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Prenatal and Delivery Management to Reduce Adverse Pregnancy Outcomes Associated with Maternal Weight

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Prenatal and Delivery Management to Reduce Adverse Pregnancy Outcomes Associated with Maternal Weight

By

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Prenatal and Delivery Management to Reduce Adverse Pregnancy Outcomes Associated with Maternal Weight

By Cassandra M. Gibbs Pickens

Pre-pregnancy obesity increases the risk of cesarean delivery, excess fetal growth, and maternal and infant morbidity. However, there is limited evidence on how to prevent adverse pregnancy outcomes among obese gravidas. Similarly to maternal pre-pregnancy weight, gestational weight gain (GWG) has important effects on perinatal health. However, little is known about the association between GWG and stillbirth.

This dissertation explored ways to reduce the risk of adverse pregnancy outcomes associated with maternal weight. **Aim 1** evaluated the association between GWG z-scores and stillbirth among 1,885 singleton deliveries in the Stillbirth Collaborative Research Network Case-Control Study. Gaining ≤35th percentile of GWG z-score increased the odds of stillbirth (adjusted odds ratio [aOR] for the 10th versus 50th percentile: 1.5 [95% Confidence Interval {CI} 1.3, 1.7]). Among overweight women, stillbirth odds were elevated for GWG z-scores ≥75th percentile. **Aims 2 and 3** assessed whether term elective induction of labor (elective IOL, induction without indication) or expectant management (delivery in later weeks) was associated with lower odds of adverse pregnancy outcomes among obese women (**Aim 2**) and their offspring **(Aim 3**). The data source for Aims 2-3 was the 2007-2011 California Linked Patient Discharge Data/Birth Cohort file (N=219,360). Elective IOL between 37 and 40 weeks reduced the odds of cesarean delivery among obese women (aORs between 0.6 and 0.9). From 38-40 weeks' gestation, elective IOL reduced the odds of postpartum hemorrhage and severe maternal morbidity (aORs from 0.7-0.8). Elective IOL at 37 weeks was associated with increased infant mortality among obese parous women (aOR: 3.5 [95% CI 1.4, 8.5]). Term elective IOL was associated with reduced odds of macrosomia, infant hospital stay >5 days, meconium aspiration syndrome, chorioamnionitis, shoulder dystocia, and brachial plexus injury.

This dissertation highlights possible ways to improve pregnancy outcomes among obese gravidas and their offspring. Gaining sufficient weight during pregnancy may reduce the risk of stillbirth among obese women; this was also true in normal weight and overweight women. Avoiding elective IOL <39 weeks' gestation may reduce the risk of infant mortality, while elective IOL between 39 and 41 weeks' gestation may decrease the risk of maternal and neonatal morbidity.

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CHAPTER 1, INTRODUCTION AND SPECIFIC AIMS

ABBREVIATIONS IN DISSERTATION

ACOG: The American College of Obstetricians and Gynecologists

AOR: Adjusted Odds Ratio

BMI: Body mass index in kg/m^2 (pre-pregnancy BMI unless otherwise specified)

CI: Confidence interval

COR: Crude odds ratio

CD: Cesarean delivery

CSL: Consortium for Safe Labor

EIOL: Elective induction of labor

EM: Expectant Management

FGLS: Fetal Growth Longitudinal Study

GA: Gestational age

GDM: Gestational diabetes mellitus

GEE: Generalized Estimating Equations

GWG: Gestational weight gain

HIV: Human Immunodeficiency Virus

HMO, Health Maintenance Organization

ICU: Intensive care unit

IOL: Induction of labor

IOM: Institute of Medicine

IRB: Institutional Review Boards

NICU: Neonatal intensive care unit

OR: Odds ratio

OSHPD: Office of Statewide Health Planning and Development

PRAMS: Pregnancy Risk Assessment Monitoring System

RCT: Randomized controlled trial

RERI: Relative Excess Risk of Interaction

RDS: Respiratory distress syndrome

SCRN: Stillbirth Collaborative Research Network

WIC: Special Supplemental Nutrition Program for Women, Infants, and Children

BACKGROUND: MATERNAL WEIGHT BEFORE AND DURING PREGNANCY

PREVALENCE OF PRE-PREGNANCY OVERWEIGHT AND OBESITY

Worldwide, approximately 250 million women of reproductive age (15-44) are overweight (body mass index [BMI] 25.0-<30.0 kg/m^2).[1] An estimated 100 million more are obese (BMI ≥30 kg/m^2).[1] In the U.S., the prevalence of both pre-pregnancy overweight and obesity are increasing. Nearly half of U.S. women now enter pregnancy overweight (24.2%) or obese (20.5%).[2] Temporal increases in maternal BMI parallel increases in gestational diabetes mellitus (GDM), large for gestational age (LGA) infants, cesarean delivery (CD), and childhood overweight.[3]

In June 2013, the American Medical Association voted to classify obesity as a disease due to its association with premature death and serious chronic illnesses.[4] Obesity is the most frequent risk factor for maternal mortality in industrialized countries[5] and is associated with a wide range of adverse pregnancy outcomes. Its high prevalence results in high attributable risks for many conditions, such as macrosomia; in fact, the attributable risk for macrosomia is higher for obesity than for maternal diabetes.[6] Current research, although limited, shows that the risks of adverse maternal, fetal, neonatal, and labor and delivery outcomes rise as BMI category increases from normal weight (BMI 18.5- <25.0 kg/m^2) to overweight, obese class 1 (BMI 30.0-<35.0 kg/m^2), obese class 2 (BMI 35.0-<40.0 kg/m^2), obese class 3 (BMI ≥40.0 kg/m^2), and beyond (i.e., risks continue to increase with rising BMI among class 3 obese women).[7-9] Medical treatment of maternal obesity carries a high financial cost.[5] Overweight and obese pregnant women require additional medical care before delivery, around the time of delivery, and

postpartum.[5,9-11] Additional hospital equipment to accommodate obese gravidas (e.g., bariatric lifts) also adds to the cost of caring for these women.[12] Pre-pregnancy obesity is of particular concern given the high costs of prenatal, delivery, and postpartum care in the U.S., which have tripled in the past 18 years.[13] Although it is ideal to address high BMI prior to conception, women may be more receptive to weight management interventions during pregnancy because they are concerned about the health of their fetus. Pregnancy may be a "teachable moment" in that respect.[14]

MATERNAL AND INFANT COMPLICATIONS OF OVERWEIGHT AND OBESITY

Maternal or fetal pregnancy complications occur in 5 to 20% of pregnancies,[15] and the burden of disease is higher among overweight and obese women. Overweight and obese women are at higher risk of developing medical conditions during pregnancy, such as gestational hypertension, preeclampsia, GDM, and venous thromboembolism.[9,10,16,17] Furthermore, obese women are not only more likely to have hypertensive disorders but also more likely to have *severe* forms of these disorders, such as HELLP Syndrome (Hemolysis, Elevated Liver enzymes, and Low Platelet count Syndrome).[18] Among obese women, there is evidence of a dose-response relation between obesity severity and preeclampsia.[7,8,19] In a recent study of 2000-2006 Missouri deliveries, women with a pre-pregnancy BMI of 40.0-49.99 kg/m^2 were 1.4 times as likely to have preeclampsia as women with a BMI of 30.0-39.99 kg/m^2, while women with a pre-pregnancy BMI ≥50.0 kg/m^2 were 1.7 times as likely to have preeclampsia as women with a BMI of 30.0-39.99 kg/m^2.[7] Others have reported a dose-response association between obesity severity and GDM.[6] In a recent analysis among women without chronic

disease, Kim et al. reported adjusted risk ratios for GDM of 2.97, 3.97, and 5.47 for classes 1, 2, and 3 obese women, respectively (versus a normal weight referent).[9] These maternal medical conditions are risk factors for maternal death, cesarean delivery, stillbirth, and fetal and infant morbidity and mortality. Various investigators have found an increased risk of maternal mortality among overweight and obese women.[5,20,21] For instance, between 2003 and 2005 in the United Kingdom, more than 50% of identified maternal deaths occurred to overweight or obese women.[21] These included women with both direct (e.g., amniotic fluid embolism) and indirect (e.g., psychiatric reasons) causes of maternal death.[21]

Overweight and obese women are more likely to have their labor induced and to deliver by cesarean section than women of lower BMIs.[8,9,17,22,23] In addition, even among obese women, the risks of induction of labor (IOL) and CD continue to increase with BMI category.[7-9,24-26] For example, among 2002-2008 deliveries to U.S. women without chronic disease, the unadjusted frequency of IOL increased from 38.9% among normal weight women to 41.9% in overweight women, 42.6% in class 1 obese women, 44.7% in class 2 obese women, and 48.6% among class 3 obese women.[9] Obese women are twice as likely as normal weight women to deliver by cesarean,[27] with up to half of pregnancies to obese women ending in cesarean delivery.[28] Post-cesarean complications, such as wound infection,[16] endometritis,[16] postpartum hemorrhage,[16,22] and urinary tract infection,[17] are also more frequent in obese women than in women of lesser BMIs. In addition to placing a large financial burden on the healthcare system,[5,13] even routine cesarean deliveries carry health risks. Labor induction is also financially costly ($1 billion annually among women of all BMIs).[29]

Among obese women, the risk of unscheduled/emergency cesarean delivery is up to 1.7 times that among normal weight women,[24,26,27] even among obese gravidas without other comorbidities.[28] The risk of emergency cesarean increases with obesity severity.[7,30] The risk of unscheduled CD is also elevated among overweight women without preexisting disease.[9] Cesarean delivery *after labor* commences is more common in induced, as well as spontaneously laboring, overweight and obese women[9] (notably, some cesarean deliveries after labor begins could have been planned). Unplanned CDs carry more health risks than planned CDs[31] because they are more often conducted in urgent situations (e.g., in the presence of fetal hypoxia or asphyxia[32]), where delayed delivery can be catastrophic to the mother or her fetus. Lasting damage may result if intervention is not sufficiently timely. For instance, fetal hypoxia can lead to brain damage or death, depending on duration of exposure.[33]

Overweight and obese women are also at increased risk of scheduled/prelabor CD, and this risk increases with obesity severity[7,9] (notably, these deliveries could either be elective or medically indicated). Among U.S. women without chronic disease who delivered between 2002 and 2008, adjusted risk ratios for prelabor cesarean delivery were 1.36, 1.64, and 2.02 for classes 1, 2, and 3 obese women, respectively (as compared to normal weight women).[9] *Elective* CD also appears to be moderately elevated among overweight and obese women,[24,26] although some studies did not observe this association,[22] and others found that elective CD was only elevated in morbidly obese women.[30]

Some authors have found that obese women are at increased odds of operative vaginal delivery (i.e., forceps- or vacuum-assisted vaginal delivery).[8] Operative vaginal

delivery may increase the risk of severe perineal lacerations and related sequelae, such as infections[34] and incontinence.[35] However, others have reported no increased risk among overweight women, and a reduced risk of operative vaginal delivery in obese women.[9] The reduced risk of operative vaginal delivery among obese gravidas may be due to an *increased* likelihood of *unsuccessful* operative vaginal delivery (i.e., an attempted forceps/vacuum vaginal delivery that ultimately ends in cesarean).[22] In addition, physicians may be more likely to choose CD for obese women due to concerns about slow labor progression, macrosomia, and shoulder dystocia.[36] The use of epidurals,[27] labor augmentation agents,[9] and analgesics[37] is also increased in overweight and obese women.

Obese women are at higher risk of post-cesarean complications[27] (e.g., wound infection[16]), endometritis,[16] postpartum hemorrhage[16,22] (which increases with obesity class[8,38]), and urinary tract infection.[17] Obese women also have longer hospital stays[27] (including postpartum stays[39,40]) than non-obese women. A 2008 systematic review found the mean length of maternal hospital stay to be 0.9 days longer in morbidly obese versus normal weight women (3.3 versus 2.4 days).[27]

In addition to obese women, overweight women also appear to be at slightly increased risk of postpartum hemorrhage,[9,38] maternal fever,[9] and puerperal infection.[9] Some studies have found an increased risk of shoulder dystocia among infants born to obese women.[8] However, evidence on maternal obesity and shoulder dystocia is conflicting; one meta-analysis found no evidence of an association.[41] Shoulder dystocia is an obstetric emergency[42] that is associated with increased risks of fetal hypoxia, fetal death, and neonatal birth trauma (e.g., spinal cord or brachial plexus injury).[43] Brachial

plexus injury can result in life-long complications for the child.[43] Shoulder dystocia may also increase the risk of perineal trauma,[43] uterine rupture,[43] and related complications (e.g., uterine hysterectomy after rupture). Uterine rupture,[44] maternal sepsis,[45] and excess postpartum blood loss[46] are obstetric emergencies and are risk factors for maternal death. These complications are financially costly and increase the need for additional postpartum care, including longer hospital stays.[47] Unplanned hysterectomies can be physically and emotionally traumatic for the mother and typically occur in emergency situations.[48]

Overweight and obese women are at higher risk than non-obese women of delivering a stillborn infant.[8,16,49,50] In the Stillbirth Collaborative Research Network Case-Control Study, adjusted odds ratios for stillbirth were 1.43 for pre-pregnancy overweight, 1.72 for pre-pregnancy class 1 obesity, and 1.73 for pre-pregnancy morbid obesity (BMI $\geq$35.0 kg/m^2), as compared to a pre-pregnancy normal weight referent group.[50] This association may increase over gestational age (GA) and may be driven by placental dysfunction or other unexplained causes.[51] Although there is established evidence for an association between overweight/obesity and antepartum stillbirth, it is unknown whether overweight and obese women are at higher risk of intrapartum stillbirth.[49]

Maternal overweight and obesity are associated with increased risk of macrosomia and LGA.[9,52] In fact, maternal obesity may be a stronger risk factor for macrosomia than maternal diabetes.[52] In turn, macrosomia and LGA are associated with increased risks of serious neonatal complications such as brachial plexus injury,[6] nerve damage,[26] birth asphyxia,[26] clavicular fracture,[26] low APGAR scores,[26] and fetal death.[6]

Some evidence suggests that obesity increases the risk of fetal growth restriction,[8,53] although certain researchers found this association for morbidly obese women only.[8] The association between obesity and infant birthweight may vary by GA; although postterm infants of obese women are more likely to be macrosomic, preterm infants of obese women may be more likely to be growth restricted.[54]

Overweight and obese women are at higher risk than non-obese women of delivering a postterm infant.[22,55] For example, one study from the United Kingdom reported adjusted risk ratios for postterm delivery of 1.17, 1.35, and 1.24 among overweight, obese (BMI 30.0-<40.0 kg/m^2), and morbidly obese (BMI ≥40.0 kg/m^2) women, as compared to normal weight women.[55] This may be partially due to incorrect GA dating (obese women are more likely to overestimate GA due to irregular menses[56]). Recent systematic reviews and meta-analyses have shown that overweight and obese women are more likely to deliver preterm (<37 weeks) than normal weight women.[27,57] However, one review found this association to be present only for induced, rather than spontaneous, preterm delivery[57] (induced preterm deliveries are typically performed due to medical indications). This review found that the odds of induced preterm birth were up to 71% higher among severely obese, versus normal weight, women.[57]

Offspring of overweight and obese women are at elevated risk of neonatal morbidity,[9,22,58,59] which increases the risk of infant death and lifelong health complications.[42,43,60,61] Neonatal complications may cause parental psychological stress[43] and result in costly neonatal care.[61] In particular, infants of overweight and obese women are at elevated risk of meconium aspiration syndrome.[8,59,62] Multiplie studies have reported a nearly three-fold increase in the odds of meconium aspiration syndrome

among infants of morbidly obese (BMI ≥40.0 kg/m^2), versus normal weight, mothers.[8,62] Some research has also shown elevated odds of respiratory distress syndrome (RDS) in preterm infants born to obese, but not overweight, mothers without preexisting chronic disease.[9] RDS is associated with increased use of neonatal interventions (e.g., mechanical ventilation),[60] longer and more intense hospital stays (e.g., neonatal intensive care unit [NICU] admission),[61] and organ damage due to oxygen deprivation.[60] RDS and meconium aspiration syndrome are risk factors for infant death.[60] Infants of morbidly obese women may be at higher risk of jaundice,[63] which could be due to conditions like GDM.[64] In addition, infants of overweight and obese women are at higher risk of NICU admission.[9,22] After accounting for covariates, the risk of NICU admission is up to 38% higher among infants of class 3 obese, versus normal weight, women without chronic disease.[9] Neonates of obese women are also at increased risk of incubation and tube feeding.[22]

Overweight and obese women are more likely to deliver an infant with congenital anomalies,[9,10,16,36] and the risk of neural tube defects is twice as high among infants of obese (versus normal weight) women.[16] These associations may be partially caused by the fact that birth defects are more difficult to detect prenatally among overweight women due to their excess adipose tissue.[16,36,65] A lower prenatal detection rate could result in fewer terminations,[66] and consequently, a higher prevalence of birth defects among liveborn infants of overweight and obese women.

