomial model

^d Excluding site 6 which did not report neonatal apnea

^e All comparisons significant to p<0.001

Table 11. Delivery mode bias-corrected risk estimates for neonatal outcomes in the cesarean-to-outcome pathway (n=62,464)

Neonatal outcome	$\pi_{11}=0.05, \pi_{01}=0.50$			$\pi_{11}=0.10, \pi_{01}=0.75$			$\pi_{11}=0.15, \pi_{01}=0.80$			
	RR	Odds of Cesarean			Odds of Cesarean			Odds of Cesarean		
		2.0	5.0	10.0	2.0	5.0	10.0	2.0	5.0	10.0
Newborn Resuscitation	1.47	2.10	3.68	5.65	2.33	4.20	5.88	2.30	3.87	5.07
NICU Admission	2.66	3.80	6.65	10.23	4.22	7.60	11.08	4.16	7.00	9.17
NICU LOS	1.70	2.43	4.25	6.54	2.70	4.86	6.80	2.66	4.47	5.86
Respiratory Distress Syndrome	4.76	6.80	11.90	18.31	7.56	13.60	19.04	7.44	12.53	16.41
Apnea	4.55	6.50	11.38	17.50	7.22	13.00	18.20	7.11	11.97	15.69
Asphyxia	7.40	10.57	18.50	28.46	11.75	21.14	29.60	11.56	19.47	25.52
Perinatal Death	5.48	7.83	13.70	21.08	8.70	15.66	21.92	8.56	14.42	18.90

π_{11} = Estimated prevalence of unmeasured causes of cesarean in the abruption group

π_{01} = Estimate prevalence of unmeasured causes of cesarean in the non-abruption group

^a Risk estimates are adjusted for unmeasured common causes (confounding) of cesarean delivery and the specified outcomes. For newborn resuscitation under “2.0” in the first column, the scenario is that 5% of the abruption group and 50% of the non-abruption group have unmeasured common causes (confounding) of cesarean delivery and newborn resuscitation and that these unmeasured causes result in a 2-fold increase in risk for newborn resuscitation. In this scenario, the original adjusted risk for newborn resuscitation was RR=1.47 and the bias factor yielded a corrected RR=2.10.

Chapter 4: Discussion

The purpose of this study was to examine the labor, delivery, and neonatal outcomes associated with placental abruption using a large, U.S.-based cohort with detailed clinical information. Specifically, I evaluated whether there were differences between women with placental abruption and without abruption in terms of 1) duration of labor and mode of delivery, 2) use of newborn resuscitation and duration of stay in the NICU, and 3) risk of neonatal outcomes associated with hypoxia and prematurity. This is the first study to examine the duration of labor (by stage) associated with abruption and the first study in a U.S. population to report the mode of delivery associated with abruption, regardless of timing or type of abruption. This is also the first study in a U.S. population to examine the association between abruption and neonatal morbidities associated with prematurity and hypoxia.

Incidence of Abruption

The incidence of abruption in this sample (1.6%) was higher than previous U.S. reports (0.6-1%),^{7,30,68,93,94} as well as European and Asian studies (0.09- 0.9%),^{4,26,56,60,63,95} but was lower than the reported incidence for Pakistan and India (3.5- 4.7%).⁹⁶⁻¹⁰⁰ A likely explanation for the difference in incidence between this sample and other U.S. studies is that previous studies had utilized the medical record or birth certificate data only to identify cases, whereas in this sample, cases were identified from the maternal and neonatal medical records, supplemented with hospital discharge codes (ICD-9).¹⁰¹ Alternatively, it is also possible that the incidence of abruption has actually

increased over time since this study extends roughly 6 years past the latest previously published data in the U.S. A previous study examining incidence of abruption from 1979-2001 in the U.S. also reported that there was an increasing trend and suggested it may be due to either improved diagnoses or increasing prevalence of risk factors.⁵⁵ The explanation behind differences between this sample and reports coming from other countries are less clear, but are likely due to a combination of differences in cases definitions, as well as underlying population and practice differences.

Mode of Delivery

Pregnancies complicated by placental abruption were more likely to be delivered by cesarean compared to pregnancies that were not complicated by an abruption. The reported incidence of cesarean use in this dataset (47.9% and 51.3%, for nulliparous and multiparous women respectively) is lower than the two previous reports out of the U.S., which had ranged from 53.3% - 96%.^{102,103} However, both of these studies focused on higher risk subpopulations. Witlin and Sibai only included cases of abruption with greater than 20% detachment and excluded cases secondary to trauma, as well as those that were considered chronic, marginal or partial abruptions.¹⁰² Similarly, Allred and Batton only included abruptions that were accompanied by preterm birth.¹⁰⁴ However, the incidence in my sample was also much lower than previous (combined parity) estimates from other countries: Israel (67.7%),¹⁰⁵ Japan (71.7%),¹⁰⁶ Sweden (81.3%),¹⁰⁷ Thailand (84.5%),¹⁰⁸ France (90.3%),¹⁰⁹ and Finland (74.1-91%).^{95,110} The exceptions were estimates from India and Pakistan (25-40%), which also reported significantly worse maternal and neonatal outcomes.^{97-100,111-115}

This lower rate of cesarean delivery for abruption in my sample is not explained by an overall lower cesarean use: the U.S. also had the highest cesarean rate for non-abruption deliveries (26.4-29.5%) compared to the other countries, which ranged from 12.8% (Israel) to 27.7% (Japan).^{105,106} In developing countries, differences in access to health care (especially prenatal care) or inadequate access to resources at the time of delivery may result in more severe cases of abruption, which may necessitate a cesarean more often. Another explanation for discrepancies in cesarean rates may be due to differences in case definitions. While two of the studies did not provide details of their case definitions,^{4,63} those that did typically defined their cases based on symptoms present at the delivery (e.g. substantial blood loss, painful contractions) or presence of retroplacental blood clots during either clinical or pathological examination of the placenta.^{56,60,107,110} One study explicitly excluded mild forms of abruption that resolved.³¹ The current sample included all cases of abruption regardless of the presence of symptoms or pathological findings.

In my sensitivity analysis examining the timing of the abruption relative to labor, my finding of elevated use of cesarean delivery among intrapartum (37.6%- 49.2%) abruption cases was similar to the reported cesarean incidence of 46.9% in the only other study examining outcomes of abruption by timing relative to labor. On the other hand, my finding of elevated use of cesarean (36.8%-40.3%) among antepartum cases was considerably lower than their report of 65.8%.³² The previous study focused exclusively on emergency cesarean deliveries and the high incidence is likely a function of their case definitions, which only included instances of antepartum and intrapartum abruption that required emergent treatment.³² In instances where abruption occurs prior to the onset of

labor, it may be reassuring for patients to know that the likelihood of a cesarean delivery may not be as high as previously reported.

Duration of Labor

Despite the fact that 26.1% - 30.1% of pregnancies complicated by abruption present with hypertonic uterine contractions,^{56,60} placental abruption was not associated with differences in stage 1 or stage 2 labor duration for either nulliparous and multiparous women, regardless of whether they presented in spontaneous labor or were induced. Conversely, abruption was associated with a shorter duration of stage 3 labor among multiparous women with spontaneous labor. However, an adjusted difference of only about one minute could not be considered clinically meaningful. These findings are largely in contrast to the two previous studies which found an elevated incidence of abruption among women with precipitous (<3 hrs) labor.^{61,62} When the total duration of labor was examined in post-hoc analysis in my sample, the overall incidence of abruption was nearly identical between precipitous and non-precipitous labor groups (1% and 1.1%, respectively).

In contrast to the current sample which was restricted to singleton gestations, Mahon et al. restricted their analysis to precipitous labor occurring among singleton pregnancies with vertex presentation, a birthweight greater than or equal to 2500g, and a gestational age greater than or equal to 37 weeks.⁶² Abruption is associated with an incidence of low birthweight ranging from 44.7% to 61.6%^{31,105,106} and an incidence of preterm birth ranging from 39.6% to 69.2%,^{7,56,60,95,105,106,110,113} therefore, Mahon et al. would have likely excluded many typical cases of abruption, which may partly explain their results. However, in a post-hoc analysis restricting my own data to a birthweight

greater than or equal to 2500g and a gestational age greater than or equal to 37 weeks, I was unable to replicate the findings of Mahon's study: there was actually a higher incidence of abruption among women without precipitous labor (0.74%) compared to those with precipitous labor (0.47%). It is possible that underlying population risk factors for abruption may have been more prevalent in that sample compared to the current sample population. Sheiner et al. had a more comparable sample to the one used in the current study, but they did not stratify their models by induction and parity.¹¹⁶ In contrast, I modeled duration of labor as a continuous variable for all three stages and calculated risk separately for nulliparous and multiparous women, as well as for induced and spontaneous labor. This approach allows for a more clinically meaningful analysis because the relationship between abruption and labor duration functioned differently within each of these groups.

In my sensitivity analysis examining the impact of the timing of abruption, many of the comparisons failed to reach statistical significance, but there were trends suggesting that this area may be worth further investigation. In contrast to the main analysis, the labor duration associated with abruption was in some cases much longer and, in others, much shorter depending on parity, the timing of the abruption, and whether the labor was spontaneous or induced. For instance, compared to women without an abruption, stage 1 labor duration among nulliparous women with induced labor was trending toward being significantly *shorter* for women with intrapartum abruption, and women with both antepartum and intrapartum abruption. In contrast, compared to women without an abruption, stage 1 labor duration among multiparous women with either induced or spontaneous labor was trending toward being significantly *longer* for women

with intrapartum abruption, but showed little to no difference for women with both antepartum and intrapartum abruption. Similar patterns of differences can be seen in stage 2 labor duration. Stage 3 labor duration was the only outcome that showed consistency across groups: all induced labor groups showed no significant differences and all spontaneous labor groups showed either significantly shorter labor or trended toward shorter labor.