Infants of overweight and obese women are also more likely to die during their first year of life,[49,54,67,68] and the association appears to be strongest for early neonatal death.[49] A recent meta-analysis found an adjusted risk ratio for neonatal death of 1.31

(95% Confidence Interval [CI] 1.22, 1.41) for every 5-unit gain in maternal BMI.[49] Risks of neonatal and infant death are stronger for obese than for overweight women. Adverse impacts of obesity are not limited to the perinatal period. Offspring of obese women are more likely to be obese as children[16] and adults,[69] leading to increased risks of chronic disease and premature death.[69]

The risk of most adverse pregnancy outcomes is higher in obese than in overweight individuals.[9,27,49,62] In addition, there is evidence that the risks of many of fetal, neonatal, and infant complications during pregnancy increase with obesity severity. These include stillbirth,[8] early neonatal death,[8] preterm delivery,[8,57] postterm delivery,[8] LGA or macrosomia,[7,8,25,30] shoulder dystocia,[8] birth trauma,[7,70] meconium aspiration,[8] fetal distress,[8] 1- minute[25] or 5-minute Apgar score <7,[8,25] birth asphyxia,[70] bacterial sepsis,[70] seizures,[70] birth defects,[25] RDS,[70] neonatal hypoglycemia,[7,70] feeding problems,[70] neonatal length of stay >5 days,[7] and a composite neonatal morbidity outcome that included meconium aspiration syndrome, 5-minute Apgar score <7, infection, hypoglycemia, RDS, seizures, length of stay >5 days, and birth trauma).[7]

BIOLOGICAL PLAUSIBILITY: MATERNAL OVERWEIGHT/OBESITY

Although there are many studies on the maternal and fetal complications of overweight and obesity, there are fewer on the causes of these complications.[26] Many researchers have proposed plausible mechanisms through which excess maternal weight could lead to adverse maternal and perinatal outcomes, either through excess adipose tissue or metabolic disruptions.[51]

Although overweight and obesity can lead to preeclampsia, hypertension, and diabetes, the frequency of metabolic and inflammatory disorders is elevated even in overweight and obese women *without* hypertension or glucose dysregulation.[71] Similarly, obese women *without* diabetes are at higher risk of insulin resistance than non-obese women.[17] Overweight/obese pregnant women are also more likely to have elevated levels of C-reactive protein and interleukin-6 (which are markers of inflammation[72,73]), and decreased endothelial function, compared to normal weight women.[71] Inflammation and decreased endothelial function in the placenta could potentially lead to adverse fetal outcomes, such as stillbirth.[71]

In 1954, Pederson et al. speculated that excess fetal growth among offspring of diabetic mothers is due to maternal hyperglycemia, which leads to fetal hyperglycemia and hyperinsulinemia, and finally fetal overgrowth (macrosomia).[74] Similar mechanisms are likely present in *non-diabetic* obese women, who are at risk of insulin resistance and elevated triglycerides. This may result in fetal hyperinsulinemia[75] and excess fetal growth.[17] Fetal hyperinsulinemia can also result in neonatal hypoglycemia *after* birth, which is associated with neonatal seizures and adverse neurologic outcomes.[76] Metabolic abnormalities in overweight and obese women can also lead to abnormal placentation, placental infarction and abruption, and stillbirth.[51] Macrosomia can also result in emergency CD due to cephalopelvic disproportion.[77]

Obesity may influence stillbirth via placental insufficiency,[78] which is more common among obese women due to maternal hyperlipidemia and atherosclerosis; via fetal hypoxia secondary to maternal sleep apnea;[36] and via intrauterine growth restriction,[8,51,53] which may be related to placental insufficiency[78] or preeclampsia.[79]

In addition, it may be more difficult for obese women to monitor fetal movement.[36] It is also more challenging for physicians to detect problems during pregnancy. Due to additional layers of adipose tissue in obese women, it is more difficult to measure fetal heart rate;[16] to measure fetal weight using ultrasound;[36] and to detect anomalies in the fetal heart,[80,81] cerebral ventricles, spine, umbilical cord, kidneys, diaphragm, intestines, and extremities.[81] It is also more challenging to monitor uterine contractions among obese gravidas,[16] Due to these challenges in the antenatal monitoring of obese women, it may be more difficult to avoid outcomes such as stillbirth, infant death, and emergency CD.

Lucas et al. suggest that preterm infants of obese mothers, who have impaired survival, may have an altered metabolic state that makes it harder for them to survive after birth.[54] The higher risk of neonatal outcomes in offspring of overweight and obese women, including meconium aspiration syndrome,[62,82] neonatal seizure,[62,82] bacterial sepsis,[27,83,84] and RDS (for offspring of obese women only[60]) may be explained by the higher frequency of obstetric complications, metabolic abnormalities, postterm pregnancies, and medically indicated preterm deliveries in overweight and obese gravidas.

Obese women may be less likely to have an operative vaginal delivery than non-obese women, as physicians may more frequently choose CD due to slow labor progression, fetal distress,[28] macrosomia,[9,52] and shoulder dystocia,[36] which are more common in obese women.

Problems with labor and delivery may be due to poor uterine contractility, increased pelvic soft tissue that obstructs the birth canal and impedes delivery, or both.[12,85-87] These issues could increase the risk of CD.[36] However, the pelvic soft tissue

hypothesis is speculative.[26] In addition, there is evidence that uterine contractility may not be impeded in obese women after stage 1 of labor is complete.[88,89]

Arrest of labor may be more common in obese women due to problems with hormonal (i.e., oxytocin) regulation.[90] During induction of labor (IOL), the same quantity of oxytocin is administered to overweight and obese women as to normal weight women due to fears of overdosing.[91] However, oxytocin's effectiveness may decrease with increasing BMI.[91] This may partially explain the higher rate of failed IOL in overweight and obese women.[91] Labor augmentation with additional oxytocin may increase the chances of a non-operative vaginal delivery.[26] Researchers have called for studies evaluating whether epigenetic mechanisms are mediators in the association between obesity and adverse outcomes.[92]

In a study of Swedish women who delivered their first 2 deliveries between 1992 and 2001, interpregnancy weight gain (the difference in the BMI measured at the first prenatal visit of each pregnancy) was linearly associated with risks of maternal pregnancy complications (e.g., preeclampsia), CD, LGA, and stillbirth ≥28 weeks in the second pregnancy. The adjusted ORs (95% CIs) comparing a change of ≥3 BMI units to a change of -1 to <1 BMI units were 1.78 (1.51, 2.08) for preeclampsia, 1.32 (1.22, 1.44) for CD, 1.87 (1.72, 2.04) for LGA, and 1.63 (1.20, 2.21) for stillbirth.[71] The dose-response association was apparent even among women who had BMIs <25 before each pregnancy began. Even a BMI gain of 1-2 units conferred increased risks of preeclampsia, GDM, and gestational hypertension. Loss of ≥1 BMI unit between pregnancies was also associated with a reduction in the odds of preeclampsia and LGA. Results were adjusted for several covariates, including maternal age at the second pregnancy.[71] Although some

have criticized the idea that obesity is causally associated with adverse pregnancy outcomes, the temporal relationship between interpregnancy weight gain and outcomes in the second pregnancy lends support to a causal effect of obesity on pregnancy outcomes.[71] It is unclear how much of the association was driven by gestational weight gain (GWG) in the first pregnancy versus postpartum weight gain after the first pregnancy was delivered.[93]

COMPLICATIONS OF MATERNAL UNDERWEIGHT

Pre-pregnancy underweight is decreasing in prevalence in the U.S. (e.g., from 4.9% in 2003 to 3.7% in 2009).[2] However, maternal underweight is still an important risk factor for many adverse pregnancy outcomes, including maternal anemia,[94] preterm labor[95,96]/preterm delivery,[94] small for gestational age,[94] and neonatal morbidity[97] (e.g., low APGAR score[97] and NICU admission[97]). One study found that NICU infants born to underweight mothers had longer hospital stays; were more likely to require mechanical ventilation and oxygen administration; and were more likely to have RDS and lower umbilical cord pH than NICU infants born to mothers with higher BMIs.[58] As well as increasing infant morbidity, maternal underweight also increases the risk of neonatal, postneonatal, and infant mortality.[68] For example, in a recent U.S. study, adjusted ORs (95% CIs) comparing infants of pre-pregnancy underweight, versus normal weight, women were 1.20 (1.01, 1.43) for neonatal mortality, 1.24 (1.02, 1.51) for postneonatal mortality, and 1.22 (1.05, 1.41) for infant mortality.[68]

Although some adverse pregnancy outcomes are more common in underweight women, many others are less frequent. For instance, the risks of GDM, gestational hypertension, emergency cesarean delivery, elective cesarean delivery, operative vaginal

delivery, postpartum hemorrhage, and LGA are reduced in underweight women compared to normal weight women.[94]

BIOLOGICAL PLAUSIBILITY: MATERNAL UNDERWEIGHT

There are several hypothesized explanations for the association between maternal underweight and poor pregnancy outcomes. During pregnancy, food restriction may increase prostaglandin concentrations at preterm gestational ages.[98,99] This could prompt uterine contractions[99] and preterm labor.[98,99] A reduction in maternal macronutrient and micronutrient supplies could also be associated with restricted fetal growth.[95]

Compared to normal weight women, underweight women have decreased plasma volume and reduced levels of aldosterone and other hormones that regulate plasma volume.[100] This could lead to placental insufficiency (i.e., a lower supply of nutrients and oxygen to the fetus) and, ultimately, SGA.[94,100]

The reduced risk of cesarean and operative vaginal delivery among underweight women may be driven by the smaller size of their offspring (i.e., infants of underweight women are less likely to be macrosomic). In turn, this decreased risk of cesarean and operative vaginal delivery may reduce the risk of postpartum hemorrhage among underweight women.

EFFECTS OF MATERNAL WEIGHT GAIN DURING PREGNANCY

Similarly to maternal pre-pregnancy weight, maternal weight gain during pregnancy also has important effects on perinatal health. The most recent Institute of Medicine (IOM) guidelines for singleton pregnancies, which were issued in 2009, recommend that preconceptionally underweight women gain 28-40 pounds during

pregnancy, normal weight women gain 25-35 pounds, overweight women gain 15-25 pounds, and obese women gain 11-20 pounds during pregnancy.[101] For each pre-pregnancy BMI category, this equates to rates of 1-1.3 lb/week, 0.8-1.0 lb/week, 0.5-0.7 lb/week, and 0.4-0.6 lb/week, respectively, during the second and third trimesters, assuming a gain of 1.1-4.4 lb in the first trimester.[101] These guidelines balance the risks of excess and inadequate GWG, both of which are on the rise in the U.S.[102] As of 2009, the IOM lacked sufficient evidence to recommend different amounts of GWG by obesity category.[103] However, it is biologically plausible that the level of optimal GWG differs by obesity class.[103] The IOM and others have called for more research on this topic.[101]

Independently of pre-pregnancy BMI, excess GWG is linked to increased risk of maternal medical conditions, such as gestational diabetes[104] and gestational hypertensive disorders.[105,106] However, is possible that GWG could actually be influenced by these conditions, rather than being a risk factor for the conditions themselves. Although it is biologically plausible that excess GWG could increase the risk of preeclampsia, the reverse could also be true.[101] Preeclamptic women may experience edema near the end of pregnancy, which could cause total GWG to increase.[101] In addition, gestational diabetes could influence women's GWG in late pregnancy.[101] Women may reduce their caloric intake after receiving a GDM diagnosis, which could lead to lower total GWG.[101]

Excess GWG is associated with altered fetal growth, such as macrosomia/LGA[3,101] and intrauterine growth restriction (via maternal hypertension[107]). A 2008 review by the Agency for Healthcare Research and Quality found that the risk of LGA increases by 1.1 times for every 1-kg increase in GWG.[108] High GWG is associated with increased preterm birth,[101] which may be due to medically indicated preterm

delivery.[109] High GWG has also been associated with higher rates of IOL,[108] failed IOL,[108,110] CD,[108] and unscheduled CD.[111] However, excess GWG may also reduce the risk of growth restriction/SGA[3] among non-hypertensive pregnancies. Excess GWG is also associated with increased risks of neonatal hypoglycemia,[110,112] low APGAR score,[110] maternal postpartum weight retention,[113] and childhood adiposity[114] and obesity.[115]

The mechanisms underlying the associations between excess GWG and poor pregnancy outcomes are likely the same as those underlying the associations between pre-pregnancy overweight/obesity and adverse outcomes,[92] although excess GWG is a risk factor independent of BMI.[112] For instance, excess GWG is associated with increases in visceral fat; excess visceral fat is associated with insulin resistance and its adverse sequelae,[116] such as neonatal hypoglycemia.[112] Excess GWG is associated with increased risk of insulin resistance even among women without diagnosed diabetes.[112] Obese women with excess GWG may be at particularly high risk of poor birth outcomes compared to women of other BMIs and GWG levels.[110,117]

Inadequate GWG is independently associated with increased risks of intrauterine growth restriction,[3] preterm birth,[118] neonatal complications,[97] and perinatal[119] or infant death.[67] The risk of delivering an SGA infant is up to three times as high among women with low, versus adequate, GWG.[101] Among underweight and normal weight women, the risk of delivering preterm is approximately doubled for women who have low GWG.[101] However, low GWG (i.e., below recommendations) could also be beneficial by reducing the risk of LGA and gestational hypertension.[3,105,120-126] The association between inadequate GWG and adverse pregnancy outcomes may differ among women of different

pre-pregnancy BMI categories. Inadequate GWG may be particularly harmful among underweight women.[97,127] Among obese women, low GWG (below IOM guidelines) or gestational weight loss could be beneficial (e.g., by reducing the risk of LGA infants).[105,120-126] Inadequate GWG is also associated with neonatal complications[97] and infant death.[67] The biological mechanisms of inadequate GWG and low pre-pregnancy BMI are likely similar.

RELEVANCE OF IOM GWG GUIDELINES

The IOM guidelines have been challenged by many investigators. Some researchers advocate that all women should gain below IOM guidelines,[126] while others have advocated for wider ranges of acceptable GWG.[128] In 2013, the American College of Obstetricians and Gynecologists (ACOG) reviewed existing literature and determined that overweight women could safely gain below IOM recommendations,[103] although research challenging this assumption has emerged since the publishing of ACOG's report.[67,129] Some authors have found slight gestational weight loss to be beneficial in overweight women.[128,130]

Similarly, many (but not all[120-124,129,131]) researchers find that obese women may be able to safely lose weight or gain less than the IOM recommends without increasing their risk of adverse outcomes such as SGA or preterm birth.[110,118,125,128,132-136] Excess maternal adipose tissue may be sufficient to support fetal growth in the presence of low GWG.[127] However, this association may only hold for classes two[125] and three[125,137] obese women.

Some researchers have found that GWG in excess of IOM recommendations is beneficial, particularly in underweight women.[97,128] For instance, Choi et al. found that the risk of neonatal complications was lowest in underweight and normal weight women who gained above IOM recommendations.[97,128] Few researchers find benefits to excess GWG in the obese. However, some *do* find that GWG above IOM guidelines reduces the risk of infant mortality and SGA in class 1 obese women.[127,137,138] Bodnar et al. found that the risk of infant mortality was minimized among normal weight, overweight, and obese women who gained slightly above IOM GWG recommendations.[67] The lowest predicted risk of infant mortality corresponded to a GWG of 35-44 lb among normal weight and overweight women, 29-37 lb among class 1 obese women, and 22-33 lb among class 2 obese women (findings for class 3 obese women were too imprecise to make firm conclusions). Notably, the predicted risk of infant mortality was increased for GWG exceeding these ranges.[67]

GWG PATTERNS IN WOMEN OF DIFFERENT BMI CATEGORIES

When weight gain by IOM recommendations is examined, overweight or obese women are more likely to exceed IOM recommendations than underweight or normal weight women.[110,112,115,139] The likelihood of exceeding IOM guidelines is highest in overweight women.[110,112,115,122] For example, more than 60% of overweight women in the 2000-2009 Pregnancy Risk Assessment Monitoring System (PRAMS) gained above IOM guidelines.[102] Among obese gravidas, the likelihood of exceeding IOM recommendations decreases with obesity severity.[110,137] For instance, nearly half of class 1 obese women in the 2000-2009 PRAMS gained above IOM guidelines, but approximately 34% of class 3 obese women gained above clinical guidelines.[102]

The likelihood of gaining below IOM guidelines is highest in underweight[115,139] and class 3 obese women.[139] Among obese women, the proportion of women gaining below IOM recommendations increases with obesity class.[110,137]

When weight gain is measured as a continuous variable, most obese women gain less weight during pregnancy than non-obese women.[110,118,140,141] Some researchers find that overweight and normal weight women gain the same amount of weight during pregnancy,[118,140] while others have found that GWG decreases with pre-pregnancy BMI category, among women who are normal weight or higher.[110]

GWG INTERVENTIONS DURING PREGNANCY

GWG is modifiable throughout all of pregnancy. Nutritional interventions during pregnancy can help ensure that women gain appropriate amounts of weight. Because second-trimester GWG predicts total GWG fairly accurately, second-trimester GWG interventions can be targeted toward women at high risk of gaining above or below recommendations.[115]

The most successful interventions that aim to restrict GWG combine nutritional counseling, physical activity, and weight monitoring.[142] Limiting caloric intake as well as increasing fiber and polyunsaturated fatty intake may decrease the risk of excess GWG.[143] GWG counseling may be particularly important for obese women who recently lost weight prior to conception: recent evidence shows that these women may be at higher risk of excessive GWG than obese women who maintained or gained weight during this time period.[144] GWG counseling is also vital for underweight women to ensure that they do not gain below IOM recommendations.

DISSERTATION EMPHASIS AND OVERVIEW

This dissertation explored ways to reduce the risk of adverse pregnancy outcomes associated with maternal weight. Each specific aim of this dissertation emphasized a modifiable exposure.

Aim 1 evaluated the association between gestational weight gain and stillbirth among normal weight, overweight, and obese women. Although GWG is associated with many risk factors for stillbirth, little is known about the association between GWG and stillbirth itself. GWG may be a particularly important modifiable risk factor among obese women, whose risk of stillbirth is twice that of normal weight women.

The second and third aims examined how elective induction of labor (IOL) influenced maternal morbidity and mode of delivery **(Aim 2)** and infant morbidity and mortality **(Aim 3)** among obese women and their offspring. Among the general population, elective IOL (induction without medical indication) ≥39 weeks' gestation has been associated with reduced risk of maternal and infant complications.[145] Among certain high-risk subgroups, elective IOL at earlier gestational ages has been associated with reduced pregnancy complications (e.g., elective induction appeared beneficial at ≥37 weeks' gestation among women with gestational hypertension/mild preeclampsia[146]). However, the risks and benefits of elective IOL, as compared to expectant management (delayed delivery in later weeks), have not been thoroughly evaluated among obese women and their offspring.

The following two sections of this chapter contain a more detailed literature review specific to **Aim 1** (GWG and stillbirth) and **Aims 2-3** (elective induction of labor [eIOL] and pregnancy outcomes among obese women and their offspring).

BACKGROUND: AIM 1 (GWG AND STILLBIRTH)

SPECIFIC AIM (AIM 1 OVERVIEW)

Stillbirth (fetal death ≥20 weeks' gestation) occurs in 1 of every 168 U.S. pregnancies reaching 20 weeks' gestation.[147] The stillbirth rate among overweight and obese women is even higher; over 1% of pregnancies to obese women end in stillbirth.[50] Although the overall stillbirth rate has decreased slightly in the past two decades, the gestation-specific rate for 20-27 week deliveries has not changed, and stillbirth is now more common than infant mortality in the U.S.[147] There is limited research on potentially modifiable risk factors such as gestational weight gain,[148] which may be especially relevant for the nearly 50% of pregnant U.S. women[2] who are at elevated risk of stillbirth[50] due to preconception overweight or obesity.

Ideally, women should attain a healthy weight *before* conception in order to minimize the risk of stillbirth.[16,17,27,50] This goal is challenging given both the difficulty of sustaining weight loss[149] and the fact that 50% of pregnancies are unplanned.[150] In particular, women who were not trying to conceive may not have focused on reaching a proper preconception weight.

Fortunately, pregnancy is an opportune time for clinicians to counsel women about weight management. Pregnant women are particularly receptive to weight management counseling due to concerns about their offspring's health.[14] Furthermore, gaining an appropriate amount of weight during pregnancy lowers the chance of many adverse birth outcomes.[3,97,105,110,111,118,120-126] Promoting appropriate GWG, which is a *modifiable protective exposure*, during prenatal care may help women minimize their risk of pregnancy complications.

However, the appropriate amount of GWG—that is, the amount of GWG that confers the lowest risk—varies by pre-pregnancy BMI and pregnancy outcome. For instance, the amount of GWG that minimizes the risk of macrosomia and cesarean delivery is different from that which minimizes the risk of SGA and preterm birth.[120-123] Similarly, there may be tradeoffs between maternal and fetal outcomes at each level of GWG.[101] It is currently unknown how much weight women should gain during pregnancy to minimize the risk of stillbirth.[151,152] This is a particularly important research issue for obese women, among whom the risk of stillbirth exceeds 1%.[151,152] A recent systematic review in *JAMA* called for more investigation.[49] The four previous studies on GWG and stillbirth have numerous limitations, including restricting to stillbirths ≥28 weeks.[153] However, stillbirths at 20-27 weeks constitute half of stillbirths in the U.S.[147] All four studies also fail to account for obesity severity (a potential effect modifier).[103] This project addressed these gaps in the literature by including all stillbirths ≥20 weeks and by evaluating differences between class 1 obese and morbidly obese women.

Evaluating the relation between GWG and stillbirth is challenging because both variables are highly correlated with gestational age (GA) at delivery. GWG is time-varying and typically increases throughout pregnancy. The vast majority of stillbirths are preterm, limiting the GWG timeframe.[50] Two of the four previous studies on GWG and stillbirth failed to account for GA.[154,155] This could make low GWG look artificially harmful.

Hutcheon et al. recently created a GWG z-score measure that standardizes for GA.[156,157] The authors recently published GWG z-score charts that were developed from a follow-up study of healthy Pittsburgh women who delivered term live births.[156,157]

GWG z-scores can be calculated for either ongoing[157] or completed pregnancies[156,157] and require only three measurements: pre-pregnancy weight, weight at delivery (or weight at the GA in question), and GA at delivery (or at the time in question, e.g., mid-pregnancy). GWG percentile charts are similar in concept to fetal,[158] infant,[159] and childhood[160] growth charts. We applied these GWG z-scores in **Aim 1** of this dissertation.

Our overall study goal, to assess the relation between GWG and stillbirth, was addressed with the following specific aim:

Aim 1: Evaluate the association between GWG z-score and the risk of stillbirth among women in the Stillbirth Collaborative Research Network (SCRN) Case-Control Study. Evaluate differences by pre-pregnancy BMI.

Hypothesis: High GWG z-score (e.g., ≥75th percentile) will *increase* the odds of stillbirth among overweight and obese women. Inadequate GWG z-score (e.g., ≤25th percentile) will *increase* the odds of stillbirth among normal weight and overweight women but *decrease* the odds among obese women.

BACKGROUND AND SIGNIFICANCE

Despite stillbirth's frequency,[151,152] seriousness,[161,162] and high risk of recurrence (between two and ten times the initial risk[152]), it remains a significantly understudied outcome. Relatively little is known about stillbirth etiology. Half of all stillbirths have no determined cause. Epidemiologic research is also complicated by incomplete fetal death reporting.

These research gaps were recently addressed in the Stillbirth Collaborative Research Network Case-Control Study, which was the dataset used in Dissertation Aim 1. (This study is described in more detail in **Chapter 2, Methods: Aim 1**.) SCRN investigators created a novel classification system for etiologic causes of stillbirth and successfully determined probable cause of death for 61% of stillbirths in their sample.[163] They also examined medical and sociodemographic risk factors for stillbirth that were identifiable at pregnancy confirmation, such as pre-pregnancy BMI, history of hypertension, and parity.[50] SCRN participants who were overweight, class 1 obese, and morbidly obese (BMI ≥35 kg/m^2) before pregnancy began had elevated odds of stillbirth (adjusted odds ratios [aORs] and 95% Confidence Intervals [CIs] were 1.43 [1.09-1.88], 1.72 [1.22-2.43], and 1.73 [1.23-2.45], respectively).[50]

However, SCRN investigators did not consider certain medical risk factors occurring *during* pregnancy, which may be as important to the risk of stillbirth as pre-pregnancy exposures. This project used SCRN data to address one main gestational exposure of interest, weight gain during pregnancy, for which there is limited evidence with respect to stillbirth. In contrast to other perinatal outcomes, the association between GWG and stillbirth has been largely overlooked.[50]

This analysis is critical given the rapidly increasing prevalence of maternal pre-pregnancy obesity,[2] the growing frequency of excess GWG,[102] and the heightened risk of stillbirth among overweight and obese women.[50]

BIOLOGICAL PLAUSIBILITY: GWG AND STILLBIRTH

GWG is independently associated with many risk factors for stillbirth. For instance, excess GWG is associated with elevated risks of gestational hypertension/

preeclampsia,[105,106] gestational diabetes,[104] insulin resistance (among non-diabetic women),[112] excess fetal growth,[3] and fetal growth restriction (due to maternal hypertension[107]). These complications are risk factors for stillbirth[50,163,164] and may be intermediates on the biological pathway from excess GWG to fetal death. However, among non-hypertensive pregnancies, excess GWG reduces the risk of fetal growth restriction,[3] which is a strong risk factor for stillbirth.[163,164]

Inadequate GWG is associated with increased risks of intrauterine growth restriction[3] and preterm birth,[118] which can result in intrapartum fetal death due to fetal intolerance to labor.[163] However, inadequate GWG could also decrease the risk of stillbirth by reducing the risk of gestational hypertension and LGA.[3,105,120-126]

EVIDENCE FOR AN ASSOCIATION BETWEEN GWG AND STILLBIRTH

Despite evidence of biological plausibility, the association between GWG and stillbirth itself remains understudied. Existing evidence is limited and inconsistent, and a 2014 systematic review called for more research on this topic.[49]

Since the literature on GWG and stillbirth is sparse, it is beneficial to review research on stillbirth and infant death (which share similar biological processes[152,163,165,166]) together. Many studies have found that low or inadequate GWG is independently associated with increased risk of stillbirth, perinatal death, or infant death,[68,127,140,155,167] while others have found that excess GWG increases the risk of these outcomes.[68,167]

However, the strength and direction of these associations may vary by pre-pregnancy BMI. For instance, inadequate GWG may be harmful among underweight or

normal weight women[97] but may not be associated with perinatal or infant death among obese women.[127] Excess GWG may be beneficial in underweight women only,[97] although some researchers have found that excess GWG decreases the odds of infant mortality in obese women, as well.[67,127] For example, Bodnar et al. found that the risk of infant mortality is minimized among underweight, normal weight, and overweight women with a GWG between 35 and 44 lb; among obese class 1 women with a GWG between 29 and 37 lb; and among class 2 obese women with a GWG between 22 and 33 lb (no association between GWG and infant mortality was found among class 3 obese women).[67] These levels of GWG exceed IOM recommendations for every pre-pregnancy BMI category. Although these quantities of GWG may be beneficial for the infant, they may not be beneficial for the mother.[127]

In contrast, other studies have found no association between GWG and fetal or infant death.[97,112,135,154,168-170] There are various explanations for these null findings. Some authors speculate that secular improvements in perinatal care may have led to associations between GWG and neonatal morbidity replacing associations between GWG and perinatal death.[112] Alternatively, poor study design may be a contributing factor. Some studies were also severely underpowered.[168,170]

Studies on GWG and stillbirth specifically

A recent systematic review of GWG and perinatal outcomes identified only four studies that assessed GWG and stillbirth.[49] The single U.S. study, which used data from the 1980 U.S. National Natality and Fetal Mortality Surveys, found an inverse relation between GWG and the risk of stillbirth (for GWG up to 35 pounds).[155] Similarly, a

GWG rate ≤0.24 kg/week was associated with a 50% increase in the odds of antepartum stillbirth (aOR=1.5, 95% CI 0.9, 2.7) in a 2001 study of Swedish nulliparous women.[140] Likewise, the odds of stillbirth decreased with increasing rate of GWG in a 2005 retrospective cohort study within the Danish National Birth Cohort; however, results did not reach statistical significance (aOR for each additional 100 g- gain per week=0.94, 95% CI 0.87-1.03).[51] In contrast, there was no association between stillbirth ≥28 weeks and GWG after the first 24 weeks of pregnancy in a 1994 Swedish case-control study.[154]

Published studies suffer from numerous limitations. All previous studies were restricted to stillbirths ≥28 weeks (in concordance with the World Health Organization's definition[153]); however, stillbirths at 20-27 weeks constitute half of stillbirths in the U.S.[147] Furthermore, two studies excluded intrapartum stillbirths,[51,140] two did not account for GA in multivariable analyses,[154,155] and one excluded women with gestational diabetes or hypertensive disorders,[51] which are plausible consequences of GWG.[101] Furthermore, many of the studies are older, lacked power, or may not be widely generalizable, and no previous analyses examined morbidly obese women separately from class 1 obese women. The measurement of GWG is not standardized across studies, which complicates the interpretation of research findings. Notably, two previous studies did collect repeat weight measures throughout pregnancy,[140,154] which was an important study strength.

METHODOLOGICAL CONSIDERATIONS

There are several methodological challenges to analyzing the association between GWG and stillbirth. As noted previously, one challenge is the strong correlation of GA with both GWG and stillbirth. Most stillbirths occur at preterm gestations,[50] when a

woman's GWG will be lower (as she had less opportunity to gain weight). If GA is *not* accounted for in analyses of GWG and stillbirth, low GWG may look artificially harmful.[171] Using the average rate of GWG may also lead to misleading conclusions because the rate of GWG is not constant throughout pregnancy.[101] GWG is slower in the first than in the second and third trimesters. Consequently, an association between average GWG rate and stillbirth may exist simply due to the correlation of GA with both of these variables.[172] Although survival analysis is one possible solution in cohort studies,[173] prospective studies are impractical and uncommon for rare outcomes such as stillbirth. Hutcheon et al. propose the use of a GWG z-score measure, which standardizes for GA (i.e., a gestational weight gain *for gestational age* measure).[156,157] As described previously, Hutcheon et al. recently published GWG percentile charts that were developed from a cohort study in Pittsburgh.[156,157] The levels of GWG in Hutcheon et al.'s population are similar to many other U.S. settings.[156,157]

These GWG z-scores were designed to be independent of GA. However, it is possible that GWG z-scores may not be entirely independent of gestational duration when they are applied in populations other than that from which they were derived.[174] In a recent simulation by Hinkle et al. using Consortium for Safe Labor (CSL) data, the GWG z-score yielded spurious results for the association between GWG and preterm delivery (the simulation was designed to yield a null association).[174] Hinkle et al. speculated that the GWG z-scores in their study may have remained correlated with GA due to misspecification of the relation between GWG and GA in their dataset.[174] In order to calculate GWG percentiles at each gestational week, Hutcheon et al. originally modeled GWG trajectories as a mathematical function of gestational age.[156,157] However, if the

relation between GWG and GA differed between Hutcheon et al.'s cohort and the Consortium for Safe Labor dataset, then the GWG z-scores in the CSL dataset could remain correlated with GA using Hutcheon et al.'s GWG z-score standards.[174] This issue could also arise in the SCRN dataset.

Cheikh Ismail et al. recently published GWG percentiles for normal weight women using data from the Fetal Growth Longitudinal Study (FGLS; a large, multinational, ethnically diverse cohort of healthy, normal weight women).[175] FGLS standards may be more broadly applicable to external datasets than Hutcheon et al.'s standards. However, FGLS measures are only available for normal weight women. Both GWG z-scores have the advantage of being calculable at any time point during pregnancy if measurements of GWG and GA are available.[157,175] For instance, a physician could calculate a GWG z-score for a patient at 30 weeks' gestation using the patient's GWG up to that time point.[157,175] Investigators have recently advocated for the widespread use of the GWG z-score in research (and ultimately, clinical) settings across diverse populations.[156,157,175] However, more research is needed on the associations between GWG z-score and adverse outcomes before the GWG z-score is used in clinical settings.[156,157,175]

Utilizing the weekly rate of GWG in the second/third trimesters may be another reasonable option if data on second/third-trimester GWG are available. This rate can be calculated during pregnancy and directly pertains to clinical guidelines released by the Institute of Medicine.[101] Some researchers have calculated second/third trimester GWG as: Total GWG—*Estimated* First-trimester GWG (rather than Total GWG—*Measured* First-Trimester GWG).[110] Estimating first-trimester GWG may require investigators to

make implausible assumptions, such as a constant rate of first-trimester GWG for all women in each pre-pregnancy BMI category.[110] If women gain more or less weight than is estimated, false associations between rate of GWG and stillbirth may be induced.

Other investigators have shown that adjusting for GA as a covariate is appropriate when analyzing total GWG, provided that confounders of the association between GA and the outcome are accounted for.[174] In a recent simulation of GWG and neonatal mortality, Hinkle et al. demonstrated that adjusting for GA at delivery eliminated confounding due to time-dependent processes.[174] In Hinkle et al.'s study, there was a clear sequential, temporal association between the exposure (GWG) and the outcome (neonatal mortality): GWG inherently precedes neonatal death; GA at delivery also, by definition, precedes this outcome. In addition, it can be argued that GA confounds the association between GWG and neonatal mortality: GA influences GWG, as mothers with higher GAs have more opportunity to gain weight; GA at delivery is also a risk factor for neonatal death. This approach does not perfectly correspond to stillbirth, an outcome that occurs at or before the time of delivery. This method may be most suitable for outcomes that occur after pregnancy ends.

Another challenge to assessing the relation between GWG and stillbirth is that stillbirths may be growth restricted—and, as a consequence, low birthweight—for reasons unrelated to maternal nutritional status (e.g., congenital anomalies).[176] In studies using total GWG, bias may occur because mothers of growth-restricted stillbirths are more likely to be classified as having low GWG. Using net GWG (defined as total GWG minus infant birthweight,[177-180] or, alternatively, total GWG minus infant birthweight, placental weight, and amniotic fluid weight[181]) could avoid this bias and allow a more

thorough evaluation of the impact of maternal, rather than fetal, GWG. Accounting for GA would still be necessary in analyses of net GWG. Unfortunately, there is not currently a "net GWG z-score" (analogous to the total GWG z-score), which would allow a more thorough evaluation of the estimated impact of maternal versus fetal weight.