It may be that cases of abruption that require induction (due to maternal or fetal decline or due to being post-term) represent a different type of case compared to those that have spontaneous labor. Or, these differences may be a reflection of clinicians choosing more conservative management in cases of abruption (utilizing different induction agents or lower doses). It is also possible that cases of abruption that occur before the onset of labor may represent a different etiology than those that occur during labor. Regardless, my findings suggest that the impact of abruption on labor duration may not be as simple as previously thought: it seems that parity, the timing of the abruption, and the use of induction of labor may all play a role in the association between abruption and labor and delivery outcomes. Outcomes associated with abruption are likely to vary considerably depending on the combination of these characteristics.

Newborn Resuscitation, NICU LOS, and Neonatal Outcomes

Abruption was found to be associated with elevated risk of newborn resuscitation, longer length of stay in the NICU, respiratory distress syndrome, asphyxia, apnea, and perinatal death. My finding that 39% of the neonates in deliveries with abruption required resuscitation in the delivery room was comparatively lower than the three previous studies that had examined the need for resuscitation associated with abruption, where

estimates ranged from 50% to 63.4%.^{112,117,118} This is likely due differences in case definitions: previous samples included more severe cases of abruption, whereas my sample likely included more mild cases of antepartum abruption that could have spontaneously resolved without negatively impacting the neonate. However, admission to the NICU (47%) and the median length of stay (20 days) were higher in my sample compared to previous estimates of NICU admission ranging from 20-38.2% and average length of stay of 8.4 days.^{32,69,95} Hasegawa et al. included mild cases of abruption, but their sample's neonates had a higher average gestational age at birth compared to the current sample, which may have lowered their NICU admission rates.³² However, Ross et al. included abruption cases that were initially identified through patient self-report, which might have resulted in a recall bias (i.e. patients with poor birth outcomes would have been more likely to remember details of an abruption compared to patients that had good birth outcomes).⁶⁹ Toivonen et al. only included severe cases, which would be expected to have higher, not lower NICU admission.³¹ Although there is one possible explanation for the difference between my results and the Hasegawa et al. study, it is otherwise unclear why the neonatal admission to the NICU and NICU LOS were higher in my sample.

In my sample, 24.5% of neonates in pregnancies with abruption experienced RDS, which is substantially lower than the 40% reported by Spinillo et al.⁵⁹ However, Spinillo et al. focused on low birthweight neonates only. When my sample was stratified by birthweight, the incidence of RDS in cases of abruption with a low birthweight neonate (48.6%) was actually higher than previous estimates. Although the Spinillo et al. sample had an average gestational age ranging from 32.9-33.9 weeks (depending on the

severity of the abruption), it was unclear what percentage of their cases were born preterm.⁵⁹ It is possible that there were a relatively higher percentage of preterm births among the low birthweight neonates in my sample, which could lead to a higher incidence of RDS. In the second study examining the association between abruption and RDS, Saeed and Rana found that only 15% of the neonates experienced RDS, but there was also a very high perinatal mortality rate (50%).¹¹¹ It is likely that surviving neonates represented less severe cases which may explain the relatively low incidence of RDS.

Only one previous study reported the incidence of asphyxia (47.6%) among cases of abruption, which was substantially higher than my estimate of asphyxia (2.1%).¹⁰⁸ This relatively small (n=103) study by Pitaphrom and Sukcharoen was conducted outside of the U.S. and there was evidence to suggest that the abruption cases may have been of the more severe type.⁶⁰ I am the first to report an elevated risk of neonatal apnea associated with abruption. Neonatal apnea is due to underdevelopment of respiratory control, most frequently as a consequence of prematurity.¹¹⁹ As abruption is frequently accompanied by preterm birth, an elevated risk of apnea in the context of abruption is plausible, but it is not clear why this association was also found among term neonates. It may be that abruption is independently associated with physiologic underdevelopment. Lastly, I found an overall incidence of perinatal mortality of 6.2%, which is lower than previous reports from the U.S. from the 1990's- early 2000's which had an estimated perinatal mortality of 10.3-11.9%.^{94,120,121} Perinatal mortality associated with abruption is generally lower in the U.S. compared to other countries, which have reported incidence ranging from 8.3-67.9%.^{59,98,105,108,113,122}

In my sensitivity analysis examining the impact of the timing of abruption, the association between abruption and newborn resuscitation, NICU length of stay, and neonatal outcomes remained significant regardless of timing, but the analysis revealed some important differences between groups. Generally, I found that neonates in pregnancies complicated with both antepartum and intrapartum abruption tended to have the highest risk of poor outcomes. In contrast, with the exception of asphyxia, neonates in pregnancies complicated with antepartum abruption had the lowest relative risk across outcomes. It may be that pregnancies with both antepartum and intrapartum abruption represent more severe disease, while my antepartum group may be reflecting more mild cases of abruption that spontaneously resolved during pregnancy.

In my sample, admission to the NICU occurred in 38.3% of antepartum abruptions, 49.8% of intrapartum abruptions, and 52.3% of pregnancies with both antepartum and intrapartum abruption. The only previous study to report neonatal outcomes by timing of abruption relative to labor reported NICU admission in 73.7% of antepartum abruptions and only 21.9% of intrapartum abruptions.³² However, this discrepancy may be explained by the fact that the sample included only cases that required emergent treatment and did not distinguish cases that had both antepartum and intrapartum abruption. With the exception of NICU admission, this is the first study to report neonatal outcomes associated with abruption, while distinguishing the timing relative to labor.

In this sample, 53.3% of neonates in pregnancies complicated by abruption were born preterm, which is within estimates reported in the literature ranging from 39.6% - 69.2%.^{7,56,60,95,105,106,110,113} In my sensitivity analysis stratifying by preterm status,

abruption remained a significant risk factor for newborn resuscitation and all neonatal outcomes regardless of gestational age, indicating that the association between abruption and adverse neonatal outcomes was not strictly due to being delivered preterm. However, despite a significant risk for NICU admission in both groups, NICU LOS was significant only for the preterm group. However, consistent with the literature on perinatal mortality, my study demonstrated that there were increased risks of poor neonatal outcomes associated with abruption even among term neonates.^{68,121,123}

One of the novel findings in this study was the elevated risk of RDS among term neonates. This disorder is primarily attributed to insufficient surfactant production and underdevelopment of the lungs, and most frequently occurs in preterm neonates.¹²⁴ However, there have been some reports of increased risk of RDS in cases of chronic intrauterine hypoxia and growth restriction and perhaps this mechanism is responsible in the case of abruption.¹²⁵ I also found that RDS and apnea were twice as frequent among preterm neonates in pregnancies complicated by abruption compared to preterm pregnancies not complicated by abruption. It is important for clinicians to be aware of the increased risk of underdeveloped lung function among term neonates with abruption as well as elevated risk beyond that which would normally be expected for a preterm neonate.

In this sample, 45.4% of neonates in pregnancies complicated by placental abruption had a low birthweight, which is comparable to the reports in the literature ranging from 44.7% to 61.6%.^{31,105,106} In my sensitivity analysis stratifying the results by low birthweight status, the association between abruption and risk of newborn resuscitation and neonatal outcomes remained significant regardless of birthweight status,

indicating that the association between abruption and adverse neonatal outcomes was not strictly due to being low birthweight. NICU LOS was only significantly increased with abruption among neonates with low birthweight.

Although abruption remained a risk factor for all neonatal outcomes among both groups, it is worth noting that risk of neonatal morbidity was greatly elevated among low birthweight neonates in pregnancies complicated by abruption. In the abruption group, nearly half (48.6%) of the neonates developed RDS and 29.2% experienced apnea. In contrast, only 25.6% of low birthweight neonates without abruption developed RDS, and only 19.3% experienced apnea. This information may be useful for advising patients on what risks may be anticipated after delivery and also suggests potential for increased risks in the setting of abruption coupled with low birthweight.

Abruption was also associated with elevated risk of newborn resuscitation, longer NICU length of stay, and poor neonatal outcomes regardless of delivery mode. However, in the vaginal delivery group, the NICU length of stay was longer, and there was higher risk of RDS, apnea, and perinatal death. The interpretation of these results is more difficult because it depends on whether vaginal or cesarean delivery should be considered the optimal delivery mode. It is possible that risks in the cesarean group are underestimated because there are competing causes necessitating cesarean delivery, in which case the bias-adjusted results provide us with a range of possible estimates. It is also possible that vaginal delivery may be the risk group because it could prolong exposure to oxygen deprivation for the neonate.

Strengths

I present a large, multi-site study of 223,252 deliveries (with 3,613 cases of abruption), with detailed clinical data that allowed examination of less common outcomes, as well as the ability to adjust for a number of potential confounders. Additionally, this study is unique in the collection of labor information which allowed me to examine duration of labor by stage.

Limitations

The results of this study cannot be considered to be representative of the entire U.S. population. This sample includes only hospital births and would therefore not be generalizable to births taking place at home or in birthing centers. I utilized data from a retrospective, observational study of EMRs, and there was some missing outcome data, which slightly reduced the sample size in some instances (labor duration, apnea, NICU LOS).

The duration of labor estimates only included women who delivered vaginally, as regression methods to examine duration of labor that include intrapartum cesarean deliveries while adjusting for covariates are as of yet undeveloped.¹²⁶ Cesarean deliveries would have right censoring during either stage 1 or stage 2 labor (at the time the cesarean was performed) that would be dependent on a number of other factors not addressed in this study. If there were serious signs of neonatal distress or complications occurring, the physician may have made the decision to intervene earlier, in which case, the recorded duration of labor may be much shorter. Conversely, if the cesarean was performed as a consequence the labor progressing much slower than anticipated, the duration of labor might be much longer.