AIM 1 SUMMARY AND NEXT STEPS

Aim 1 of this dissertation focused on the association between GWG, an exposure that is modifiable throughout all of pregnancy, and stillbirth among participants in the SCRN Case-Control Study. We standardized for GA using the GWG z-score. Information on study methodology can be found in **Chapter 2, Research Questions and Methods;** results can be found in **Chapter 3**.

BACKGROUND: AIMS 2 AND 3 (ELECTIVE INDUCTION OF LABOR AMONG OBESE WOMEN)

SPECIFIC AIMS (AIMS 2-3 OVERVIEW)

The purpose of Dissertation **Aims 2** and **3** was to determine whether elective induction of labor (eIOL) or expectant management (EM) resulted in lower risks of cesarean delivery (CD) and other adverse perinatal outcomes by gestational age (GA) among obese women. These dissertation aims are critical given the high prevalence of pre-pregnancy obesity (20.5%[2]), the numerous health risks associated with this condition, the lack of evidence-based obstetric guidelines for obese gravidas, and the steep financial cost of caring for this group.

Pre-pregnancy obesity is associated with a wide range of adverse maternal, fetal,

and neonatal outcomes.[9,22] This risk persists even in the absence of other chronic diseases.[9] As a result of their elevated risk, obese women have an increased need for labor induction, CD, and other obstetric interventions compared to non-obese women.[9,22,182]

It is crucial that obese women receive high-quality obstetric care that minimizes the risk of adverse outcomes while also avoiding unnecessary interventions. However, the optimal time of delivery among obese women is unknown, and it is unclear whether eIOL to prompt earlier delivery or expectant management (watchful waiting and delayed delivery) results in lower risks of adverse pregnancy outcomes at each GA.[89] Historically, eIOL was thought to increase the risk of CD. Recent studies comparing eIOL to expectant management, rather than to spontaneous labor during the index week (which is not a viable obstetric intervention[183]), have challenged these assumptions.[145,183] However, most recent studies have not specifically examined the impact of eIOL among obese women.

Many health care providers have recently prohibited elective deliveries at <39 weeks due to higher rates of infant complications at early GAs.[184,185] However, this policy may be harmful for obese women and their offspring. Despite evidence that obesity is a risk factor for macrosomia,[8,17] shoulder dystocia,[8] brachial plexus injury,[186] meconium aspiration syndrome,[8] stillbirth,[17,49] preeclampsia,[17] and maternal morbidity[7,16,17,22]—all of which increase with gestational age[145,187,188]—obesity is not considered an indication for earlier delivery. It is plausible that these complications could be prevented through elective induction of labor and earlier delivery. Other investigators have shown that delivery <39 weeks benefits the infants of certain

high-risk women, such as those with diabetes[189,190] or severe preeclampsia.[191] However, the potential negative side effects of elective labor induction and earlier delivery (including unplanned cesarean delivery and neonatal respiratory morbidity, respectively) must also be considered.[192,193]

Our studies were some of the first to examine, at each week of gestation from 37 through 41 weeks, whether elective labor induction or expectant management is preferable among obese women. A recent analysis by Lee et al. examined the association between term eIOL (37-40 weeks) and mode of delivery (CD, operative vaginal, non-operative vaginal) by GA among obese women in California.[187] This analysis also evaluated a limited number of maternal and neonatal morbidities (postpartum hemorrhage, severe perineal lacerations, macrosomia, chorioamnionitis, shoulder dystocia, brachial plexus injury, and RDS).[187] Lee et al.'s study suggested that term eIOL may reduce the risks of CD and macrosomia among obese women and their offspring without increasing the risk of operative vaginal delivery.[187] In adjusted models, the odds of cesarean were reduced by up to 58%, while the odds of macrosomia were reduced up to 74%, among electively induced, versus expectantly managed, women.[187]

However, Lee et al. only examined a limited number of maternal and infant outcomes. In addition, Lee et al. examined only one year of data (2007), which limited their study's statistical power to detect differences in rare outcomes such as RDS, shoulder dystocia, brachial plexus injury, chorioamnionitis (for several gestational weeks), and maternal postpartum hemorrhage.

This dissertation expanded upon Lee et al.'s analysis by including 5 years of data (2007-2011); by examining additional outcomes, including severe maternal morbidity,

length of maternal and infant hospital stay, meconium aspiration syndrome, and infant mortality; by assessing interaction by obesity class; and by conducting sensitivity analyses related to the timing of intrapartum complications and the classification of expectant management.

This dissertation evaluated the following aims:

Aim 2: Beginning at 37 weeks' gestation, examine whether eIOL in a particular gestational week or expectant management results in lower risks of CD, operative vaginal delivery, or other maternal morbidities (postpartum hemorrhage, severe perineal lacerations, admission to the maternal intensive care unit (ICU), uterine rupture, length of hospital stay, and unplanned hysterectomy or other operating room procedures) among obese women.

Hypothesis: Elective IOL will reduce the odds of cesarean delivery and maternal complications without increasing the odds of operative vaginal delivery.

Aim 3: Beginning at 37 weeks' gestation, examine whether IOL in a particular gestational week or EM results in lower risks of infant mortality (≤1 year) and morbidity (infant hospital stay >5 days, macrosomia, chorioamnionitis, RDS, meconium aspiration syndrome, shoulder dystocia, brachial plexus injury) among offspring of obese women.

Hypothesis: Elective induction of labor will: 1) increase the odds of RDS and infant mortality before 39 weeks' gestation; 2) decrease the odds of RDS and infant mortality from 39-41 weeks' gestation; and 3) reduce the odds of other infant complications between 37-41 weeks' gestation.

BACKGROUND AND SIGNIFICANCE: OBSTETRIC MANAGEMENT OF OBESE WOMEN

As described previously, obese women are at increased risk of many adverse pregnancy outcomes, including obstetric complications, postterm pregnancy, failed labor induction, and stillbirth.[9,22,50,89,192,194] These risks persist among obese women without other comorbidities.[9] There is a major gap in the literature regarding how to manage obese women around the time of delivery. There is even less known about how to manage morbidly obese women, as this condition was fairly rare until recently.[195]

The optimal time and method of delivery among obese women are unknown. Although researchers have examined the gestational week-specific tradeoff between IOL and expectant management in the general population[145,196,197] and among certain other high-risk groups,[189-191] this research question has received minimal attention among the obese population.[89] Unfortunately, there is not a simple diagnostic test that can determine whether a fetus is better off induced or in utero.[198]

Obese gravidas and their offspring are at elevated risk of many adverse outcomes that could be prevented through elective IOL and earlier delivery. At term gestations, eIOL eliminates risks that continue to increase with GA, such as stillbirth,[89,163,166,199-201] intrauterine growth restriction,[202] preeclampsia,[203] growth restriction,[202] meconium[204]/meconium aspiration syndrome,[188] oligohydramnios,[183] macrosomia,[145,187,203 203] and obstructed labor.[205,206] Preventing macrosomia may lead to a reduction in cesarean delivery,[205,206] and, consequently, reduced maternal and infant morbidity.[207] Elective induction may also prevent premature rupture of membranes, and consequently, chorioamnionitis.[208] Delivering early may also reduce the risk of maternal death.[209]

In contrast, expectant management allows the fetus more time to mature. Delaying delivery until 39 weeks' gestation or later may minimize the risk of neonatal mortality, RDS, and NICU admission.[184,185,193] Neonatal morbidity (including respiratory complications) and NICU admissions may even be increased at 39 weeks, relative to later GAs.[210] Expectant management also avoids the potential negative side effects of elective labor induction, such as failed IOL and unplanned cesarean delivery[192,193] (and related post-surgical complications[16,17,22]), fetal distress,[211] postpartum hemorrhage, chorioamnionitis, and neonatal morbidity and mortality.[29] These potential negative side effects of eIOL are especially relevant among obese women, who are at elevated risk of failed induction compared to non-obese women.[192]

Notably, expectant management could occur through watchful waiting without intervention *or* through active intervention to delay delivery (e.g., bed rest or tocolytics to halt preterm labor). Although expectant management can avoid the risks associated with early term delivery (i.e., delivery 37-38 weeks' gestation), attempting to halt labor, which may be an adaptive response to underlying problems such as infection, could actually cause damage.[212] The tradeoffs of eIOL versus expectant management likely vary by GA and outcome,[213] but they have not been extensively studied among obese women. As another clinical management option (which is beyond the scope of this dissertation), planned CD may be life-saving for both mother and baby in some high-risk subgroups (e.g., obese women with eclampsia).[214]

There are also financial tradeoffs to consider: labor induction is financially costly ($1 billion/year in the U.S.)[29] and could lead to additional obstetric interventions (e.g., epidural use) since induction may result in longer and more painful labors than would

have occurred without induction.[215,216] Induced patients may also enter the hospital earlier, with respect to time of delivery. However, IOL could be cost-*saving* if it reduces the risk of cesarean delivery. The cost-effectiveness of prenatal and obstetric interventions among obese women is currently unknown.[5] Experts disagree about the appropriate level of obstetric intervention in obese women.[36] While some investigators have found that interventions are uncommon among obese women,[36] others note that the level of obstetric intervention may be inappropriately high due to overprediction of macrosomia.[36,217]

Many hospitals now discourage or prohibit elective delivery <39 weeks. More research is needed on whether this policy is appropriate for obese women, who are physiologically distinct from non-obese women (obesity is not currently considered an indication for earlier delivery). Some have argued that superobesity (BMI $\geq$50 kg/m^2) should be considered an indication for IOL.[12] In addition, research suggests that early delivery benefits certain *other* high-risk groups, such as diabetic women.[189-191] To the best of our knowledge, ours is only the second study to assess the relation between eIOL (versus expectant management) and perinatal outcomes separately for each week of term gestation.[187]

DEFINITION OF ELECTIVE AND MEDICALLY INDICATED IOL

Observational studies comparing all induced women to expectantly managed women may suffer from confounding by indication: women with medical indications are more likely to be induced, and they are also more likely to experience adverse outcomes. Consequently, IOL may appear harmful. Comparing *elective* induction of labor to expectant management may avoid confounding by indication.

Elective labor induction is defined as induction without medical indication. Elective IOL may be requested for reasons such as maternal physical discomfort, concern about labor progressing too rapidly, and logistical reasons, among others.[183] Medically indicated IOL is defined as labor induction due to a medical condition that warrants delivery.

There is a lack of consensus on which medical indications are sufficient to warrant labor induction.[29] The Joint Commission lists medical indications that may justify delivery before 39 weeks.[218] Notably, obesity is not listed as a reason that could justify early term elective delivery. Multiple investigators[145,187] have used this list to classify labor inductions as medically indicated or elective in their analyses. In this dissertation, we also used the Joint Commission's list to derive our list of indications for IOL. We selected this list because it is routinely used in clinical decision-making. See **Chapter 2, Methods: Aims 2-3** for details.

ACOG lists 15 reasons that may warrant induction.[193] ACOG's list is similar to, but slightly less extensive than, the Joint Commission's list. ACOG includes certain conditions (postterm pregnancy, preexisting pulmonary disease, and antiphospholipid syndrome) that are not found on the Joint Commission's list; however, multiple gestations is listed as an indication in the Joint Commission's list[218] only.[29] In addition, ACOG also lists several contraindications for delivery, such as vasa or placenta previa, prior cesarean, and transverse lie. In this dissertation, we excluded women with several of these contraindications (vasa or placenta previa, prior CD, transverse lie) from our study completely (**see Chapter 2, Methods: Aims 2-3**). ACOG also discusses "soft" (non-medical) indications for IOL such as psychological reasons, maternal distance from the

hospital, and the likelihood of experiencing rapid labor. These "soft" indications may be the main reasons why women in our dataset were electively induced (however, we did not have information on these specific factors). In addition to medical and "soft" indications, ACOG advises clinicians to consider patients' cervical status, GA, and other pregnancy complications when they decide whether to induce. Finally, ACOG recommends that *elective* IOL not be performed before 39 weeks or before fetal lung maturity is proven.

Other lists of medical indications for IOL or early delivery exist. For instance, the Society for Maternal/Fetal Medicine and the National Institute for Child Health and Human Development enumerate 33 medical conditions that may necessitate late preterm or early term birth.[219] Other countries, such as the United Kingdom and Canada, have guidelines that differ from those in the U.S.[29] Additional definitions exist in the research literature.[146] To the best of our knowledge, no existing lists of indications for IOL include obesity.

SECULAR TRENDS (AND POLICIES) IN EARLY ELECTIVE DELIVERY

The incidence of IOL has increased in recent decades (e.g., from 9.5% in 1990 to 23% in 2005). As of 2007, approximately 16% of deliveries ≥37 weeks were electively induced, and up to 10% of deliveries were early term elective inductions (37-38 weeks' gestation).[29] Since then, early elective delivery has declined in the U.S.[220-223] after elective delivery,[224-226] and early elective delivery in particular, was linked to higher risks of infant morbidity and mortality.[193,227-229] Some hospitals have initiated "hard-stop" policies to prohibit scheduling of IOL at early term gestations.[230] Other initiatives limit

Medicaid reimbursement for early elective deliveries and promote reductions in early elective deliveries as a quality metric.[231] These policies have been shown to be effective in reducing early term deliveries.[222,223,230,232] In addition, rates of NICU admission declined in some[221,230] (but not all[223]) hospitals after these policies were initiated; in contrast, one study observed an increase in stillbirth and macrosomia.[230] Others found that rates of stillbirth were unchanged.[222,223,232] Notably, these studies included only 1-2 years of data.[233] The impacts of policies that limit early elective delivery may differ among obese women, who are at increased risk of adverse pregnancy outcomes, and non-obese women.

PRIOR RESEARCH ON IOL VERSUS EXPECTANT MANAGEMENT

Among the general population, randomized controlled trials (RCTs) demonstrate that IOL ≥41 weeks, as well as elective IOL ≥41 weeks, reduce the risks of unplanned cesarean delivery, perinatal death, and meconium aspiration/staining, as compared to expectant management.[183,198,234] For instance, a 2009 meta-analysis found that the odds of cesarean were 1.21 times higher, and the odds of meconium staining were 2.04 times higher, in expectantly managed, versus electively induced, women ≥41 weeks' gestation.[183]

However, most previous *observational* studies used spontaneous labor during the index week as the comparison group.[183] For instance, women who were induced during week 39 would have been compared to women who delivered spontaneously during week 39. Spontaneous labor is not an intervention that can be influenced by clinicians. A more appropriate comparison group in studies of obstetric decision-making is expectant management.[183,197] The use of spontaneous labor during the index week as a comparison

group may lead to incorrect, but commonly held, opinions that IOL increases the risk of CD, whereas RCTs demonstrate that IOL actually leads to a similar or lesser risk of cesarean at most GAs. Notably, RCTs may not represent everyday clinical practice, as women in RCTs are under more detailed observation than women in standard clinical care.

Among the general population, there is limited[183] and mixed evidence about the effects of IOL (not specifically eIOL), as compared to expectant management, prior to 41 weeks. While some studies found that IOL at 38-40 weeks decreased the odds of cesarean delivery as compared to EM,[203] others found that IOL conferred no benefit[196] or even increased the risk of cesarean.[196,197] In addition, one study found that IOL increased the odds of NICU admission.[196]

These associations may differ by hospital characteristics. For instance, when a facility's risk of CD is <20%, induced and expectantly managed pregnancies may have similar risks of CD during labor; however, if a setting's overall risk of CD is ≥20%, IOL may reduce the risk of CD during labor.[197] Notably, these prior studies may be subject to confounding by indication, as women with medical indications were included in the IOL group.

There is limited research on the impacts of elective IOL versus expectant management among the general population. Using the 2006 California Linked Patient Discharge Data/Birth Cohort File, Darney et al. found that term eIOL (37-40 weeks), as compared to expectant management, reduced the odds of CD, operative vaginal delivery, 3rd-and 4th-degree perineal lacerations, RDS (for IOL ≥39 weeks only), macrosomia, and NICU admission/transfer/extended hospital stay, but slightly increased the odds of

hyperbilirubinemia.[145] Associations were stronger among parous women than in nulliparas. Darney et al. defined indications for IOL using the Joint Commission guidelines for early elective delivery, similar to Aims 2-3 of this dissertation (see **Chapter 2, Methods: Aims 2-3** for details).[145]

Evidence among high-risk subgroups

Randomized trials suggest that IOL (not specifically eIOL) <41 weeks may be beneficial in some high-risk subgroups. Among these women, the risks of continuing pregnancy may outweigh the risks of immediate delivery. For instance, eIOL may benefit preeclamptic women and their infants after 34 completed weeks' gestation.[191] Similarly, among women with gestational hypertension or mild preeclampsia, IOL ≥37 weeks' gestation may reduce maternal morbidity and mortality, the need for antihypertensive drugs, and the development of severe hypertension or HELLP syndrome as compared to expectant management.[146] Among diabetic women, IOL at 38 weeks may reduce the risk of infants' LGA and shoulder dystocia.[189] Likewise, among women with premature rupture of membranes at term, term IOL with oxytocin decreases the risk of chorioamnionitis and maternal postpartum fever.[235] In an observational study, delivery (not specifically IOL) ≥38 weeks was associated with reduced risk of perinatal mortality among infants born to women with GDM.[190]

However, eIOL to prompt earlier delivery does not always benefit high-risk groups. Among growth-restricted fetuses ≥36 weeks' gestation, investigators found similar neonatal outcomes and mode of delivery among electively induced versus expectantly managed women, although severe (<3rd percentile) growth restriction was

less common among infants of electively induced women.[202] In a randomized controlled trial (RCT) of women with presumed macrosomic fetuses, the risks of CD and infant morbidity were not significantly different between electively induced versus expectantly managed women[189] (however, this specific trial[189] may have been underpowered to detect differences[203]). Others found an increased risk of emergency CD when women with suspected macrosomic infants were induced electively.[6]

Evidence among obese women

Compared to non-obese induced women, obese induced women may be at higher risk of CD after labor,[28,37,89,236,237] second-degree perineal tears,[67] and additional obstetric interventions, such as fetal blood sampling and epidural use.[37] Others have found that length of labor, oxytocin requirements, and risk of CD were higher for women who were obese *at admission*.[237] However, the increased risk of complications may not be present among obese parous women[37] or in postterm pregnancies.[89]

There is minimal research comparing eIOL to expectant management among obese women. Most existing research in obese women compared IOL to spontaneous labor during the index week, rather than to expectant management; did not assess eIOL specifically; did not assess the tradeoffs of (e)IOL by GA; or compared obese induced women to non-obese induced women.[90] Furthermore, most prior studies were unable to detect differences in infant outcomes.

A recent simulation by Gill et al. demonstrated that a 39-week labor induction policy among obese women would reduce the risks of stillbirth and cesarean delivery, plus total healthcare costs.[238] This analysis used a decision analysis model among

100,000 simulated term pregnancies to obese women.[238]

Similarly, Schuster et al. discovered that a clinical protocol to induce obese women by their estimated due date reduced the risk of CD, as well as NICU length of stay (by 0.3 days, p=0.47), in a Pennsylvania health system.[239] However, the frequency of NICU admission increased slightly (absolute difference of 2.2%, p=0.09),[239] although increases were observed among non-obese as well as obese women.[239] However, this clinical protocol was tested in a single healthcare system, and analysis was limited to proxy indicators of neonatal morbidity. In addition, analyses of neonatal outcomes were unadjusted for covariates.

In a small hospital-based retrospective cohort study of obese nulliparas with an unfavorable cervix, Wolfe et al. found that eIOL at 39 or 40 weeks, as compared to expectant management ≥39 weeks, was associated with higher risk of cesarean delivery (crude frequency: 40.0% versus 25.9%), NICU admission (18.3% versus 6.3%), neonatal morbidity (5-minute APGAR score <7: 3.3% versus 1.7%; umbilical artery <7: 5.4% versus 1.3%), and lower mean birthweight (3508.6 versus 3387.6 grams).[240] Notably, women with an unfavorable cervix are at higher risk of cesarean delivery,[241,242] which is associated with increased neonatal morbidity.[207] Wolfe et al. accessed medical records, which is an important study strength. However, they did not assess eIOL <39 weeks, include parous women, or adjust for covariates.[240] Furthermore, the sample size was small (N=60 electively induced women), and analyses were not stratified by gestational week at induction.[240] This could obscure important differences between eIOL at 39 weeks versus 40 weeks' gestation.

Only one study has specifically evaluated the tradeoffs of eIOL at each week of

term gestation (37-40) versus expectant management among obese women.[187] As described in detail earlier, Lee et al.'s study suggested that term eIOL may reduce the risks of CD and macrosomia among obese women and their offspring.[187] Lee et al. defined eIOL using recent Joint Commission guidelines for early elective delivery, similar to Aims 2-3 of this dissertation (see **Chapter 2, Methods: Aims 2-3** for details).[187] Our study built upon this previous research in several ways, including evaluating several new outcomes, and using a large sample size, which increased statistical power.

CHAPTER 2, RESEARCH QUESTIONS AND METHODS

AIM 1 METHODS

This section describes the methods used in Dissertation **Aim 1**, which evaluates the association between GWG and stillbirth using data from the Stillbirth Collaborative Research Network Case-Control Study. This section begins with a general overview of the SCRN Case-Control Study, including its objectives and methods. Subsequently, the specific methods used in **Aim 1** of this dissertation are described.

SCRN OVERVIEW AND METHODS

OVERVIEW OF THE SCRN CASE-CONTROL STUDY

For Dissertation **Aim 1**, we analyzed data from the SCRN Case-Control Study.[243] The SCRN designed and implemented a multicenter, population-based case-control study of stillbirth.[243] Women with stillbirths (fetal death ≥20 weeks' gestation) and live births were enrolled at the time of delivery.[243] The SCRN Case-Control study included all of the following: 1) population-based live birth controls; 2) oversampling of preterm live births; 3) prospective surveillance of stillbirth, with study participants enrolled at the time of delivery; 4) comprehensive placental pathology[244,245] and fetal autopsy[246] conducted according to standard protocols; 5) abstraction of prenatal and peripartum medical records; 6) interviews with case and control mothers that were administered shortly after delivery, and before hospital discharge for most women; and 7) collection of numerous placental, fetal tissue, and blood specimens.[243] The study aimed to ascertain ≥90% of live births and stillbirths in the geographically defined catchment areas.[243] Catchment areas included Rhode Island and counties in Massachusetts, Georgia, Texas, and Utah.[243]

SCRN investigators devised a novel classification system for etiologic causes of

stillbirth using participants' clinical and pathological data.[247] The system had six categories for cause of fetal death: 1) Maternal medical conditions during pregnancy; 2) Obstetric complications (e.g., placental abruption, premature rupture of membranes); 3) Maternal/fetal hematologic conditions; 4) Fetal karyotypic, genetic, or structural abnormalities; 5) Placental and/or fetal infection, and 6) Pathologic placental conditions.[247] The authors successfully assigned a possible or probable cause to 76% of stillbirths using this system.[163] There were differences in causes of death by timing of stillbirth (intrapartum or antepartum) and GA, with stillbirths at <24 weeks' gestation most likely to be caused by obstetric complications or infection.[163] There were also differences in causes of death by race/ethnicity, as stillbirths to non-Hispanic black women were more often caused by infections or obstetric complications than stillbirths to non-Hispanic white or Hispanic women.[163] Data on cause of fetal death were utilized in a sensitivity analysis in this dissertation (this sensitivity analysis is described in a subsequent section).

SCRN researchers also built predictive models investigating stillbirth risk factors that were identifiable at the beginning of pregnancy.[50] Statistically significant predictors included maternal age, maternal race/ethnicity, pregnancy history, pre-pregnancy BMI category, diabetes, plurality, and others.[50] Several of these predictors were strong risk factors for stillbirth (e.g., adjusted odds ratio [OR] comparing women with versus without a clinical history of diabetes: 2.50 [95% CI 1.39-4.48]).[50] However, these factors only explained 19% of the variability in stillbirth, and additional subgroup-specific models (e.g., stillbirths at ≥24 weeks' gestation) failed to explain more.[50] Other analyses of the SCRN data have examined abnormal fetal growth,[164] placental lesions,[248]

significant life events,[249] and bile acids[250] as risk factors for stillbirth. However, SCRN investigators have not examined certain maternal risk factors *during* pregnancy—such as GWG—which this dissertation aim addresses.

SCRN STUDY DESIGN

The SCRN case-control study was conducted in 59 hospitals in five geographic areas associated with the following sites: Brown University (Providence, RI); Emory University (Atlanta, GA); the University of Texas Health Sciences Center at San Antonio (San Antonio, TX); the University of Texas Medical Branch at Galveston (Galveston, TX); and the University of Utah Health Sciences Center (Salt Lake City, UT).[243]

SCRN's goal was to identify at least 90% of stillbirths and live births in each geographic catchment area.[243] Eligible women were ≥13 years of age;[243] resided within a geographic catchment area at the time of their delivery;[243] delivered a stillborn or liveborn infant ≥20 weeks' gestation at a study site hospital;[243] were identified as a potential study participant before they were discharged from the hospital;[243] and provided informed consent or assent ≤48 hours after delivery[251] (if a woman's health problems caused her to be unable to consent/assent within 48 hours of delivery, she could consent/assent >48 hours after delivery but before hospital discharge[251]). Women were ineligible for the study if they were incarcerated or had a mental or language barrier that could affect informed consent or assent.[243] Deliveries involving the termination of a live fetus were excluded.[243] Interviews were conducted in English or Spanish.[243] Hospital interpreters assisted participants who spoke other languages.[243]

The study sample size requirements included ≥500 women with stillbirths who agreed to fetal autopsy;[251] an adequate sample of controls to supply a minimum 1:1 ratio

of live births to stillbirths among all race/ethnicity categories (non-Hispanic white, non-Hispanic black, Hispanic); [243] and sufficient controls to conduct stratified analyses at various GAs.[243] Live birth controls from 20-31 weeks' gestation were oversampled to provide approximately equivalent numbers of stillbirths and live births at these preterm gestations.[243] Live births of ≥32 weeks' gestation were sampled using a probability sampling approach.[243] Approximately 18% of live births in the SCRN were <32 weeks' gestation.[243]

Recruitment lasted from March 2006-September 2008, during which 663 women with a stillbirth (69% of those eligible) enrolled into the study, and 1,932 women with a live birth (63% of those eligible) enrolled.[243] The original sampling plan resulted in a live birth: stillbirth ratio of approximately 2:1 for Hispanics and white non-Hispanics but approximately 1:1 for black non-Hispanics.[243] A protocol addendum successfully increased the number of live births to black non-Hispanic women.[243]

Separate analysis weights were created for live births <32 weeks' gestation, live births ≥32 weeks' gestation, and stillbirths.[243] The weights accounted for SCRN's sampling design (including the different study enrollment dates at each hospital) and for unequal probabilities of participation.[243]

SCRN DATA COLLECTION INSTRUMENTS

In the parent study, data collection instruments included a maternal interview,[243] placental pathological exam,[244] and postmortem[246] and neuropathologic[245] exams (for stillbirths). Medical record abstraction was also performed using records from prenatal care providers, hospitals, and emergency rooms.[243] Records for the current pregnancy, neonatal discharge summary for live born children, and records for prior stillbirths were

accessed.[243,251] These data were used in this secondary data analysis.

DISSERTATION AIM 1 METHODS

Objective: Evaluate the association between GWG z-score and stillbirth among women in the SCRN Case-Control Study. Assess differences by pre-pregnancy BMI category (normal weight [BMI 18-<25.0 kg/m^2], overweight [BMI 25.0-<30.0 kg/m^2], obese [BMI ≥30 kg/m^2]).

Hypothesis: Excess GWG (e.g., GWG z-score >75th percentile) will *increase* the odds of stillbirth among overweight and obese women. Inadequate GWG (e.g., GWG z-score <25th percentile) will *increase* the odds of stillbirth among normal weight and overweight women but *decrease* the odds among obese women.

AIM 1 DATA SOURCES AND EXCLUSION CRITERIA

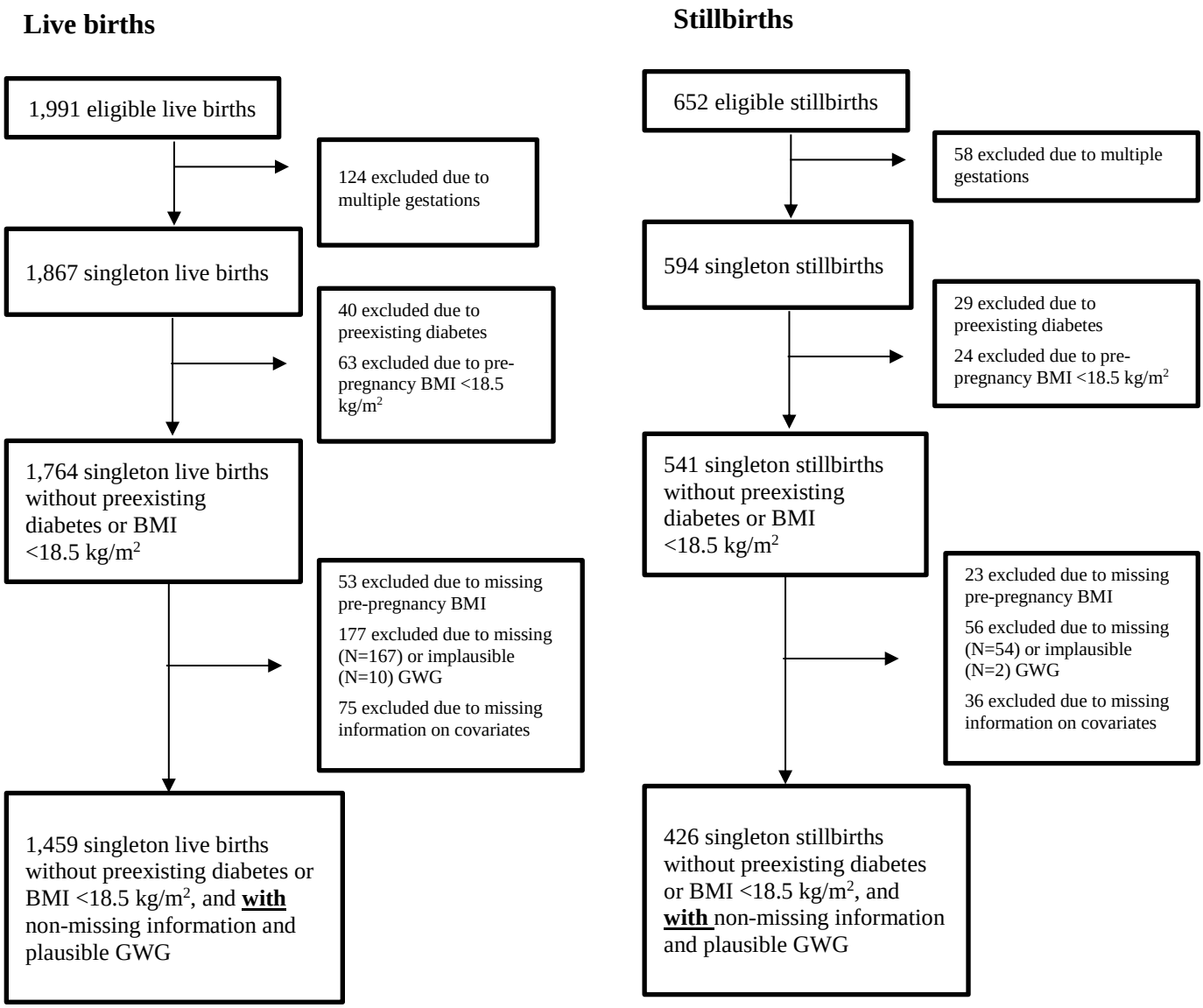
In Dissertation **Aim 1**, we utilized data from the medical record abstraction, maternal interview, placental pathology, and fetal autopsy.[243] Maternal health data, including height and pre-pregnancy weight, were abstracted from medical records and the maternal interview. Up to three maternal weight measurements were evaluated in our study: pre-pregnancy weight (abstracted from medical records and likely based on self-report), weight at last prenatal visit, and weight at delivery.

Sociodemographic information was derived from the maternal interview. GA at delivery for both live births and stillbirths was determined via an algorithm that incorporated date and reliability of last menstrual period, ultrasound estimates of GA, and GA at study screening.[252] GA at death (used in sensitivity analyses) was determined via an algorithm based on measures such as fetal foot length, head circumference, and

crown-rump length.[252] Using this algorithm, 47% of stillbirths were assigned a GA at death that was estimated to be precise within ≤7 days.[252]

We excluded non-singleton pregnancies[110] because the amount of recommended GWG differs by plurality status.[101] We also excluded women with preexisting diabetes, who have unique nutritional needs during pregnancy,[253] women with pre-pregnancy BMI <18.5 kg/m^2 (due to insufficient observations for stratified analyses), missing or implausible GWG (weight loss >50 lb or gain >150 lb[110]), or missing pre-pregnancy BMI or covariates (see **Figure 2-1** on next page)**.**

Figure 2-1. Aim 1 Study Exclusions by Case-Control Status



EXPOSURE MEASURE

Total GWG was defined as maternal weight at delivery minus pre-pregnancy weight. The exposure variable in this study was the GWG z-score. To calculate the GWG z-score, we transformed each woman's GWG (in kilograms) to a z-score using Hutcheon et al.'s formula, $\frac{\ln(GWG+c)-mean\ (\ln(GWG))}{standard\ deviation(\ln(GWG))}$.[156,157] The mean and standard deviation depended on BMI category (normal weight, overweight, class 1 obese, class 2 obese, class 3 obese) and GA, while c was a constant that transformed ln(GWG) to a positive value (means, standard deviations, and the constant c were taken from published references[156,157]). Published GWG z-score charts end at 40 weeks for normal weight women and 41 weeks for overweight/obese women; GAs above these cutoffs were rounded down to 40 or 41 weeks, respectively, in main analyses and were excluded in sensitivity analyses.