Finally, there are limitations for my sensitivity analyses examining the impact of the timing of abruption. Approximately half of the sites failed to report whether the abruption occurred before or during labor, likely due to the way that the information was recorded in the EMR. However, it is important to note that there was a very large remaining sample size (n=145,212). For those sites that did report the information, I only know whether the abruption occurred before or after the onset of labor, but I do not have more specific information in terms of gestational age (for antepartum) or exact timing in the labor process (for intrapartum). It is possible that an abruption classified as “intrapartum” was actually an undetected antepartum abruption. However, in order to understand how this misclassification would affect results, I would need to know what outcomes are associated with verified cases of antepartum and intrapartum abruption, data for which are not yet available. The fact that neonates in the intrapartum category had the lowest average birthweight suggested that it is more likely that those cases represent a chronic process, but it is not clear whether it was an antepartum abruption or more general chronic placental malfunctioning.

Clinical Implications

Abruption is associated with higher risk of cesarean delivery, but it remains unclear whether cesarean is the optimal delivery mode when abruption occurs. However, determining the optimal delivery mode is not straightforward. Recently, there has been a growing effort to reduce the use of medically unnecessary cesarean delivery since it is a major surgical procedure associated with significant short- and long-term risks for both the mother and the neonate.^{127,128} There are certain clinical indications in which cesarean delivery is medically necessary, for example as a life saving measure for either the

mother or the neonate in the setting of a uterine rupture, but there are other circumstances in which cesarean delivery may be avoidable (e.g., not allowing enough time in labor before performing a cesarean for failed induction or failure to progress).¹²⁷ The decision of whether a cesarean is indicated should be based on the balance of risks and benefits for both the mother and child, which includes a number of factors. In addition, the decision for cesarean can also be influenced by fear of legal ramifications for the physician and hospital if there is a poor outcome.¹²⁷

In the case of acute or more severe abruption, for which there is significant risk of blood loss for the mother and oxygen deprivation for the neonate, the benefits associated with cesarean delivery may outweigh the risks. However, a prospective study capturing detailed information about the presentation of each case (maternal and fetal symptoms, severity of the abruption), labor progress, the indication for the cesarean, and both short- and long-term maternal and neonatal outcomes would be necessary to accurately determine whether cesarean really is the optimal route of delivery with lesser degrees of abruption with no other clinical indications.

This study also revealed some important new information about the neonatal morbidities associated with abruption. This information can inform prospective parents about the potential risk of certain outcomes after birth, but it should be cautioned that these risks are also a function of the severity of the abruption, which was not captured in this study. An increased risk does not mean that the event will definitely occur, only that there is a higher likelihood. Increased risks of apnea and respiratory distress syndrome suggest that clinicians should be aware that neonates may require closer monitoring after birth.

Future Directions for Research

One potential direction of study would be a natural history or developmental study that captures detailed, serial measurements during pregnancy on placental morphology (size, thickness, location in the uterus, percentage of detachment of placenta when abruption occurs), Doppler measurements (to understand blood flow to and from the placenta and any vascular abnormalities), which can be linked with detailed pathological analysis of the placenta following birth. Cumulatively, this information would greatly improve our understanding of how the placenta develops and changes over the course of pregnancy both in normal and pathological cases. Coupled with outcome measures (including abruption), this information may provide us with new insight into normal placental functioning and perhaps new and/or earlier markers for poor placental functioning.

Examining the latency period between antepartum abruption and the onset or induction of labor would be another area for future exploration. Determining the duration of time between the gestational age at which the antepartum abruption occurs, as well as its severity, and the gestational age at delivery would provide information about how often antepartum abruptions trigger contractions or necessitate medical intervention, as well as how much time elapses between these events. With that knowledge, we would have a better understanding of how often abruptions spontaneously resolve, as well as the conditions under which it is unlikely to resolve, and we would be better able to advise patients as to their prognosis for preterm labor and/or need for intervention.

Another direction for future research would be to evaluate the long-term consequences of abruption for surviving neonates. Beyond outcomes such as sudden

infant death syndrome and cerebral palsy, it would be interesting to determine whether there are long-term developmental, respiratory or other chronic disease issues in childhood and adulthood. It would also be informative to investigate whether the associated risks were different depending on whether the abruption occurred term or preterm, antepartum or intrapartum, as well as whether the outcomes were different among neonates with or without low birth weight.

Lastly, as there are considerable ethical issues with experimental research in pregnancy, another area of future study should focus on the search and development of animal models of more representative models of human placental disorders. Although animal models have proven useful for studying many other types of diseases, the human placenta has a combination of unusual characteristics that are not seen in any other species. The mouse, which is highly utilized and relatively inexpensive to maintain, has very shallow trophoblastic invasion of the uterine arteries (vs. the extensive invasion seen in humans) and a labyrinthine placental exchange area (vs. a villous area in humans).¹²⁹ There are certainly other differences between the mouse and human pregnancy models (immunological and endocrine), but these differences in the attachment type are very important when modeling remodeling and repair of the attachments, as well as fetal growth restriction.¹²⁹ There are even placentation differences between humans and non-human primates, including the development of the attachment between the placenta and the uterine wall and establishment of the maternal placental circulation. Although non-human primates may be most similar to humans, they are less likely to become a commonly used animal model because of the ethical considerations that arise and because of the cost involved with caring for large animals with long lifespans.¹²⁹ There are several

species that are under investigation, but as of now, we have not yet identified an animal model with the same type of placental attachment as is seen in humans. If we were able to successfully develop an animal model (or even a series of models for different aspects of placentation), it would greatly increase our understanding of placental function and dysfunction and would allow for investigation of potential interventions and treatments.

Summary and Conclusions

In this study, I examined labor, delivery and neonatal outcomes associated with placental abruption. I found that abruption was associated with elevated risk of cesarean delivery and shorter duration of stage 3 labor duration among multiparous women with spontaneous labor; however, the difference in duration was only about one minute and was not clinically meaningful. The main analysis results, in combination with the sensitivity analyses, revealed that the relationship between abruption and labor duration is more complicated than previously reported and is likely variable depending on parity, the presence or absence of induction of labor, as well as the timing of the abruption relative to labor.

I also found that abruption was associated with an elevated risk of newborn resuscitation, NICU admission and longer LOS, apnea, asphyxia, respiratory distress syndrome, and perinatal mortality. According to the results of this study, abruption was associated with elevated risk beyond the initial delivery period, and these risks were not solely attributable to an association with preterm birth, low birth weight, or cesarean delivery.

This is the first study to examine labor duration associated with abruption and is the largest study in a U.S. population to examine the association between abruption and

cesarean delivery. I am also the first to report an increased risk of apnea among cases of abruption and the first to report the incidence and risk of newborn resuscitation, NICU length of stay (LOS), RDS, and asphyxia in cases of abruption in the U.S. Additionally, with the exception of NICU admission, I am the first to report associations between neonatal morbidity and mortality separately for antepartum and intrapartum abruption, which represents an important step forward for understanding the consequences of this disorder. Lastly, I am the first to report neonatal morbidities associated with abruption separately by gestational age and birthweight, which provided valuable clinical information about the unique risks associated with abruption for term, preterm, low birthweight and non-low birthweight groups.

In conclusion, although relatively rare, placental abruption is associated with elevated risk of cesarean delivery, as well as neonatal risks that can extend beyond the immediate birth period. These findings add to the burgeoning literature highlighting the importance of placental functioning on health during infancy.

APPENDIX A

Appendix A.1 Original Coding of Variables Included in Current Study

Variable	Source	Original Coding
Race	Demographics	White/non-Hispanic Black/non-Hispanic Hispanic Asian/Pacific Islander Multi-racial Other race Unknown Missing
Marital status	Demographics	Married Not married: divorced/widowed Not married: single Unknown Missing
Insurance type	Demographics	Private Public Self-pay Other Unknown Missing
Maternal Age (years)	Demographics	Duration between birthdate and date of delivery
History of cesarean delivery	Reproductive History	No Yes Unknown Missing
Parity	Reproductive History	Continuous variable
Pre-pregnancy body mass index (BMI) (kg/m ²)	Medical History	Continuous variable
Antepartum abruption	Prenatal history of current pregnancy	No/Unknown ^a Yes Missing
Number of fetuses	Prenatal history of current pregnancy	Continuous variable
Date/time of spontaneous onset of labor	Admission to L&D	Date-time
Cervical dilation at first exam (cm)	Labor & Delivery	Continuous variable
Gestational age	Admission to L&D	Continuous variable
Intrapartum abruption	Labor & Delivery	No/Unknown ^a Yes Missing

Variable	Source	Original Coding
Date/time of induction of labor	Labor & delivery	Date-time
Date/time of complete dilation	Labor & delivery	Date-time
Date/time of delivery	Labor & delivery	Date-time
Date/time of placental delivery	Labor & delivery	Date-time
Mode of delivery	Labor & delivery	Vaginal Vaginal-assisted VBAC Cesarean Cesarean-repeat Missing
ICD-9 code for abruption	Discharge codes	No Yes
Neonatal outcomes		
Resuscitate	Newborn resuscitation	No/unknown ^a Yes Missing
Birthweight (grams)	Newborn information	Continuous variable
NICU admission	Newborn information	No Yes
NICU length of stay (days)	Newborn information	Continuous variable
Asphyxia	NICU Outcomes	No Yes Unknown Missing
Hypoxic-Ischemic Encephalopathy	NICU Outcomes	No Yes Unknown Missing
Respiratory distress syndrome	NICU Outcomes	No Yes Unknown Missing
Apnea	NICU Outcomes	No Yes Unknown Missing
Neonatal death	NICU Outcomes	No Yes Unknown Missing

^a For checkbox type items in data collection, an outcome was recorded as ‘yes’ if the box was checked. For the sites that reported that variable, an unchecked box was considered as “no” or “unknown.” However, in

the case of all three affected variables, it would be highly unlikely for these events to go unrecorded. Therefore, unchecked boxes will generally be interpreted as the absence of the specified variable. If a site did not report a particular variable, then the entire variable was coded as missing for that site.