STATISTICAL METHODS

We conducted data analysis in SAS Version 9.4 (Cary, NC) and SAS-callable SUDAAN (Research Triangle Park, NC). We used multivariable logistic regression models in SUDAAN, which were weighted to account for SCRN's sampling design and individuals' probabilities of participating and completing all parts of the data collection process.[243] We assessed multiplicative interaction between pre-pregnancy BMI category and GWG z-score using a likelihood ratio test. If no multiplicative interaction was detected ($p>0.20$), interaction terms were dropped. Potential confounders, including maternal race/ethnicity, were selected *a priori* using directed acyclic graphs and based on evidence of their associations with GWG and stillbirth.[50] Multivariable models were

adjusted for maternal age at delivery, maternal race/ethnicity, mother born in the United States, maternal education, marital status/cohabitating, health insurance type, trimester prenatal care began, family income in the last 12 months, WIC enrollment, average cigarettes/day during the 3 months prior to pregnancy, alcohol consumption in the 3 months prior to pregnancy, lifetime drug use, pregnancy history, pre-pregnancy BMI category, history of hypertension, history of thyroid disorder, and history of autoimmune disorder. We did not control for gestational diabetes, although a gestational diabetes diagnosis could plausibly influence women's GWG in late pregnancy. This was a purposeful decision, as gestational diabetes may be an intermediate between GWG and stillbirth. Similarly, we did not adjust for pregnancy-induced hypertension/preeclampsia. Although it is possible that preeclampsia could influence GWG (through edema), GWG is a known risk factor for preeclampsia,[105,106] and pregnancy-induced hypertension is a potential mediator of the association between GWG and stillbirth.

We modeled GWG z-score as a restricted cubic spline with 3 knots at the 5th, 50th, and 95th percentiles (these percentiles were calculated among live birth controls only using SCRN analysis weights in SAS).[254] The restricted cubic spline accounts for the non-linear relation between GWG and adverse outcomes.[255] This method is similar to Hutcheon and Bodnar et al.'s modeling approach in studies of GWG z-score and other perinatal outcomes (infant mortality,[67] preterm birth,[255] SGA,[255] LGA,[255] and unplanned CD[255]). We calculated odds ratio contrasts of interest by comparing the 10th, 15th, 25th, 35th, 45th, 55th, 65th, 75th, 85th, and 90th percentiles of GWG z-score to the 50th percentile referent (these percentiles were also calculated among control mothers using SCRN analysis weights in SAS).

In addition, we also used GWG z-score models stratified by pre-pregnancy BMI category (normal weight, overweight, obese) to more closely approximate the method of Bodnar and Hutcheon et al.[67,171] Models among obese women were adjusted for obesity class (1, 2, 3).

The logistic model for outcome **Y** (stillbirth, a dichotomous outcome) that accounts for repeated observations within individuals can be written as:

$Y_{ij} = g^{-1}(\mu_{ij}) + e_{ij}$, where

$g(\mu_{ij})$ is the logit link function and

$g(\mu_{ij}) = \ln [\mu_{ij}(1-\mu_{ij})] = \beta_0 + \beta_1(\text{GWG z-score}) + \sum_{a=1}^{m} \beta_a cov_a + \sum_{n=1}^{3} \beta_n interactionterm_n$, and

- Y_{ij} is the value of stillbirth for observation *j* on individual *i* (0 if live birth, 1 if stillbirth)
- GWG z-score= GWG z-score modeled as a continuous exposure using a restricted cubic spline (with 3 knots at the 5th, 50th, and 95th percentile)
- $\sum_{a=1}^{m} \beta_a cov_a$ = a vector of confounding variables [described earlier] and their coefficients, from a=1 to *m*
- $\sum_{n=1}^{3} \beta_n interactionterm_n$= a vector of interaction terms between GWG z-score and pre-pregnancy BMI category, from n=1 to 3 (BMI category is a 4-category variable [normal weight, overweight, class 1 obese, morbidly obese] that is represented by 3 dummy variables)
- e_{ij}= residual error assumed to be ~N (0, σ^2)

SENSITIVITY ANALYSES

To examine how different assumptions affected results, we conducted various sensitivity analyses. We recalculated GWG z-scores among normal weight women using newly-published GWG percentiles from the Fetal Growth Longitudinal Study.[175] In addition, we used separate models for class 1 obese and morbidly obese women. Models for obese women should ideally be stratified by obesity class (1, 2, 3). However, our sample size of obese women—particularly those with BMI ≥35 kg/m^2—was small. In another sensitivity analysis, we excluded normal weight deliveries >40 weeks and overweight/obese deliveries >41 weeks. We also used estimated GA at death[252] for stillbirths rather than GA at delivery. In additional sensitivity analyses using stillbirths' estimated GA at death, we: 1) excluded stillbirths that had an estimated GA at fetal death <20 weeks[252], despite having a GA at delivery ≥20 weeks; 2) fit separate models for antepartum and intrapartum stillbirths because of their differing pathophysiology[163]; 3) excluded stillbirths with causes of death related to fetal genetic, structural, or karyotypic abnormalities or maternal/fetal hematologic conditions[247] because fetal weight (a large component of total GWG) may be driven more by congenital abnormalities than by maternal nutritional status in these pregnancies[176]; 4) used weight at last prenatal visit as an estimate of weight at delivery for women missing delivery weight (last prenatal visit is typically a few days before delivery[91]); 5) controlled for weight and height squared as separate variables because of concern about introducing bias with the use of ratio measures[256]; and 6) excluded mummified stillbirths (grade IV or higher maceration among fragmented fetuses and grade V or higher maceration among intact fetuses) because these stillbirths may have a significant discrepancy between fetal weight at death and delivery.

ETHICS APPROVAL

This study was approved by the data coordinating center (RTI International) and by the Institutional Review Boards [IRBs] of each participating site (Brown University, Emory University, University of Texas Health Science Center at San Antonio, University of Texas Medical Branch at Galveston, University of Utah) (#IRB00000764).

AIM 2 METHODS

This section describes the methods used in **Dissertation Aim 2**, which evaluated the association between elective induction of labor (eIOL), as compared to expectant management (EM), and maternal morbidity and mode of delivery.

Objective: Beginning at 37 weeks' gestation, assess whether elective induction of labor (eIOL) in a particular week or expectant management (EM) results in lower risks of cesarean section (CD), operative vaginal delivery, or maternal morbidity (postpartum hemorrhage, severe perineal lacerations, admission to the intensive care unit [ICU], uterine rupture, unplanned hysterectomy or other operating room procedures, and length of postpartum hospital stay) among obese women in the 2007-2011 California Linked Patient Discharge Data/Birth Cohort File.

Hypothesis*:* Elective IOL ≥37 weeks will reduce the odds of cesarean and maternal complications without increasing the odds of operative vaginal delivery.

Study Design: Retrospective cohort study.

AIM 2 (AND 3) DATA SOURCE

We used the 2007-2011 California Linked Patient Discharge Data/Birth Cohort File[257] in **Aims 2** and **3**. This dataset contains information on 2,622,927 deliveries with birth or fetal death certificate data. To create this dataset, the California Office for Statewide Health Planning and Development linked vital records, maternal hospital discharge records, and infant hospital discharge records for all California live births and

stillbirths (excluding elective terminations), as well as out-of-state births to California residents. Deliveries occurring to the same woman but in different years were not linked in this dataset. Discharge data are available for hospital visits occurring during the prenatal period, at delivery, and during the first year after delivery. In this dissertation, we used maternal and infant hospital discharge data from the delivery visit, which contained ICD-9-CM procedure and diagnostic codes. Except where otherwise specified, we used both vital records and hospital discharge data to classify obstetric procedures (including labor induction), pregnancy characteristics, and maternal and infant outcomes. This methodology enhances the sensitivity of detection while only marginally increasing the false positive detection rate.[258-260]

ETHICS APPROVAL

To obtain this dataset, we submitted an application for data to the California Office of Statewide Health Planning and Development (OSHPD). Our application and study plans were approved by the California Committee for the Protection of Human Subjects, the California OSHPD, the California Department of Public Health, and the Emory University Institutional Review Board (IRB; #IRB00074702). Because our dataset was de-identified, informed consent was not required.

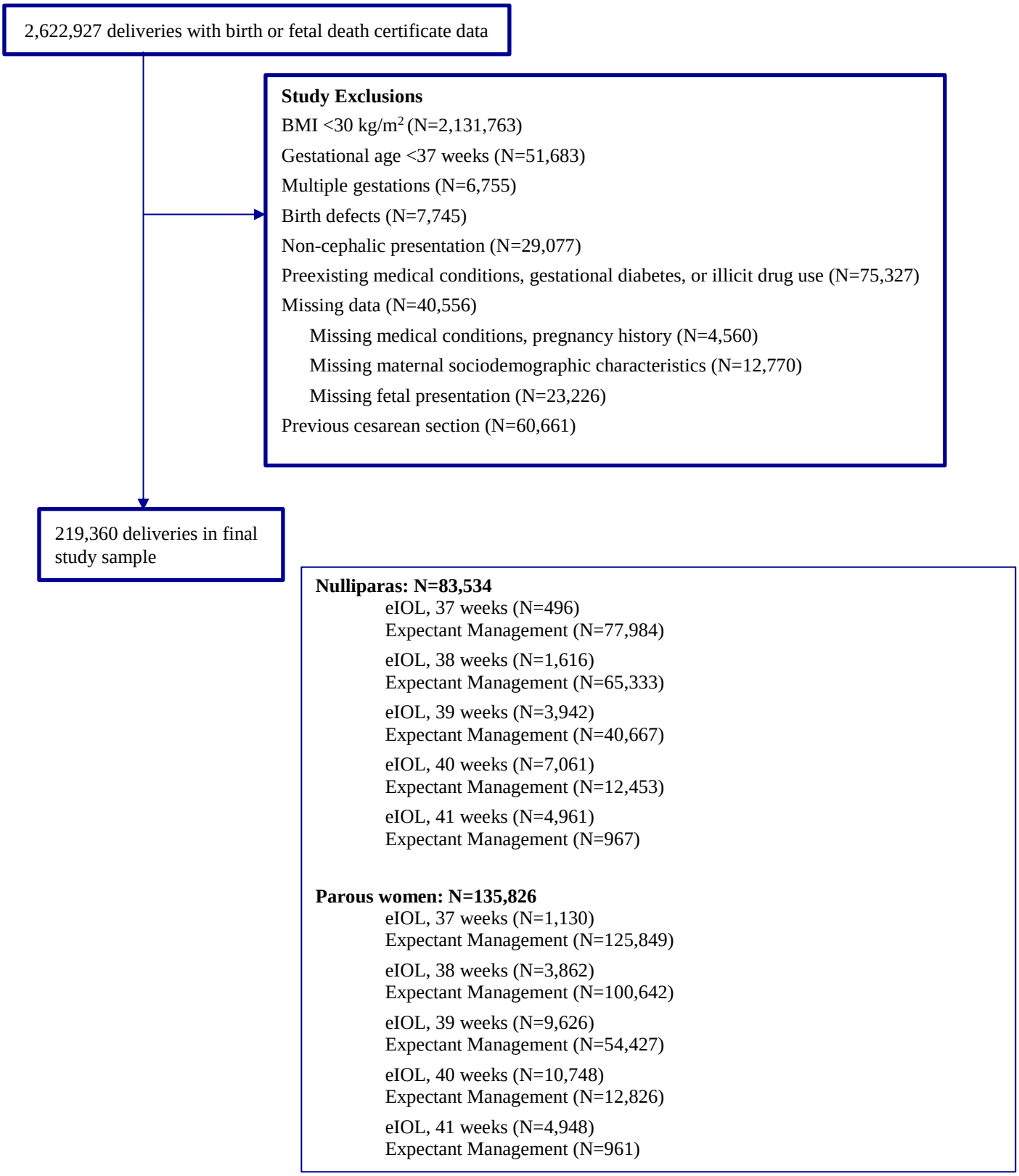
AIM 2 STUDY EXCLUSIONS

We excluded deliveries with pre-pregnancy BMI <30 kg/m^2, gestational age <37 weeks, multiple gestations, previous CD, non-cephalic presentation, major fetal anomaly, missing data, or medical conditions known before term that influence mode of delivery (e.g., gestational diabetes) (see **Figure 2-2 on following page**). In this figure, the number of women with expectant management is calculated as the number still pregnant at the

beginning of the next gestational week. That is, all women with spontaneous deliveries (i.e., delivery after spontaneous labor), induced deliveries, or cesarean deliveries during the index week were removed from the expectant management group.

Body mass index was calculated from pre-pregnancy height and weight as reported on vital records. GA in weeks was based on the best obstetric estimate. Parity was defined as the number of prior pregnancies reaching ≥20 weeks' gestation.

Figure 2-2. Aims 2 and 3 Study Exclusion Criteria



We performed this series of exclusions because clinical management may differ significantly for obese women with, versus those without, the aforementioned factors.[15,196] For instance, women with a prior CD are at increased risk of uterine scar rupture during labor. Hence, they may not be allowed to attempt a vaginal birth after CD, instead opting for a planned repeat CD.[261] Similarly, early delivery may be suggested for high-risk women, such as those with cardiovascular or endocrine disorders.[15]

We did not exclude women with scheduled CD or CD before labor. In studies evaluating IOL, some researchers exclude these women because they were not 'candidates' for the exposure (labor induction). This may have been done to limit confounding by contraindication. For instance, women with scheduled CD may have contraindications to IOL, such as prior cesarean delivery, which could bias associations against expectant management. **In our retrospective cohort studies, we did not exclude women with scheduled CD or CD before labor for the following reasons:**

1. Our dataset does not include information on whether a CD was scheduled or not.
2. Excluding women with "CD before labor" could lead to selection bias because it amounts to excluding women from a cohort study based on their outcome status.
    a. "CD before labor" is not an outcome that can be ascertained prospectively; rather, it can only be ascertained after delivery.
    - In addition, women with "CD before labor" do not necessarily represent all women with scheduled CDs.

- Rather, some women with scheduled CDs may enter spontaneous labor before their planned CD date. If this occurs, their pregnancy could either end in vaginal delivery or CD during labor.

3. It could be argued that women who had scheduled CDs (regardless of the outcome) should be included in the expectant management group until they are delivered. For instance, women who deliver via planned CD at 40 weeks are expectantly managed, compared to women who are electively induced at 37, 38, and 39 weeks.
4. Confounding by contraindication should not be a large problem in Dissertation **Aims 2** and **3**. We excluded deliveries complicated by non-cephalic presentation, a prior cesarean delivery, multiple gestations, major fetal anomaly, and preexisting medical conditions. These are contraindications to IOL and may require a planned CD. In other words, we do not believe that excluding "CD before labor"/scheduled CD would make a large difference in our study.

EXPOSURE DEFINITION

We evaluated our research question independently for each term (37-41) gestational week. Exposed women were those who underwent elective labor induction (i.e., induction without medical indication) in the given week. Medical indications for IOL were derived from the Joint Commission's list of conditions that may justify delivery <39 weeks.[187,218] Indications for IOL are detailed in **Table 2-1** below).

Unexposed women were those who underwent expectant management (watchful

waiting and delayed delivery in later weeks). The expectant management group consisted of all women who delivered in later weeks, regardless of delivery method or labor onset type. That is, the expectant management group included all deliveries that went on to have spontaneous labor, induced labor, or cesarean delivery *without* labor in later weeks. This expectant management definition ensured that the expectantly managed group truly represented delayed delivery, relative to eIOL.

Expectant management is the optimal comparison group in this study of obstetric decision-making. Although elective labor inductions in a given week are often compared to spontaneous labors occurring that same week, spontaneous labor is not a medical intervention that can be influenced by clinicians.[183]

Table 2-1. Indications for Induction of Labor[a]

Condition	**ICD-9 code**	**N of induced women (weeks 37-41) with this indication in final study sample[b]**
Human Immunodeficiency Virus (HIV)	042, 079.53, V08	4
Coagulation disorders	286.0, 286.1, 286.2, 286.3, 286.4, 286.5, 286.7	72
Placenta previa	641.0,[c] 641.1,[c] 762.0[c]	0 (study exclusion criteria)
Vasa previa	663.5[c]	0 (study exclusion criteria)
Placental abruption	641.2,[d] 762.1[d]	363
Antepartum hemorrhage	641.8, 641.9	101
Preexisting hypertension	401,[c] 402,[c] 403,[c] 404,[c] 405,[c] 642.0,[c] 642.1,[c] 642.2,[c] 642.7[c]	0 (study exclusion criteria)
Gestational hypertension	642.3	4,555 (using ICD-9 codes) + up to 2,343 additional (using vital records)[e]
Preeclampsia/eclampsia	642.4, 642.5, 642.6, 642.7	4,510 (using ICD-9 codes) + up to 1,855 additional (using vital records)[e]
Other hypertension	437.2, 642.9, 760.0	783
Liver/biliary tract disorder	570, 571.1, 571.2,[c] 571.5,[c] 571.6,[c] 572.2,[c] 572.4,[c] 646.7	93
Diabetes mellitus (preexisting or gestational)	249,[c] 250,[c] 357.2,[c] 362.0,[c] 648.0,[c] 648.8,[c] 775.0[c]	0 (study exclusion criteria)
Renal disease	403,[c] 404,[c] 580, 581,[c] 582,[c] 583, 584, 585,[c] 586, 587, 642.1,[c] 646.2, V42.0[c]	239
Cardiovascular disease	394,[c] 395,[c] 396,[c] 397,[c] 398,[c] 402,[c] 404,[c] 410, 411,	4

	412,[c] 413,[c] 414.0,[c] 414.1, 414.2,[c] 414.3,[c] 414.4,[c] 414.8,[c] 414.9,[c] 415, 416,[c] 417.0,[c] 417.1, 417.8,[c] 417.9,[c] 420, 421, 422, 423,[c] 424,[c] 425,[c] 426,[c] 427.0,[c] 427.1,[c] 427.2,[c] 427.3,[c] 427.4,[c] 427.5, 427.6,[c] 427.8,[c] 427.9,[c] 428, 648.5,[c] 648.6,[c] 760.3[c]	
Multiple gestations	651,[c] 652.6,[c] 761.5[c]	0 (study exclusion criteria)
Major fetal abnormality	653.6,[b] 655.0,[b] 655.1,[b] 740.0,[b] 740.1,[b] 740.2,[b] 741.0,[b] 741.9,[b] 742.0,[b] 742.2,[b] 742.3,[b] 742.1,[b] 743.0,[b] 743.1,[b] 743.2,[b] 743.3[0,1,2,3,4],[b] 743.45,[b] 744.0,[b] 744.01[b],744.23[b] 745.0,[b] 745.1,[b] 745.2,[b] 745.3,[b] 746.01,[b] 746.02,[b] 746.1,[b] 746.2,[b] 746.3,[b] 746.7,[b] 747.0,[b] 747.10,[b] 747.41,[b] 748.0,[b] 748.5[b]	0 (study exclusion criteria)
Fetal-maternal hemorrhage	656.0,[d] 772.0[d]	5
Isoimmunization	656.1, 656.2, 773.0,[c] 773.1, 773.2,[c] 773.3[c]	2,026
Intrauterine death	656.4,[f] 768.0,[f] V27.1[f]	0 (all excluded during sample selection)
Poor fetal growth	656.5, 764.0, 764.1, 764.9	1,162
Polyhydramnios	657.0, 761.3	401
Oligohydramnios	658.0, 761.2	4,644
Premature rupture of membranes	658.1, 761.1	3,133
Fetal distress or fetal heart rate abnormality <u>before</u> onset of labor	768.2, 763.81	17
Pregnancy with poor reproductive history	V23.5	206
Other fetal conditions affecting management of mother	655.0,[c] 655.1,[c] 655.3, 655.4, 655.5, 655.6, 655.8	219
Indications in sensitivity analysis only		
Fetal distress or fetal heart rate abnormality with <u>unspecified</u> time of onset	656.3, 659.7, 763.83, 768.4	14,371

Coagulation deficiency hemorrhage	641.31, 649.3	293
Amniotic infection/chorioamnionitis	658.41, 762.7	2,187

[a]We used vital records and hospital discharge data ICD-9 codes to classify indications. An indication was classified as present if detected in vital records or hospital discharge data.

[b]Women could have more than one indication for induction.

[c]Considered an exclusion criteria for our study.

[d]Not classified as an indication in a sensitivity analysis that accounted for the uncertain timing of intrapartum complications.

[e]Gestational hypertension and preeclampsia were combined into one item on vital records.

[f]All stillbirths were excluded from this study due to exclusion criteria or missing data.

STUDY OUTCOMES

Study outcomes included mode of delivery (CD, operative vaginal delivery [forceps or vacuum], and non-operative vaginal delivery), postpartum hemorrhage, severe (third-or-fourth degree) perineal lacerations, and severe maternal morbidity (SMM; a composite outcome of postpartum hemorrhage, severe perineal lacerations, unplanned surgical procedure, uterine rupture, maternal intensive care unit admission, maternal sepsis, and endometritis), and length of maternal postpartum stay. Outcomes such as uterine rupture were too rare to analyze individually.

STATISTICAL ANALYSES

Data analysis was conducted in SAS Version 9.4 (Cary, NC). All analyses were stratified by parity (nulliparous, parous) because associations may differ between these two groups. Nulliparous and parous women are physiologically distinct; for example, the frequency of cesarean delivery is higher in obese nulliparous women than in obese parous women with no previous cesarean deliveries.[187] Parous women with a previous vaginal delivery have shown that they are capable of delivering without extensive obstetric surgical intervention. In contrast, less is known about the potential pregnancy outcomes of nulliparous women, as they have not delivered before. In addition to cesarean delivery, obstetric complications, neonatal morbidity, and perinatal mortality are also more frequent among nulliparous women than among parous women who have one to three previous deliveries.[262] (Parous women who have delivered four or more times may be at increased risk compared to parous women who have delivered between one and three

times,[262] but our dataset lacked adequate sample size to examine these two groups of parous women separately.)

Nulliparous and parous women are also managed differently in the clinical setting. For instance, obese nulliparous women are more likely to be electively induced than obese multiparous women who have no previous cesarean deliveries.[187] Because of these differences in physiology and clinical management, we chose to stratify all models into two parity categories.

Differing baseline risks of the outcome variables among nulliparous versus parous women could also influence results from our additive interaction models,[263] which were a unique contribution of this dissertation. These additive interaction models are described in more detail on the following pages.

Among each parity category, we used five models for each outcome; each model compared eIOL in a specific week (37 through 41) to expectant management. For each comparison (e.g., eIOL during week 37 versus delivery ≥38 weeks), spontaneous or medically indicated deliveries that occurred during the index week (e.g., week 37) were excluded from the given analysis (**see Figure 2-2** for the sample sizes of exposed and unexposed women in each model). In our models, gestational age was not simply a time scale; rather, delivery in later weeks of gestation was the "intervention" for the unexposed group. In other words, we were not simply comparing eIOL at time "X" to non-eIOL at time "X;" instead, we were comparing eIOL at time "X" to all deliveries in later weeks (>X). This modeling approach is consistent with others in the literature.[145,187]

We used multinomial logistic regression to model crude and adjusted associations between eIOL and mode of delivery (CD, operative vaginal delivery, and non-operative

vaginal delivery). Because most binomial, log-binomial and Robust Poisson regression models did not converge for dichotomous outcomes, we used logistic regression to model crude and adjusted associations of eIOL with postpartum hemorrhage, severe perineal lacerations, and SMM. We analyzed models for severe perineal lacerations among all deliveries as well as among vaginal deliveries only, as women undergoing cesarean are generally not at risk of this outcome. We log-transformed maternal postpartum hospital stay (in days), which was not normally distributed, and modeled its crude and adjusted associations with eIOL using linear regression. This outcome variable was defined using hospital discharge data only.

For all dichotomous outcomes, we assessed multiplicative interaction between eIOL and obesity class using likelihood ratio tests ($p<0.20$). We chose to evaluate multiplicative, rather than solely additive, interaction for two main reasons. First, using only a single likelihood ratio test in a single model, we could obtain an overall assessment of multiplicative interaction between eIOL and obesity class, which was a three-level covariate. This is in contrast to additive interaction models, where interaction between eIOL and obesity class would need to be assessed in 3 separate models[263] (one comparing obesity classes 2 and 1, the second comparing obesity classes 3 and 2, and the third comparing obesity classes 3 and 1). Similarly, using only one model and one likelihood ratio test, we could assess whether there was multiplicative interaction between eIOL and obesity class with respect to our 3-level mode of delivery outcome.

However, tests of multiplicative interaction can sometimes lead to misleading results about whether the exposure variable is more or less beneficial or risky among certain groups.[263] For this reason, we also chose to evaluate additive interaction.[263] In

addition, analyses of additive interaction models may be more statistically powerful than analyses of multiplicative interaction.[263]

We assessed additive interaction between eIOL and obesity class using the Relative Excess Risk of Interaction[263] for dichotomous outcomes (including CD and operative vaginal delivery, modeled separately). For postpartum hospital stay, we assessed additive interaction between eIOL and obesity class using Type 3 likelihood ratio tests of the interaction terms ($p<0.20$).

For dichotomous outcomes, we used SAS code provided by VanderWeele and Knol to test for additive interaction.[263] In SAS, each *dichotomous* logistic regression model permitted the assessment of additive interaction between *two* levels of an exposure variable and *two* levels of a covariate.[263] That is, for each dichotomous outcome, one model evaluated additive interaction between eIOL (two categories) and obesity classes 2 versus 1 (two categories), a second model evaluated additive interaction between eIOL (two categories) and obesity classes 3 versus 1 (two categories), and a third model evaluated additive interaction between eIOL (two categories) and obesity classes 3 versus 2 (two categories). Cesarean delivery and operative vaginal delivery were modeled separately for the purposes of additive interaction assessment.

Models were adjusted for maternal age, education, race/ethnicity, and obesity class; first-trimester prenatal care initiation; source of payment for delivery; birth year; weekday delivery; delivery at a teaching hospital; and hospital obstetric volume. These covariates were selected *a priori* based on evidence of their associations with eIOL and the outcomes.[6,9,145,187] We chose not to control for epidural use (as some have done[197,203]) because labor induction may influence epidural use via faster and possibly stronger

contractions. Likewise, we did not adjust for variables that may be intermediates between eIOL/EM and CD or maternal morbidity, such as macrosomia, intrauterine growth restriction, hypertension, preeclampsia, and placental insufficiency.[203]

Data on maternal sociodemographic characteristics, prenatal care initiation, and weekday delivery came from vital records. Information on remaining covariates came from discharge data.

LOGISTIC MODEL FOR DICHOTOMOUS OUTCOMES

A logistic model for dichotomous outcome Y, which compares eIOL in week X to all deliveries in weeks ≥X (37≤X≤42) could be represented in logit form as follows:

$Ln\left(\frac{P(D=1)}{P(D=0)}\right) = \beta_0 + \beta_1(EIOL_X) + \sum_{a=1}^{m} \beta_a cov_a + \sum_{n=1}^{2} \beta_n interactionterm_n$, where

- p is the risk of the dichotomous outcome **Y** for a particular individual
- $EIOL_x$=Elective labor induction at week X (1 if eIOL at X weeks, 0 if born at week ≥X by any method)
- $\sum_{a=1}^{m} \beta_a cov_a$ = a vector of confounding variables [described earlier] and their coefficients, from a=1 to *m*
- $\sum_{n=1}^{z} \beta_n interactionterm_n$= a vector of interaction terms between eIOL (at week X) and obesity class, and their coefficients, from n=1 to 2 (obesity class is a 3-category variable that is represented by 2 dummy variables

A different model is analyzed for each term gestational week (37-41).

A polytomous logistic regression model for mode of delivery (a 3-category outcome: cesarean delivery, operative vaginal delivery, non-operative vaginal delivery [referent]) which compares eIOL at week X to all deliveries in weeks ≥X, could be represented as follows:

$Ln\left(\frac{P(D=g)}{P(D=0)}\right) = \beta_{g0} + \beta_{g1}(\text{EIOL}_X) + \sum_{a=1}^{m} \beta_{ga}\text{cov}_a + \sum_{n=1}^{2} \beta_{gn}\text{interactionterm}_n$, where

- g=1 if the outcome is cesarean delivery, g=2 if the outcome is operative vaginal delivery, and
- Other variables are as defined above

A linear regression model for length of maternal postpartum stay, which compares eIOL at week X to all deliveries in weeks ≥X, could be represented as follows:

$$Y = \beta_0 + \beta_1(\text{EIOL}) + \sum_{a=1}^{m} \beta_a\text{cov}_a + \sum_{n=1}^{2} \beta_n\text{interactionterm}_n, \text{ where}$$

- **Y** is the length of postpartum hospital stay in days for a particular individual, and
- Other variables are as defined above

SENSITIVITY ANALYSES

Our dataset did not include information on whether certain intrapartum complications, such as fetal distress, occurred prior to labor, in which case they could be indications for IOL, or during labor, in which case they could be consequences of IOL. In sensitivity analyses, we varied our assumptions about the timing of these complications (see **Table 2-1** for a list of revised indications for IOL).

In main analyses, our expectant management definition ensured that the

unexposed group represented delayed delivery relative to our exposed group. In sensitivity analyses, we expanded the expectant management group to include spontaneous deliveries occurring during the same week as the exposed were induced.[145] For instance, in a sensitivity analysis of elective labor induction at 37 weeks versus expectant management, the revised comparison group would become: spontaneous deliveries during week 37 + all deliveries ≥38 weeks. This second expectant management definition accounted for the fact that some spontaneous deliveries during the index week could be considered expectantly managed, relative to elective inductions occurring earlier in the week. (Our dataset lacked an obstetric estimate of GA in *days*, so we were unable to actually compare the gestational ages of elective inductions and spontaneous deliveries that occurred during the same week.)

Notably, some women with spontaneous labor onset and cesarean delivery may not have been detected in our dataset (these women should have been included in the revised expectant management group). This is because there was not a simple indicator variable for labor onset type (e.g., induced, spontaneous, no labor) for women with cesarean deliveries. For cesarean deliveries, we deduced labor onset type using 2 sources of information: 1) whether a woman was induced, and 2) whether an attempted trial of labor was recorded. Women with cesarean deliveries were classified as having spontaneous labor onset if they 1) had an attempted trial of labor recorded, and 2) were not induced.

The phrase '**attempted** trial of labor' seems to reflect an intentional plan to allow laboring during a woman's delivery. A trial of labor could be attempted to avoid cesarean delivery, or alternatively, to confer some benefits to the fetus before cesarean delivery is

initiated.

However, it is plausible that some women who delivered via cesarean after spontaneous labor onset may not have been recorded as having an '**attempted** trial of labor.' For instance, this could happen for women who *planned* a cesarean without trial of labor, but who instead delivered via cesarean after experiencing spontaneous labor onset at home. In other words, if the spontaneous labor was not planned or desired for women delivering via cesarean, an 'attempted trial of labor' may not have been recorded in our dataset. In this case, these women would be incorrectly coded as having 'cesarean deliveries without labor,' and they would be excluded from the revised expectant management group. This limitation in available data is a major reason that this revised expectant management definition as used only in sensitivity analyses, rather than in main analyses.

We hypothesized that eIOL would appear less beneficial with respect to CD using the revised EM classification.

AIM 3 METHODS

Objective: Between 37 and 41 weeks' gestation, examine whether eIOL in each particular gestational week or EM is associated with lower risks of infant mortality (≤1 year) and morbidity (infant hospital stay >5 days, macrosomia, chorioamnionitis, respiratory distress syndrome [RDS], meconium aspiration syndrome, shoulder dystocia, brachial plexus injury) among offspring of obese women in the California Linked Patient Discharge Data/Birth Cohort File.

Hypothesis*:* Elective induction of labor will: 1) increase the odds of RDS and infant mortality before 39 weeks' gestation; 2) decrease the odds of RDS and infant mortality from 39-41 weeks' gestation; and 3) reduce the odds of other infant complications between 37-41 weeks' gestation.

Study design: Retrospective cohort study.

DATA SOURCE, STUDY EXCLUSIONS, AND EXPOSURE DEFINITION

The data source, study exclusions, and exposure definition are the same in Aim 3 as in Aim 2. See descriptions under Aim 2.

STATISTICAL ANALYSIS

Statistical analyses in Aim 3 were similar to those in Aim 2. We modeled crude and adjusted associations of elective labor induction with infant outcomes using logistic regression, after most binomial, log-binomial and Robust Poisson regression models failed to converge. With a separate model for each gestational age-specific comparison, we calculated crude and adjusted odds ratios comparing elective labor induction in each week (37-41) to expectant management, stratifying by parity (nulliparous, parous). In each model, spontaneous and medically indicated deliveries that occurred during the index week were excluded (see **Figure 2-2** for the sample sizes of exposed and unexposed women in each model).

Similarly to Aim 2, we assessed additive interaction between elective labor induction and obesity class using the Relative Excess Risk of Interaction.[263] We also evaluated multiplicative interaction between eIOL and obesity class using likelihood ratio

tests ($p<0.20$). To account for confounding, we adjusted for maternal sociodemographic characteristics (age, race/ethnicity, education, obesity severity, payment source for delivery, first-trimester prenatal care initiation), delivery characteristics (weekday delivery, birth year), and hospital characteristics (hospital type [community or teaching], annual obstetric volume). Hospital type, obstetric volume, payment source, and birth year were classified using hospital discharge data. Other control variables were classified using vital records.

In supplementary analyses of shoulder dystocia and brachial plexus injury, we restricted our sample to vaginal deliveries only. In contrast to cesarean deliveries, vaginal deliveries more closely represent women whose fetuses are at risk of experiencing these outcomes.

SENSITIVITY ANALYSES

The sensitivity analyses in Aim 3 were the same in Aim 3 as in Aim 2 (see descriptions under Aim 2).