Appendix A.2 Summary Table of Study Variables

Variable Name	D.V.	I.V.	C.
Objective 1: Determine whether the duration of labor and the mode of delivery are different among women with placental abruption compared to women without abruption.			
Placental abruption		X	
Duration of labor (stage 1)	X		
Duration of labor (stage 2)	X		
Duration of labor (stage 3)	X		
Delivery Mode	X		
- Vaginal			
- Cesarean			
Cervical dilation at first exam			X
Induction of labor ^a			X
- No			
- Yes			
Maternal age			X
Parity ^a			X
- Nulliparous			
- Multiparous			
Gestational age			X
Birthweight			X
Race			X
- White/non-Hispanic			
- Black/non-Hispanic			
- Hispanic			
- Asian/Pacific Islander			
- Multi-racial/Other			
Insurance			X
- Private			
- Public			
- Self-pay/Other			
Marital status			X
- Single			
- Married			
Pre-pregnancy BMI			X
History of cesarean delivery			X
Study site			
Objective 2 & 3: Determine whether the use of newborn resuscitation, neonatal admission to and duration of stay in the NICU, and neonatal outcomes are different among women with placental abruption compared to women without abruption.			
Variable Name	D.V.	I.V.	C.
Placental abruption		X	
NICU length of stay (LOS)	X		

Variable Name	D.V.	I.V.	C.
<i>Dichotomous Variables</i>			
Newborn resuscitation required	X		
NICU admission	X		
Respiratory distress syndrome	X		
Hypoxic-Ischemic Encephalopathy ^b	X		
Apnea	X		
Asphyxia	X		
Perinatal (stillbirth + neonatal) Mortality	X		
Maternal age			X
Parity			X
- Nulliparous			
- Multiparous			
Gestational age ^c			
Birthweight ^c			
Mode of delivery ^c			X
- Vaginal			
- Cesarean			
Race			X
- White/non-Hispanic			
- Black/non-Hispanic			
- Hispanic			
- Asian/Pacific Islander			
- Multi-racial/Other			
Insurance			X
- Private			
- Public			
- Self-pay/Other			
Marital status			X
- Single			
- Married			
Pre-pregnancy BMI			X
Study site			X

D.V.= Dependent Variable, I.V. = Independent Variable, C.= Covariate

^a Stratification variables

^b Subsequently dropped from analysis due to too few cases

^c Sensitivity analyses

APPENDIX B

Appendix B.1 Original and imputed overall pregnancy characteristics (n=223,252)

Pregnancy sample characteristics	Original Data ^a	Imputed Values
Maternal Age, years ^b	27.6 ± 6.2	27.6 ± 6.2
<i>Missing, n (%)</i>	<i>239(0.1)</i>	
Maternal Race, n (%)		
White	110,447 (51.6)	115,788 (51.9)
Black	50,233 (23.5)	52,461 (23.5)
Hispanic	39,037 (18.2)	40,155 (18.0)
Asian	9,207 (4.3)	9,417 (4.2)
Multi/Other	5,295 (2.5)	5,431 (2.4)
<i>Missing, n (%)</i>	<i>9,033 (4.1)</i>	
Pre-pregnancy BMI ^b	25.4 ± 6.2	25.7 ± 6.6
<i>Missing, n (%)</i>	<i>74,855 (33.5)</i>	
Insurance, n (%)		
Private	124,865 (62.4)	138,563 (62.1)
Public	72,130 (36.1)	80,910 (36.2)
Self-pay/Other	2,980 (1.5)	3,779 (1.7)
<i>Missing, n (%)</i>	<i>23,277 (10.4)</i>	
Marital Status, n (%)		
Single	84,999 (39.3)	87,980 (39.4)
Married	131,177 (60.7)	135,272 (60.6)
<i>Missing, n (%)</i>	<i>7,076 (3.2)</i>	
Parity, n (%)		
Nulliparous	88,975 (39.9)	
Multiparous	134,277 (60.2)	
History of Cesarean ^c , n (%)		
No	90,724 (74.8)	102,882 (76.6)
Yes	30,622 (25.2)	31,395 (23.4)
<i>Missing, n (%)</i>	<i>12,931 (9.6)</i>	
Cervical Dilation at first exam, cm ^b	3.2 ± 2.1	3.1 ± 2.1
<i>Missing, n (%)</i>	<i>46,804 (21.0)</i>	
Induction of Labor, n (%)		
No	146,124 (65.5)	
Yes	77,128 (34.6)	
Birthweight, grams ^b	3,244 ± 606	3242 ± 610
<i>Missing, n (%)</i>	<i>2,468 (1.1)</i>	
Gestational Age, weeks ^b	38.3 ± 2.4	

^a Descriptive statistics prior to imputation are reported as percentages within non-missing data; the missing percentage is reported out of all data

^b Data are given as mean ± SD

^c Among multiparous women

APPENDIX C

Appendix C.3s Maternal, Pregnancy, and neonatal characteristics according to timing of placental abruption

	No Abruption (n=143,054)	Antepartum Abruption ^a (n=967)	Intrapartum Abruption ^a (n=629)	Antepartum + Intrapartum ^a (n=562)	P value ^d
Maternal age, years ^b	27.8 ± 6.2	27.3 ± 6.2	27.6 ± 6.2	27.7 ± 6.0	0.03
Maternal race, n (%)					
White	73,862 (51.6)	472 (48.8)	152 (24.2)	398 (70.8)	<0.001
Black	33,673 (23.5)	327 (33.8)	294 (46.7)	68 (12.1)	
Hispanic	26,619 (18.6)	132 (13.7)	153 (24.3)	77 (13.7)	
Asian	4,663 (3.3)	17 (1.8)	9 (1.4)	16 (2.9)	
Multi/Other	4,237 (3.0)	19 (2.0)	21 (3.3)	3 (0.5)	
Pre-pregnancy BMI ^b	25.6 ± 6.4	26.4 ± 7.0	26.6 ± 7.3	24.9 ± 5.8	<0.001
Insurance, n (%)					
Private	87,544 (61.2)	492 (50.9)	231 (36.7)	363 (64.6)	<0.001
Public	53,013 (37.1)	461 (47.7)	387 (61.5)	197 (35.0)	
Self-pay/other	2,497 (1.8)	14 (1.4)	11 (1.8)	2 (0.4)	
Marital status, n (%)					
Single	54,578 (38.2)	473 (48.9)	373 (59.3)	160 (28.5)	<0.001
Married	88,476 (61.8)	494 (51.1)	256 (40.7)	402 (71.5)	
Parity, n (%)					
Nulliparous	57,447 (40.2)	320 (33.1)	210 (33.4)	193 (34.3)	<0.001
Multiparous	85,607 (59.8)	647 (66.9)	419 (66.6)	369 (65.7)	
Cervical dilation at first exam, cm ^b	3.1 ± 2.1	2.9 ± 2.3	2.8 ± 2.3	2.9 ± 2.3	<0.001
History of Cesarean, n (%) ^c					
No	65,408 (76.4)	475 (73.4)	292 (69.7)	293 (79.4)	0.002
Yes	20,199 (23.6)	172 (26.6)	127 (30.3)	76 (20.6)	
Induction of Labor, n (%)					
No	88,379 (61.8)	703 (72.7)	457 (72.7)	475 (84.5)	<0.001
Yes	54,675 (38.2)	264 (27.3)	172 (27.3)	87 (15.5)	
Birthweight, grams ^b	3260 ± 594	2695 ± 867	2361 ± 984	2478 ± 882	<0.001
Gestational age, weeks ^b	38.4 ± 2.2	34.4 ± 4.7	34.4 ± 4.9	34.9 ± 4.3	<0.001

^a Antepartum abruption are cases that occurred prior to the onset of labor, intrapartum abruption are cases that occurred during labor and the combined group are those who had abruption documented both before and during labor; ^b Data are given as mean ± SD; ^c Among multiparous women; ^d Significance values for the 4-group comparison

Appendix C.6s Maternal, pregnancy, and neonatal characteristics according to abruption status among term and preterm deliveries

	Term (n=197,155)			Preterm (n=26,097)		
	No Abruptio	Abruptio	P value	No Abruptio	Abruptio	P value
Maternal Age, years ^a	27.6 ± 6.1	27.8 ± 6.2	0.37	27.5 ± 6.6	27.4 ± 6.4	0.57
Maternal Race, n (%)						
White	103,841 (53.1)	836 (49.6)	<0.001	10,268 (42.5)	843 (43.8)	0.001
Black	43,267 (22.1)	491 (29.1)		8,015 (33.2)	688 (35.7)	
Hispanic	35,145 (18.0)	272 (16.1)		4,430 (18.3)	308 (16.0)	
Asian	8,556 (4.4)	69 (4.1)		754 (3.1)	38 (2.0)	
Multi/Other	4,659 (2.4)	19 (1.1)		704 (2.9)	49 (2.5)	
Pre-pregnancy BMI ^a	25.6 ± 6.5	25.8 ± 6.6	0.37	26.4 ± 7.1	26.1 ± 6.9	0.10
Insurance, n (%)						
Private	124,062 (63.5)	905 (53.6)	<0.001	12,701 (52.6)	895 (46.5)	<0.001
Public	68,223 (34.9)	762 (45.2)		10,935 (45.2)	990 (51.4)	
Self-pay/Other	3,183 (1.6)	20 (1.2)		535 (2.2)	41 (2.1)	
Marital Status, n (%)						
Single	74,386 (38.1)	727 (43.1)	<0.001	11,831 (49.0)	1,036 (53.8)	<0.001
Married	121,082 (61.9)	960 (56.9)		12,340 (51.0)	890 (46.2)	
Parity, n (%)						
Nulliparous	117,564 (60.1)	1,096 (65.0)	<0.001	14,392 (59.5)	1,225 (63.6)	<0.001
Multiparous	77,904 (39.9)	591 (35.0)		9,779 (40.5)	701 (36.4)	
Birthweight, grams ^a	3369 ± 452	3199 ± 484	<0.001	2327 ± 765	1,788 ± 744	<0.001
Gestational Age, weeks ^a	39.0 ± 1.1	38.6 ± 1.2	<0.001	33.6 ± 3.2	31.2 ± 3.9	<0.001

^aData are given as mean ± SD; ^b Among Multiparous women

Appendix C.8s Maternal, pregnancy, and neonatal characteristics according to abruption status among neonates without and with low birthweight

	Non- Low Birthweight (n=204,466)			Low birthweight (n=18,786)		
	No Abruption	Abruption	P Value	No Abruption	Abruption	P Value
Maternal Age ^a	27.6 ± 6.1	27.9 ± 6.2	0.10	27.1 ± 6.7	27.2 ± 6.5	0.25
Maternal Race, n (%)						
White	107,603 (53.1)	992 (50.6)	<0.001	6,506 (38.0)	687 (41.5)	<0.001
Black	44,866 (22.2)	544 (27.8)		6,416 (37.4)	635 (38.4)	
Hispanic	36,527 (18.0)	321 (16.4)		3,048 (17.8)	259 (15.7)	
Asian	8,717 (4.3)	79 (4.0)		593 (3.5)	28 (1.7)	
Multi/Other	4,794 (2.4)	23 (1.2)		569 (3.3)	45 (2.7)	
Pre-pregnancy BMI ^a	25.6 ± 6.5	25.9 ± 6.6	0.12	26.0 ± 7.0	26.0 ± 7.0	0.92
Insurance, n (%)						
Private	128,327 (63.4)	1,068 (54.5)	<0.001	8,436 (49.2)	732 (44.3)	<0.001
Public	70,838 (35.0)	862 (44.0)		8,320 (48.6)	890 (53.8)	
Self-pay/Other	3,342 (1.7)	29 (1.5)		376 (2.2)	32 (1.9)	
Marital Status, n (%)						
Single	76,992 (38.0)	835 (42.6)	<0.001	9,225 (53.8)	928 (56.1)	0.08
Married	125,515 (62.0)	1,124 (57.4)		7,907 (46.2)	726 (43.9)	
Parity, n (%)						
Nulliparous	122,711 (60.6)	1,298 (66.3)	<0.001	9,245 (54.0)	1,023 (61.9)	<0.001
Multiparous	79,796 (39.4)	661 (33.7)		7,887 (46.0)	631 (38.1)	
Birthweight ^a	3369 ± 435	3179 ± 441	<0.001	1910 ± 568	1580 ± 593	<0.001
Gestational Age ^a	38.8 ± 1.4	38.0 ± 1.9	<0.001	33.5 ± 4.1	30.8 ± 4.1	<0.001

^a Reported as mean ± standard deviation

Appendix C.10s Maternal, pregnancy, and neonatal characteristics according to abruption status among vaginal and cesarean deliveries

	Vaginal Delivery (n=160,788)			Cesarean Delivery (n=62,464)		
	No Abruption	Abruption	P Value	No Abruption	Abruption	P Value
Maternal Age ^a	27.1 ± 6.0	26.8 ± 6.0	0.06	29.0 ± 6.4	28.4 ± 6.6	<0.001
Maternal Race, n (%)						
White	85,657 (53.9)	947 (51.5)	<0.001	28,452 (46.9)	732 (41.2)	<0.001
Black	35,236 (22.2)	537 (29.2)		16,046 (26.4)	642 (36.2)	
Hispanic	27,786 (17.5)	283 (15.4)		11,789 (19.4)	297 (16.7)	
Asian	6,616 (4.2)	40 (2.2)		2,694 (4.4)	67 (3.8)	
Multi/Other	3,655 (2.3)	31 (1.7)		1,708 (2.8)	37 (2.1)	
Pre-pregnancy BMI ^a	24.8 ± 6.1	25.0 ± 6.5	0.77	27.8 ± 7.2	27.0 ± 6.9	<0.001
Insurance, n (%)						
Private	99,753 (62.8)	903 (49.1)	<0.001	37,010 (61.0)	897 (50.5)	<0.001
Public	56,327 (35.4)	902 (49.1)		22,831 (37.6)	850 (47.9)	
Self-pay/Other	2,870 (1.8)	33 (1.8)		848 (1.4)	28 (1.6)	
Marital Status, n (%)						
Single	62,242 (39.2)	884 (48.1)	<0.001	23,975 (39.5)	879 (49.5)	<0.001
Married	96,708 (60.8)	954 (51.9)		36,714 (60.5)	896 (50.5)	
Parity, n (%)						
Nulliparous	97,135 (61.1)	1,209 (65.8)	<0.001	34,821 (57.4)	1,112 (62.6)	<0.001
Multiparous	61,815 (38.9)	629 (34.2)		25,868 (42.6)	663 (37.4)	
Birthweight ^a	3263 ± 539	2553 ± 898	<0.001	3232 ± 717	2337 ± 987	<0.001
Gestational Age ^a	38.5 ± 2.0	35.2 ± 4.6	<0.001	38.0 ± 2.7	34.1 ± 4.9	<0.001

^a Reported as mean ± standard deviation

Glossary

Advanced Maternal Age	Maternal age >35 at time of pregnancy
Advanced Resuscitation	Resuscitation beyond basic techniques- includes tracheal intubation, cardiac defibrillation and administration of medications
Amniotic Fluid	Protective liquid contained within amniotic sac of pregnant female
Anemia	Lack of sufficient healthy red blood cells to carry sufficient oxygen to tissue
Antepartum	Before Labor
Apgar Scores	Score representing health of newborn immediately after birth: Appearance, Pulse, Grimace, Activity, Respiration. Frequently assessed/recorded at 1 minute and 5 minutes after birth; Ranges from 0-10, with scores 7+ considered normal (add info on interpretation)
Apnea	Suspension of external breathing (no movement of muscles for inhaling and no volume change of lungs)
Artificial Rupture of Membranes (AROM)	A technique for inducing or augmenting labor; Puncturing the amniotic membrane with a tool; this allows the amniotic fluid to drain, which stimulates uterine contractions; this is in contrast to spontaneous rupture of membranes in which the membrane breaks on it's own during the labor process
Assisted Ventilation	a method to assist or replace spontaneous breathing; examples include air being pushed into the lungs by a medical professional using a bag/bellows or with a ventilating machine paired with a tube that is placed in the person's throat

Basic Resuscitation	Non-invasive resuscitation techniques includes cardiopulmonary resuscitation, bag-mask ventilation, oxygen supplementation
Birth Asphyxia	a medical condition that occurs when a neonate's brain and other organs do not get enough oxygen before, during or immediately after; the oxygen deprivation occurs long enough to cause physical damage- most frequently to the brain
Birthweight: Appropriate for Gestational Age (AGA)	Measurement based on estimated gestational age, gender and what birthweight is considered normal for the timing of delivery; appropriate weight for a full-term infant is between 2,500-4,000 grams
Birthweight: Large for Gestational Age (LGA)	Typically a birthweight, length or head circumference that lies about 90th percentile for the gestational age
Birthweight: Small for Gestational Age (SGA)	Neonates born smaller than normal for the gestational age- typically weight below the 10th percentile; also sometimes referred to as growth restriction
Cardiovascular Disease	Generally refers to disease of the heart and blood vessels, frequently due to atherosclerosis (plaque builds up on walls of arteries); heart attacks, ischemic stroke, heart failure, arrhythmia, heart valve problems and stroke
Chorioamnionitis	inflammation of fetal membranes (amnion and chorion) due to bacterial infection
Chronic Kidney Disease	Includes conditions damaging the kidneys or decreasing their ability to function properly; can be caused by diabetes, high blood pressure or other disorders; can progress to kidney failure which will require either dialysis or transplantation
Chronic Lung Disease	In infants, typically damaged tissue in the lungs which can then trap air or collapse, filling with fluid; also known as bronchopulmonary dysplasia; generally a term for long-term respiratory problems in premature neonates; can also refer to asthma and chronic obstructive pulmonary disease (chronic

bronchitis and emphysema)

Coagulation Disorder

A disorder dealing with the body's ability to control blood clotting; hemophilia is the most common coagulation disorder (body bleeds for an extended period of time before clotting)

Coronary Artery Disease

Disease in which plaque builds up inside the coronary arteries which can block blood flow

Disseminated Intravascular Coagulopathy (DIC)

Disease in which proteins that control blood clotting become over-active; small blood clots can form and cut off blood supply to organs; it also leads to the clotting factors being used up too quickly, which can then lead to uncontrolled bleeding

Dysfibrinogenemia

Typically inherited abnormality that results in defective fibrin clot formation, which can lead to bleeding complications

Emergency Hysterectomy

Emergency removal of the uterus - typically necessitating due to uncontrolled bleeding of the uterus

Endocrine system

Glands that secrete hormones directly into the circulatory system

Endometrium

Inner mucous membrane of the mammalian uterus

Fetal Death

Spontaneous intrauterine death of a fetus at any time during pregnancy, but typically refers to fetal death prior to 20 weeks gestation; also sometimes termed 'stillbirth'

Fetal Distress

Presence of signs before or during childbirth that suggest fetus is not well; typical signs are decreased movement; meconium in the amniotic fluid; abnormally fast or slow heart rate, decreased variability in the heart rate, metabolic acidosis, elevated lactate levels

Fetal Membrane	Consist of chorion, amnion, yolk sac and allantois
Fetal Viability	Ability of the fetus to survive outside of the uterus; in the US, it is typically considered 23-24 weeks of gestation
Fibrinogen	a glycoprotein in vertebrates that helps form blood clots
First Stage of Labor	Duration of time from the start of labor contractions to full dilation of the cervix (10 cm)
First Trimester of Pregnancy	0-13 weeks of gestation
Growth Restriction	A fetus that is smaller than it should be due to abnormal growth rate; typically it is a neonate that is smaller than 90% of neonates at the same gestational week
Hypertension	high blood pressure (>140/90mmHg). Chronic/pre-existing hypertension is disease existing prior to the start of pregnancy
Hypofibrinogenemia	Deficiency of fibrinogen
Hypoxia	Condition in which body or region of body is deprived of adequate oxygen supply
Hypoxic-Ischemic Encephalopathy	Evidence of acute of sub-acute brain injury due to asphyxia; also called perinatal asphyxia
Induction of Labor	Artificially starting the process of labor through one of several methods including AROM, separating the amniotic sac from wall of uterus ('stripping the membranes'), mechanical dilation, and medications like Pitocin
Intrapartum	During labor

Intraventricular Hemorrhage	Bleeding into the fluid-filled areas (ventricles) of the brain; most frequently occurs in neonates that are born premature; primarily due to the under-developed, fragile blood vessels
Low Birthweight	birthweight <2,500 g or 5lbs, 8 ounces
Miscarriage	Spontaneous loss of fetus before 20 weeks of pregnancy; sometimes also referred to as stillbirth or fetal death
Multiparous	Having had at least one previous pregnancy carried to a viable gestational age; multiparous women are delivering their second (or higher) baby
Neonatal Death	Death of a neonate any time after birth during the first 28 days of life
Non-Reassuring Fetal Heart Tracing (NRFHT)	A fetal heartbeat pattern that signals that the neonate may be in distress of some sort; typical non-reassuring patterns include tachycardia (heart beating too fast), bradycardia (heart beating too slow), and late decelerations of heart rate associated with uterine contractions
Parity	The number of pregnancies carried to a viable gestational age
Perinatal Mortality	Death of a fetus or neonate (still birth + neonatal death)
Placenta Previa	A placental disorder in which the placenta is either partially or completely overlapping the internal cervical opening of the uterus (os)- which obstructs the neonate from being delivered vaginally; often requires a cesarean delivery
Placental Abruptio	Premature separation of the placenta prior to delivery
Placental Infarct	death of part of the placenta due to interruption of the blood supply

Post-partum Hemorrhage	Excessive blood loss after birth; leading cause of maternal mortality worldwide
Preeclampsia	Development of high blood pressure and protein in the urine after 20th week of gestation
Pregnancy-Induced Hypertension	High blood pressure that develops after 20 weeks of gestation and resolves after delivery; also called 'gestational hypertension'; can co-occur with chronic hypertension
Premature Rupture of Membranes (PROM)	Rupture of the membrane after 37 weeks of gestation, but before the onset of labor; preterm PROM (PPROM) is the same rupturing prior to 37 weeks gestation; prolonged rupture of membranes is rupture more than 24 hours before the onset of labor
Preterm Birth	Birth prior to 37 weeks of gestation
Nulliparous	Having had no previous pregnancies carried to a viable gestational age
Respiratory Distress Syndrome	Breathing disorder affecting newborns- typically those born prematurely; in these cases, the lungs are not able to make enough surfactant which is a liquid that coats the inside of the lungs and allows the infant to breath- without it, the lungs collapse
Second Stage of Labor	Duration of time from when the cervix has fully dilated to 10 cm until the neonate has been delivered
Second Trimester of Pregnancy	14-26 weeks of gestation
Stillbirth	Fetal death occurring after 20 weeks of gestation
Sudden Infant Death Syndrome (SIDS)	Unexplained death, usually during sleep, of a seemingly healthy neonate less than a year old

Surfactant	a liquid made by the lungs that coats the inside of the lungs and allows infants to breath after being born- too little leads to lungs collapsing
Tetanic Uterus	When the uterine contractions are so frequent that the muscles are in a constantly contracted state
Third Stage of Labor	Duration of time from when the neonate has been delivered until the placenta has been delivered
Third Trimester of Pregnancy	27-40 weeks of gestation
Threatened Miscarriage	Any vaginal bleeding other than spotting during early stages of pregnancy
Thrombocytopenia	Low platelet count (the component that helps blood to clot)
Thrombophilia	An increased tendency to form abnormal blood clots in blood vessels
Trophoblast	Cells that form the outer layer of the blastocyst which provide nutrients to the embryo and develop into a large part of the placenta
Uterine Hypertonicity	A series of single contractions lasting 2 minutes or more or contraction frequency of 5 or more in 10 minutes (uterus is contracting too much)
Vasoconstriction	narrowing of the blood vessels resulting from contraction of the muscular wall of the vessels

References

1. Tikkanen M. Placental abruption: epidemiology, risk factors and consequences. *Acta Obstetrica et Gynecologica Scandinavica*. 2011;90:140-149.
2. Drake AJ, Liu L. Intergenerational transmission of programmed effects: Public health consequences. *Trends in Endocrinology and Metabolism*. 2009;21(4):206-213.
3. Ananth CV, Vintzileos AM. Maternal-fetal conditions necessitating a medical intervention resulting in preterm birth. *American Journal of Obstetrics and Gynecology*. 2006;195(1557-63).
4. Pariente G, Wiznitzer A, Sergienko R, Mazor M, Holcberg G, Sheiner E. Placental abruption: critical analysis of risk factor and perinatal outcomes. *The Journal of Maternal-Fetal and Neonatal Medicine*. 2010;24(5):698-702.
5. Ananth CV. Ischemic placental disease: a unifying concept for preeclampsia, intrauterine growth restriction, and placental abruption. *Seminars in Perinatology*. 2014;38:131-132.
6. Parker SE, Werler MM. Epidemiology of ischemic placental disease: a focus on preterm gestations. *Seminars in Perinatology*. 2014;38:133-138.
7. Ananth CV, Berkowitz GS, Savitz DA, Lapinski RH. Placental abruption and adverse perinatal outcomes. *JAMA*. 1999;282:1646-1651.
8. Zhang J, Landy H, Branch D, Burkman R, Et al ftCoSL. Contemporary patterns of spontaneous labor with normal neonatal outcomes. *Obstetrics & Gynecology*. 2010;116(6):1281-1287.
9. Logitharajah P, Rutherford MA, Cowan FM. Hypoxic-ischemic encephalopathy in preterm infants: antecedent factors, brain imaging, and outcome. *Pediatric Research*. 2009;66(2):222-229.
10. Osterman M, Martin J. Recent declines in induction of labor by gestational age. Hyattsville, MD: National Center for Health Statistics; 2014.

11. Bhandari S, Raja E, Shetty A, Bhattacharya S. Maternal and perinatal consequences of antepartum haemorrhage of unknown origin. *British Journal of Gynecology*. 2014;121:44-52.
12. Klinman HJ. From trophoblast to human placenta. *The Encyclopedia of Reproduction* 2006:1-23.
13. Red-Horse K, Zhou Y, Genbacev O, et al. Trophoblast differentiation during embryo implantation and formation of the maternal-fetal interface. *J Clin Invest*. 2004;114(6):744-754.
14. Cross JC, Werb Z, Fisher SJ. Implantation and the placenta: Key pieces of the developmental puzzle. *Science*. 1994;266:1508-1518.
15. Mor G, Cardenas I. The immune system in pregnancy: A unique complexity. *Am J Reprod Immunol*. 2010;63:425-433.
16. Gude NM, Roberts CT, Kalionis B, King RG. Growth and function of the normal human placenta. *Thromb Res*. 2004;114:397-407.
17. Burton GJ, Barker DJ, Moffett A, Thornburg K. Introduction. In: Burton GJ, Barker DJ, Moffett A, Thornburg K, eds. *The Placenta and Human Developmental Programming*. New York, NY: Cambridge University Press; 2011:1-4.
18. Yetter JF. Examination of the placenta. *Am Fam Physician*. 1998;57(5):1045-1054.
19. Brown HL. Stages of development of the fetus. *Merck Manual* 2014.
20. Wang Y, Zhao S. Chapter 2, Placental Blood Circulation. *Vascular Biology of the Placenta*. San Rafael, CA: Morgan & Claypool Life Sciences; 2010.
21. Smith JR, Brennan BG. Management of the third stage of labor. 2012; <http://emedicine.medscape.com/article/275304-overview>. Accessed October 25th, 2014.

22. Sepilian VP. Miscarriage overview. 2014; http://www.emedicinehealth.com/miscarriage/article_em.htm. Accessed October 26th, 2014.
23. Ananth CV, Oyelese Y, Prasad V, Getahun D, Smulian JC. Evidence of placental abruption as a chronic process: Associations with vaginal bleeding early in pregnancy and placental lesions. *Eur J Obstet Gynecol Reprod Biol.* 2006;128:15-21.
24. Yeo L, Ananth CV, Vintzileos AM. Placental abruption. *The Global Library of Women's Medicine*2008.
25. Page EW, King EB, Merrill JA. Abruptio Placentae: Dangers of delay in delivery. *Obstet Gynecol.* 1954;3(4):385-393.
26. Tikkanen M, Nuutila M, Hiilesmaa V, Paavonen J, Ylikorkala O. Clinical presentation and risk factors of placental abruption. *Acta Obstetrica et Gynecologica Scandinavica.* 2006;85:700-705.
27. Han CS, Schatz F, Lockwood CJ. Abruption-associated prematurity. *Clin Perinatol.* 2011;38:407-421.
28. Hurd WW, Miodovnik M, Hertzberg V, Lavin JP. Selective management of abruptio placentae: A prospective study. *Obstet Gynecol.* 1983;61:467-473.
29. Oyelese Y, Ananth CV. Placental abruption. *Obstetrics & Gynecology.* 2006;108:1005-1016.
30. Ananth CV, Getahun D, Peltier MR, Smulian JC. Placental abruption in term and preterm gestations. *Obstetrics & Gynecology.* 2006;107(4):785-792.
31. Toivonen S, Heinonen S, Antilla M, Kosma V-M, Saarikoski S. Reproductive risk factors, doppler findings, and outcome of affected births in placental abruption: A population-based analysis. *Am J Perinatol.* 2002;19(8):451-459.
32. Hasegawa J, Nakamura M, Hamada S, et al. Capable of identifying risk factors for placental abruption. *J Matern Fetal Neonatal Med.* Jan 2014;27(1):52-56.

33. Misra DP, Ananth CV. Risk factor profiles of placental abruption in first and second pregnancies: Heterogeneous etiologies. *J Clin Epidemiol.* 1999;52(5):453-461.
34. Reis PM, Sander CM, Pearlman MD. Abruptio placentae after auto accidents: A case-control study. *J Reprod Med.* 2000;45(1):6-10.
35. Ananth CV, Smulian JC, Demissie K, Vintzileos AM, Knuppel RA. Placental abruption among singleton and twin births in the United States: risk factor profiles. *American Journal of Epidemiology.* 2001;153(8):771-778.
36. Ananth CV, Oyelese Y, Srinivas N, Yeo L, Vintzileos AM. Preterm premature rupture of membranes, intrauterine infection, and oligohydramnios: Risk factors for placental abruption. *Obstet Gynecol.* 2004;104:71-77.
37. Holmgren PA, Olofsson JI. Preterm premature rupture of membranes and the associated risk for placental abruption. Inverse correlation to gestational length. *Acta Obstet Gynecol Scand.* 1997;76:743-747.
38. Facchinetti F, Marozio L, Grandone E, Pizzi C, Volpe A, Benedetto C. Thrombophilic mutations are a main risk factor for placental abruption. *J Hematol.* 2003;88(7):785-788.
39. Springel EH, Peng TCC. Thrombophilias in pregnancy. 2013; <http://emedicine.medscape.com/article/2056429-overview#a0156>. Accessed October 27th, 2014.
40. Edwards RZ, Rijhsinghani A. Dysfibrinogenemia and placental abruption. *Obstet Gynecol.* 2000;95(6).
41. Ness PM, Budzynski AZ, Olexa SA, Rodvien R. Congenital hypofibrinogenemia and recurrent placental abruption. *Obstet Gynecol.* 1983;61:519-523.
42. Balasa VV. Inherited abnormalities of fibrinogen. 2012; <http://emedicine.medscape.com/article/960677-overview#a0199>. Accessed October 27th, 2014.

43. Getahun D, Oyelese Y, Salihu HM, Ananth CV. Previous cesarean delivery and risks of placenta previa and placental abruption. *Obstet Gynecol.* 2006;107(4):771-778.
44. Ananth CV, Peltier MR, Kinzler WL, Smulian JC, Vintzileos AM. Chronic hypertension and risk of placental abruption: Is the association modified by ischemic placental disease? *Am J Obstet Gynecol.* 2007;197:273.e271-273.e277.
45. Ananth CV, Smulian JC, Vintzileos AM. Incidence of placental abruption in relation to cigarette smoking and hypertensive disorders during pregnancy: A meta-analysis of observational studies. *Obstet Gynecol.* 1999;93:622-628.
46. Chaiworapongsa T, Chaemsaitong P, Yeo L, Romero R. Pre-eclampsia part 1: current understanding of its pathophysiology. *Nat Rev Nephrol.* 2014;10:466-480.
47. Burd L, Roberts D, Olson M, Odendaal H. Ethanol and the placenta: A review. *J Matern Fetal Neonatal Med.* 2007;20(5):361-375.
48. Gabriel K, Hofman C, Glavas M, Weinberg J. The hormonal effects of alcohol use on the mother and fetus. *Alcohol Health Res World.* 1998;22(3):170-177.
49. Darby M, Caritis S, Shen-Schwarz S. Placental abruption in the preterm gestation: An association with chorioamnionitis. *Obstet Gynecol.* 1989;74:88-92.
50. Deutsch AB, Lynch ON, Alio AP, Salihu HM, Spellacy WN. Increased risk of placental abruption in underweight women. *American Journal of Perinatology.* 2009;27:235-240.
51. Salihu HM, Diamond E, August EM, Rahman S, Mogos MF, Mbah AK. Maternal pregnancy weight gain and the risk of placental abruption. *Nutrition Reviews.* 2013;71(s1):S9-S17.
52. Saftlas AF, Olson DR, Atrash HK, Rochat R, Rowley D. National trends in the incidence of abruptio placentae, 1979-1987. *Obstet Gynecol.* 1991;78:1081-1086.
53. Shen TT, DeFranco EA, Stamilio DM, Chang JJ, Muglia LJ. A population-based study of race-specific risk for placental abruption. *BMC Pregnancy Childbirth.* 2008;8(43).

54. Tikkanen M, Riihimaki O, Gissler M, et al. Decreasing incidence of placental abruption in Finland during 1980-2005. *Acta Obstet Gynecol Scand.* 2012;91:1046-1052.
55. Ananth CV, Oyelese Y, Yeo L, Pradhan A, Vintzileos AM. Placental abruption in the United States, 1979 through 2001: Temporal trends and potential determinants. *Am J Obstet Gynecol.* 2005;192:191-198.
56. Boisrime T, Sananes N, Fritz G, et al. Placental abruption: Risk factors, management and maternal-fetal prognosis. Cohort study over 10 years. *European Journal of Obstetrics & Gynecology and Reproductive Biology.* 2014;179:100-104.
57. Chang YL, Chang SD, Cheng PJ. Perinatal outcome in patients with placental abruption with and without antepartum hemorrhage. *Int J Gynaecol Obstet.* 2001;75:193-194.
58. Sheiner E, Shoham-Vardi L, Hadar A, Hallak M, Hackmon R, Mazor M. Incidence, obstetric risk factors and pregnancy outcome of preterm placental abruption: A retrospective analysis. *J Matern Fetal Neonatal Med.* 2002;11:34-39.
59. Spinillo A, Fazzi E, Stonati M, Ometto A, Iasci A, Guaschino S. Severity of abruptio placentae and neurodevelopmental outcome in low birth weight infants. *Early Human Development.* 1993;35:45-54.
60. Pitaphrom A, Sucharoen N. Pregnancy outcomes in placental abruption. *J Med Assoc Thai.* 2006;89(10):1572-1578.
61. Sheiner E, Levy A, Mazor M. Precipitate labor: higher rates of maternal complications. *European Journal of Obstetrics & Gynecology and Reproductive Biology.* 2004;116:43-47.
62. Mahon TR, Chazotte C, Cohen WR. Short labor: characteristics and outcome. *Obstetrics & Gynecology.* 1994;84:47-51.
63. Morikawa M, Yamada T, Cho K, Yamada T, Sato S, Minakami H. Prospective risk of abruptio placentae. *The Journal of Obstetrics and Gynaecology Research.* 2014;40(2):369-374.

64. Jackson S, Fleege L, Fridman M, Gregory K, Zelop C, Olsen J. Morbidity following primary cesarean delivery in the Danish National Birth Cohort. *Am J Obstet Gynecol*. 2012;206:139.e131-e135.
65. Kennare R, Tucker G, Heard A, Chan A. Risks of adverse outcomes in the next birth after a first cesarean delivery. *Obstet Gynecol*. 2007;109(2 pt 1):270-276.
66. Smith GCS, Pell JP, Dobbie R. Caesarean section and risk of unexplained stillbirth in subsequent pregnancy. *Lancet*. 2003;362:1779-1784.
67. Ananth CV, Williams MA. Placental abruption and placental weight- implications for fetal growth. *Acta Obstet Gynecol Scand*. 2013;92:1143-1150.
68. Ananth CV, Wilcox AJ. Placental abruption and perinatal mortality in the United States. *American Journal of Epidemiology*. 2001;153(4):332-337.
69. Ross MG, Downey CA, Bemis-Heys R, Nguyen M, Jacques DL, Stanziano G. Prediction by maternal risk factors of neonatal intensive care admissions: evaluation of >59,000 women in national managed care programs. *American Journal of Obstetrics and Gynecology*. 1999;181:835-842.
70. Gibbs JM, Weindling AM. Neonatal intracranial lesions following placental abruption. *Eur J Pediatr*. 1994;153:195-197.
71. Afjeh S-A, Sabzehei M-K, Esmaili F. Neonatal resuscitation in the delivery room from a tertiary level hospital: risk factors and outcome. *Iranian Journal of Pediatrics*. 2013;23(6):675-680.
72. Lee KG. Neonatal respiratory distress syndrome. 2014; <http://www.nlm.nih.gov/medlineplus/ency/article/001563.htm>. Accessed December 1st, 2014.
73. Morales P, Bustamante D, Espina-Marchant P, et al. Pathophysiology of perinatal asphyxia: Can we predicto and improve individual outcomes? *EPMA Journal*. 2011;2(211-230).
74. Barker DJ. The fetal and infant origins of adult disease. *Br Med J*. 1990;301:1111.

75. Barker DJ. Fetal programming of coronary heart disease. *Trends in Endocrinology and Metabolism*. 2002;13(9):364-368.
76. Carmody JB, Charlton JR. Short-term gestation, long-term risk: Prematurity and chronic kidney disease. *Pediatrics*. 2013;131:1168-1179.
77. El Mazloum D, Moschino L, Bozzeto S, Baraldi E. Chronic lung disease of prematurity: Long-term respiratory outcome. *Neonatology*. 2014;105:352-356.
78. Tauzin L. Alterations in viscoelastic properties following premature birth may lead to hypertension and cardiovascular disease development in later life. *Acta Paediatr*. 2014;Early Online Access:1-8.
79. Crump C, Sundquist K, Sundquist J, Winkleby MA. Gestational age at birth and mortality in young adulthood. *JAMA*. 2011;306(11):1233-1240.
80. The Office of the National Coordinator for Health Information Technology (ONC). Update on the adoption of health information technology and related efforts to facilitate the electronic use and exchange of health information. In: Services DoHaH, ed. Washington, DC2013:1-82.
81. National Institute of Child Health and Human Development. Consortium on Safe Labor Protocol: Version 2.0. Unpublished2007:1-24.
82. Zhang J, Troendle J, Reddy U, et al ftCoSL. Contemporary cesarean delivery practice in the United States. *American Journal of Obstetrics and Gynecology*. 2010;203:326.e321-310.
83. Harper LM, Caughey AB, Odibo AO, Roehl KA, Zhao Q, Cahili AG. Normal progress of induced labor. *Obstetrics & Gynecology*. 2012;119:1113-1118.
84. VanderWeele TJ, Mumford SL, Schisterman EF. Conditioning on intermediates in perinatal epidemiology. *Epidemiology*. 2012;23(1):1-9.
85. Berglund P, Heeringa S. *Multiple imputation of missing data using SAS*. Cary, NC: SAS Institute Inc.; 2014.

86. Burton P, Gurrin L, Sly P. Tutorial in biostatistics: Extending the simple linear regression model to account for correlated responses: An introduction to generalized estimating equations and multi-level mixed modeling. *Stat Med*. 1998;17:1261-1291.
87. Zhou G. A modified poisson regression approach to prospective studies with binary data. *Am J Epidemiol*. 2004;159(7):702-706.
88. Austin PC, Rothwell DM, Tu JV. A comparison of statistical modeling strategies for analyzing length of stay after CABG surgery. *Health Services & Outcomes Research Methodology*. 2002;3(107-133).
89. Allison PD. Regression for Count Data. *Logistic Regression Using SAS: Theory and Application*. Cary, NC: SAS Institute Inc.; 2012:265-290.
90. McNutt L-A, Wu C, Xue X, Hafner JP. Estimating the relative risk in cohort studies and clinical trials of common outcomes. *Am J Epidemiol*. 2003;157(10):940-943.
91. StackExchange. Beta confidence intervals in transformed linear regression. 2014; <http://stats.stackexchange.com/questions/93230/beta-confidence-intervals-in-transformed-linear-regression>. Accessed April 20th, 2015.
92. Cornell Statistical Consulting Unit. Interpreting coefficients in regression with log-transformed variables. *StatNews* 2012; #83:<https://www.cscu.cornell.edu/news/statnews/stnews83.pdf>. Accessed April 20th, 2015.
93. Raymond EG, Mills JL. Placental abruption: Maternal risk factors and associated fetal conditions. *Acta Obstetrica et Gynaecologica Scandinavica*. 1993;72:633-639.
94. Salihu HM, Bekan B, Aliyu MH, Rouse DJ, Kirby RS, Alexander GR. Perinatal mortality associated with abruptio placenta in singletons and multiples. *Am J Obstet Gynecol*. 2005;193(1):198-203.
95. Toivonen S, Heinonen S, Anttila M, Kosma V, Saarikoski S. Reproductive risk factors, Doppler findings, and outcome of affected births in placental abruption: a population-based analysis. *American Journal of Perinatology*. 2002;19(8):451-459.

96. Dars S, Sultana F, Akhter N. Abruptio placentae: Risk factors and maternal outcomes at a tertiary care hospital. *Journal of the Liaquat University of Medical and Health Sciences*. 2013;12(3):198-202.
97. Qamarunisa, Memon H, Ali M. Frequency, maternal and fetal outcome of abruptio placenta in a rural medical college hospital, Mirpurkhas Sindh. *Pakistan Journal of Medical Sciences*. 2010;26(3):663-666.
98. Sarwar I, Abbasi A, Islam A. Abruptio placentae and its complications at Ayub Teaching Hospital Abbottabad. *J Ayub Med Coll Abbottabad*. Jan-Mar 2006;18(1):27-31.
99. Bibi S, Ghaffar S, Pir MA, Yousfani S. Risk factors and clinical outcome of placental abruption: A retrospective analysis. *Journal of the Pakistan Medical Association*. 2009;59(10):672-674.
100. Mukherjee S, Bawa AK, Sharma S, Nandanwar YS, Gadam M. Retrospective study of risk factors and maternal and fetal outcome in patients with abruptio placentae. *Journal of Natural Science, Biology and Medicine*. 2014;5(2):425-428.
101. Goff SL, Pekow PS, Markenson G, Knee A, Chasan-Taber L, Lindenauer PK. Validity of using ICD-9-CM codes to identify selected categories of obstetric complications, procedures and co-morbidities. *Paediatric and Perinatal Epidemiology*. 2012;26(5):421-429.
102. Witlin AG, Sibai BM. Perinatal and maternal outcome following abruptio placentae. *Hypertens Pregnancy*. 2001;20(2):195-203.
103. Allred LS, Batton D. The effect of placental abruption on the short-term outcome of premature infants. *American Journal of Perinatology*. 2004;21(3):157-162.
104. Allred LS, Batton D. The effect of placental abruption on the short-term outcome of premature infants. *Am J Perinatol*. 2004;21(3):157-162.
105. Pariente G, Wiznitzer A, Sergienko R, Mazor M, Holcberg G, Sheiner E. Placental abruption: Critical analysis of risk factors and perinatal outcomes. *Journal of Maternal-Fetal and Neonatal Medicine*. 2011;24(5):698-702.

106. Morikawa M, Yamada T, Cho K, Yamada T, Sato S, Minakami H. Prospective risk of abruptio placentae. *Journal of Obstetrics and Gynaecology Research*. 2014;40(2):369-374.
107. Lindqvist PG, Happach C. Risk and risk estimation of placental abruption. *European Journal of Obstetrics Gynecology and Reproductive Biology*. 2006;126(2):160-164.
108. Pitaphrom A, Sukcharoen N. Pregnancy outcomes in placental abruption. *Journal of the Medical Association of Thailand*. 2006;89(10):1572-1578.
109. Boisrame T, Sananes N, Fritz G, et al. Placental abruption: Risk factors, management and maternal-fetal prognosis. Cohort study over 10 years. *European Journal of Obstetrics Gynecology and Reproductive Biology*. 2014;179:100-104.
110. Tikkanen M, Nuutila M, Hiilesmaa V, Paavonen J, Ylikorkala O. Clinical presentation and risk factors of placental abruption. *Acta Obstet Gynecol Scand*. 2006;85(6):700-705.
111. Saeed M, Rana T. Fetomaternal outcome in pregnancies complicated with placental abruption. *Pakistan Journal of Medical and Health Sciences*. 2011;5(1):140-143.
112. Naz F, Shakoor U, Sharafat S, Khan S, Iqbal K, Zareen A. Comparison of pregnancy outcome in placenta previa versus placenta abruption. *Pakistan Journal of Medical and Health Sciences*. 2010;4(2):149-152.
113. Hossain N, Khan N, Sultana SS. Abruptio placenta and adverse pregnancy outcome. *J Pak Med Assoc*. Jun 2010;65(6):443-446.
114. Talpur NN, Memon SR, Jamro B, Korejo R. Maternal and fetal morbidity with abruptio placentae. *Rawal Medical Journal*. 2011;36(4).
115. Tasleem H, Tasleem S, Siddique MA, Nazir F, Iqbal T. Outcome of pregnancy in placental abruption. *Rawal Medical Journal*. 2011;36(1):57-59.
116. Sheiner E, Levy A, Mazor M. Precipitate labor: Higher rates of maternal complications. *European Journal of Obstetrics Gynecology and Reproductive Biology*. 2004;116(1):43-47.

117. Afjeh SA, Sabzehei MK, Esmaili F. Neonatal resuscitation in the delivery room from a tertiary level hospital: Risk factors and outcome. *Iran J Pediatr*. 2013;23(6):675-680.
118. Boisrame T, Sananes N, Fritz G, et al. Abruptio placentae. Diagnosis, management and maternal-fetal prognosis: A retrospective study of 100 cases. *Gynecologie Obstetrique Fertilité*. 2014;42(2):78-83.
119. Abu-Shaweesh JM, Martin RJ. Neonatal apnea: What's new? *Pediatric Pulmonology*. 2008;49:937-944.
120. Ananth CV, Wilcox AJ. Placental abruption and perinatal mortality in the United States. *American Journal of Epidemiology*. 2001;153(4):332-337.
121. Ananth CV, VanderWeele TJ. Placental abruption and perinatal mortality with preterm delivery as a mediator: disentangling direct and indirect effects. *Am J Epidemiol*. Jul 1 2011;174(1):99-108.
122. Rasmussen S, Irgens LM, Bergsjø P, Dalaker K. Perinatal mortality and case fatality after placental abruption in Norway 1967-1991. *Acta Obstetrica et Gynaecologica Scandinavica*. 1996;75:229-234.
123. Sheiner E, Shoham-Vardi I, Hallak M, et al. Placental abruption in term pregnancies: Clinical significance and obstetric risk factors. *Journal of Maternal-Fetal and Neonatal Medicine*. 2003;13(1):45-49.
124. Hermansen CL, Lorah KN. Respiratory distress in the newborn. *Am Fam Physician*. 2007;76:987-994.
125. Pike K, Pillow JJ, Lucas JS. Long term respiratory consequences of intrauterine growth restriction. *Seminars in Fetal & Neonatal Medicine*. 2012;17:92-98.
126. Vahratian A, Troendle JF, Siega-Riz AM, Zhang J. Methodological challenges in studying labour progression in contemporary practice. *Paediatric and Perinatal Epidemiology*. 2006;20:72-78.
127. Spong CY, Berghella V, Wenstrom KD, Mercer BM, Saade G. Preventing the first cesarean delivery. *Obstet Gynecol*. 2012;120:1181-1193.

- 128.** Gibbons L, Belizan JM, Lauer JA, Betran AP, Merialdi M, Althabe F. *The global numbers and costs of additionally needed and unnecessary caesarean sections performed per year: Overuse as a barrier to universal coverage*: World Health Organization;2010.
- 129.** Carter AM. Animal models of human placentation- A review. *Placenta*. 2007;28(Supplement A, Trophoblastic Research):S41-S47.