CHAPTER 3, THE ASSOCIATION BETWEEN GESTATIONAL WEIGHT GAIN Z-SCORE AND STILLBIRTH: A CASE-CONTROL STUDY

ABSTRACT

Background: Evaluating the association between gestational weight gain (GWG) and infant outcomes such as stillbirth is challenging because both variables are correlated with gestational age at delivery (GA). The GWG z-score has recently been proposed as a way to account for this correlation. Our purpose was to explore the association between GWG and stillbirth using the GWG z-score.

Methods: We analyzed 426 stillbirths and 1,459 live births from the Stillbirth Collaborative Research Network case-control study. Women with multiple gestations, preexisting diabetes, or pre-pregnancy underweight were excluded from analysis. We evaluated the association between GWG z-score (modeled as a restricted cubic spline with knots at the 5th, 50th, and 95th percentiles) and stillbirth using multivariable logistic regression, adjusting for pre-pregnancy body mass index (BMI) and other confounders. In addition, we conducted analyses stratified by pre-pregnancy BMI category (normal weight, overweight, obese).

Results: Mean GWG and GWG z-score were 18.59 lb and -0.42, respectively, among case mothers and 30.86 lb and -0.17, respectively, among control mothers. In adjusted analyses, the odds of stillbirth were elevated for women gaining $\leq 35^{th}$ percentile of GWG z-score (e.g., adjusted odds ratio [aOR] and 95% Confidence Interval [CI] for the 10^{th} versus 50^{th} percentile=1.45 [1.25, 1.68]; aOR [95% CI] for the 25^{th} versus 50^{th} percentile=1.15 [1.08, 1.23]). Results differed slightly by pre-pregnancy BMI. The odds of stillbirth were elevated among overweight women with GWG z-scores $\geq 75^{th}$ percentile

(e.g., aOR [95% CI] for the 90th versus 50th percentile=1.43 [0.93, 2.20]).

Conclusions: Gaining below the 35th percentile of GWG z-score is associated with a small increase in the risk of stillbirth among normal weight, overweight, and obese women.

INTRODUCTION

Stillbirth (fetal death ≥20 weeks' gestation) occurs in 1 of every 168 U.S. pregnancies reaching 20 weeks' gestation.[147] The stillbirth rate among overweight and obese women is even higher.[50] Although the overall stillbirth rate decreased slightly in the past two decades, the gestation-specific rate for 20-27 week deliveries has not changed, and stillbirth is now more common than infant mortality in the U.S.[147] There are limited data on potentially modifiable risk factors for stillbirth such as gestational weight gain (GWG).[148] This is especially relevant for the nearly 50% of pregnant U.S. women[2] who are at elevated risk of stillbirth[50] due to preconception overweight or obesity.

Gestational weight gain is associated with many risk factors for stillbirth independently of pre-pregnancy body mass index (BMI). High GWG is linked to maternal medical conditions, such as gestational diabetes[104] and hypertensive disorders,[105,106] and to altered fetal growth, such as macrosomia[3] and intrauterine growth restriction (via maternal hypertension[107]). In contrast, inadequate GWG increases the risks of fetal growth restriction[3] and preterm birth.[118]

Evidence regarding the association between stillbirth itself and maternal weight gain is limited, and a 2014 systematic review called for more investigation.[49] The four previous studies on GWG and stillbirth have numerous limitations, including restricting to stillbirths ≥28 weeks,[153] despite the fact that stillbirths at 20-27 weeks constitute half of stillbirths in the U.S.[147]

Evaluating the relation between GWG and stillbirth is challenging because both variables are highly correlated with gestational age (GA) at delivery. GWG varies over time and typically increases throughout pregnancy. The vast majority of stillbirths are

preterm, limiting the GWG timeframe[50] Hutcheon et al. propose using a GWG z-score measure, which standardizes for GA, to account for this correlation.[156,157] The authors recently published GWG z-score charts for normal weight, overweight, and obese women that were developed from a follow-up study of healthy Pittsburgh women who delivered term live births (GWG was measured at various time points throughout pregnancy).[156,157] GWG z-scores can be calculated for either ongoing[157] or completed pregnancies[156,157] and only require three measurements: pre-pregnancy weight, weight at delivery (or weight at the GA in question), and GA at delivery (or at the time in question, e.g., mid-pregnancy). GWG percentile charts are similar in concept to fetal,[158] infant,[159] and childhood[160] growth charts.

Our objective was to evaluate the association between GWG z-score and the risk of stillbirth, while accounting for pre-pregnancy BMI.

METHODS

DATA SOURCE

The Stillbirth Collaborative Research Network (SCRN) Study was a multicenter case-control study conducted from 2006-2008 at five sites throughout Rhode Island and selected counties in Georgia, Massachusetts, Utah, and Texas. SCRN's study methodology has been described in detail elsewhere.[243] Women with stillbirths (cases) and live births (controls) were enrolled at the time of delivery, with oversampling of non-Hispanic Black women with live births and all women with preterm live births. Data collection included medical record abstraction, maternal interview (conducted in-hospital before discharge for most women), placental pathology, and fetal autopsy.[243]

Maternal health data, including height and pre-pregnancy weight, were abstracted

from medical records and the maternal interview. Up to four maternal weight measurements were evaluated: self-reported pre-pregnancy weight, weight at first and last prenatal visits, and weight at delivery. GA at delivery for both live births and stillbirths was determined via an algorithm that incorporated date and reliability of last menstrual period, ultrasound estimates of GA, and GA at study screening.[252] GA at fetal death (used in sensitivity analyses) was determined via an algorithm based on fetal foot length and other measures.[252] Sociodemographic information was derived from the maternal interview.

We excluded women with multiple gestations, preexisting diabetes mellitus, pre-pregnancy BMI <18.5 kg/m^2 (due to insufficient observations for stratified analyses; additionally, GWG z-score charts for underweight women were not available[156,157]), missing or implausible GWG (weight loss >50 pounds or gain >150 pounds), and missing pre-pregnancy BMI or covariates (**Figure 3-1**).

EXPOSURE MEASURE

Total GWG was defined as maternal weight at delivery minus pre-pregnancy weight. To calculate the GWG z-score, we transformed each woman's GWG (in kilograms) to a z-score using Hutcheon et al.'s formula, $\frac{\ln(GWG+c)-mean\,(\ln(GWG))}{standard\ deviation(\ln(GWG))}$.[156,157] The mean and standard deviation depended on BMI category (normal weight, overweight, class 1 obese, class 2 obese, class 3 obese) and GA, while c was a constant that transformed ln(GWG) to a positive value (means, standard deviations, and the constant c were taken from Hutcheon et al.'s published references[156,157]). Published GWG z-score charts end at 40 weeks for normal weight women and 41 weeks for overweight/obese

women; GAs above these cutoffs were rounded down to 40 or 41 weeks, respectively, in main analyses and were excluded in sensitivity analyses.

We used GWG percentile charts from Hutcheon et al.'s study to calculate GWG z-scores because Hutcheon et al. published charts for normal weight, overweight, and obese women.[156,157] This is in contrast to the Fetal Growth Longitudinal Study (FGLS; a multinational cohort of healthy, normal weight women), which released GWG percentile charts for normal weight women only.[175]

STATISTICAL ANALYSES

We conducted data analysis in SAS (Cary, NC) and SAS-callable SUDAAN (Research Triangle Park, NC). We used $\chi 2$ tests of independence to examine whether the frequencies of maternal covariates differed between cases and controls. To examine associations between GWG z-score and stillbirth, we used multivariable logistic regression models in SUDAAN, weighted to account for SCRN's sampling design and individuals' probabilities of participating and completing all parts of the data collection process.[243] We assessed multiplicative interaction between pre-pregnancy BMI category and GWG z-score using a likelihood ratio test. If no multiplicative interaction was detected ($p>0.20$), interaction terms were dropped. Potential confounders, including maternal race/ethnicity, were selected *a priori* using directed acyclic graphs based on evidence of their associations with GWG and stillbirth.[50]

We modeled GWG z-score as a restricted cubic spline with 3 knots at the 5^{th}, 50^{th}, and 95^{th} percentiles (these percentiles were calculated among live birth controls only using SCRN analysis weights in SAS).[254] We then calculated odds ratio contrasts of interest by comparing the 10^{th}, 15^{th}, 25^{th}, 35^{th}, 45^{th}, 55^{th}, 65^{th}, 75^{th}, 85^{th}, and 90^{th}

percentiles of GWG z-score to the 50th percentile referent (these percentiles were also calculated among control mothers using SCRN analysis weights in SAS).

In addition, we also used GWG z-score models stratified by pre-pregnancy BMI category (normal weight, overweight, obese) to more closely approximate the method of Bodnar and Hutcheon et al.[67,171] In sensitivity analyses, we evaluated class 1 obese women separately from morbidly obese women (BMI ≥35 kg/m^2), although sample sizes were limited.

SENSITIVITY ANALYSES

To examine how different assumptions affected results, we conducted various sensitivity analyses, including: 1) recalculating GWG z-scores among normal weight women using newly-published GWG percentiles from the Fetal Growth Longitudinal Study;[175] 2) using separate models for class 1 obese and morbidly obese women; 3) excluding normal weight deliveries >40 weeks and overweight/obese deliveries >41 weeks; and 4) using estimated GA at death[252] for stillbirths rather than GA at delivery. In additional sensitivity analyses using stillbirths' estimated GA at death, we: 1) excluded stillbirths that had an estimated GA at fetal death <20 weeks[252], despite having a GA at delivery ≥20 weeks; 2) fit separate models for antepartum and intrapartum stillbirths because of their differing pathophysiology[163]; 3) excluded stillbirths with causes of death related to fetal genetic, structural, or karyotypic abnormalities or maternal/fetal hematologic conditions[247] because fetal weight (a large component of total GWG) may be driven more by congenital abnormalities than by maternal nutritional status in these pregnancies[176]; 4) used weight at last prenatal visit as an estimate of weight at delivery for women missing delivery weight (last prenatal visit is typically a few days before

delivery[91]); 5) controlled for weight and height squared as separate variables because of concern about introducing bias with the use of ratio measures[256]; and 6) excluded mummified stillbirths (grade IV or higher maceration among fragmented fetuses and grade V or higher maceration among intact fetuses) because these stillbirths may have a significant discrepancy between fetal weight at death and delivery.

RESULTS

STUDY SAMPLE CHARACTERISTICS

Of 1,991 eligible live births and 652 eligible stillbirths, we excluded 532 live births and 226 stillbirths for reasons outlined above (**Figure 3-1**), leaving 426 stillbirths and 1,459 live births to consented participants. Mothers of stillbirths were more likely than control mothers to be non-Hispanic black, <20 or ≥35 years old, non-married/non-cohabitating, and to have a previous stillbirth (**Table 3-1**). Mothers of stillbirths were also more likely to have preexisting hypertension and an above normal pre-pregnancy weight.

Women with stillbirths had lower mean values of total GWG and GWG z-score than women with live births (**Table 3-2**). Mean total GWG was inversely associated with pre-pregnancy BMI category, while the highest mean GWG z-score was in morbidly obese women (BMI ≥35 kg/m^2). Mean GWG z-scores were negative for normal weight, overweight, and class 1 obese control mothers (**Table 3-2**).

Using Fetal Growth Longitudinal Study standards, the mean GWG z-score among normal weight control mothers was 0.34 (versus -0.20 using Hutcheon et al.'s standards; **Table 3-2**). The mean GWG z-score among normal weight case mothers was -0.05 using

FLGS standards (versus -0.63 using Hutcheon et al.'s standards; **Table 3-2**). The median GWG z-score using FGLS standards was 0.41 among normal weight control mothers in the SCRN (versus -0.17 using Hutcheon et al.'s standards); other quantiles also differed depending on the z-score referent population.

ASSOCIATION BETWEEN GWG Z-SCORE AND STILLBIRTH

There was no meaningful evidence of multiplicative interaction between pre-pregnancy BMI and GWG z-score, so interaction terms were dropped. In unadjusted analyses, gaining at or below the 35th percentile of GWG z-score was a risk factor for stillbirth (e.g., crude odds ratio [cOR] and 95% Confidence Interval [CI] for the 10th versus 50th percentile of GWG z-score=1.39 [1.22, 1.60]; cOR [95% CI] for the 25th vs. 50th percentile= 1.12 [1.05, 1.19]; see **Supplementary Table 3-1**).

Results were similar after adjusting for covariates (**Figure 3-2**). In adjusted analyses, women who gained at the 10th (versus 50th) percentile of GWG z-score had a 1.45 times increased odds of stillbirth (95% CI 1.25, 1.68). At the 25th (versus 50th) percentile of GWG z-score, the odds of stillbirth was elevated by 15% (95% CI 1.08, 1.23). Gaining above the 35th percentile of GWG z-score was not associated with any change in the odds of stillbirth.

In adjusted models stratified by pre-pregnancy BMI category, gaining at or below the 25th percentile of GWG z-score increased the odds of stillbirth (**Figure 3-3; Supplementary Tables 3-2, 3-3, and 3-4**). The odds of stillbirth were increased by 40% among normal weight women with GWG z-scores ≤10th percentile, by 81% among overweight women with GWG z-scores ≤10th percentile, and by 31% among obese women with GWG z-scores ≤10th percentile. Among overweight women, the odds of

stillbirth were also elevated at high levels of GWG z-score (e.g., aOR [95% CI] for the 90th vs. 50th percentile of GWG z-score= 1.43 [0.93, 2.20]). Among obese women, adjusted ORs decreased from 1.31 to 0.85 as GWG z-score increased from the 10th to the 90th percentile.

In sensitivity analyses, low GWG z-score (≤15th percentile) remained a risk factor for stillbirth among normal weight women using FGLS GWG standards,[175] while point estimates for high GWG z-score became moderately elevated (e.g., aOR for the 90th versus 50th percentile of FGLS GWG z-score= 1.31 [95% CI 1.01, 1.69]; **Figure 3-4**).

ADDITIONAL SENSITIVITY ANALYSES

Figure 3-5 and **Supplementary Table 3-5** display aORs for the association between GWG z-score and stillbirth, stratified by obesity severity. The median GWG z-score among control mothers differed by obesity severity (class 1 obese: -0.09; morbidly obese: 0.26). Similarly to main analyses, the odds of stillbirth were elevated for class 1 obese and morbidly obese women with GWG z-scores ≤35th percentile (e.g., aOR for the 10th versus 50th percentile among class 1 obese women: 1.47 [95% CI 0.86, 2.54]; aOR for the 10th versus 50th percentile in morbidly obese women: 1.44 [95% CI 0.95, 2.21]). However, associations were imprecise. GWG z-score >50th percentile was not associated with stillbirth among class 1 obese women. Among morbidly obese women, the odds of stillbirth were reduced for GWG z-scores ≥75th percentile (e.g., aOR for the 90th versus 50th percentile: 0.60 [95% CI 0.29, 1.26]). However, confidence intervals overlapped the null.

Point estimates moved slightly down and toward the null using GA at fetal death (see **Supplementary Table 3-1**). In models with intrapartum stillbirths only, point

estimates for low GWG z-score moved slightly up and away from the null, and aORs decreased as GWG z-score increased from the 10th to the 90th percentile (data not shown). However, confidence intervals were wide. Additional sensitivity analyses, which were described in the Methods section, yielded comparable results to main analyses.

COMMENTS

Our study suggests that gaining at or below the 35th percentile of GWG z-score (≤-0.46, versus the median of -0.1) is associated with an increased risk of stillbirth. In our analysis, the odds of stillbirth were elevated up to 45% for GWG z-scores ≤10th percentile (≤-1.43, versus the median of -0.1). Associations were strongest at the lowest levels of GWG z-score. High GWG z-score was not associated with the risk of stillbirth among normal weight women, obese women, or the overall sample (all BMI categories combined). In overweight women, the odds of stillbirth were slightly increased at GWG z-scores ≥75th percentile. In sensitivity analyses using the FGLS GWG standards,[175] which were developed from a large, multinational, and ethnically diverse cohort, point estimates for low GWG z-score moved only slightly down and toward the null, while point estimates for high GWG z-score became greater than the null. Our results appear robust to the choice of GWG z-score referent population for GWG z-scores ≤15th percentile.

One pathway through which low GWG could influence stillbirth is through preterm labor.[118,163] Low GWG is a risk factor for preterm delivery.[118] If a fetus cannot tolerate preterm labor, intrapartum stillbirth could occur.[163] Alternatively, the association between low GWG z-score and stillbirth may be driven by intrauterine growth restriction.[3] Beginning in the second trimester, low GWG z-score may be an indicator of

poor fetal weight gain. However, we cannot determine whether poor fetal growth caused stillbirth or, alternatively, whether fetuses at higher risk of stillbirth simply stopped growing as a result of congenital or placental/intrauterine complications. It is unlikely that the associations between low GWG z-score and stillbirth in our study were driven by stillbirths with birth defects or hematologic conditions, as a sensitivity analysis excluding stillbirths with these conditions produced similar results to main analyses.

A "net" z-score (total GWG minus fetal, placental, and amniotic fluid weight) would allow a more thorough evaluation of the impact of fetal versus maternal weight gain, but there are no published "net GWG" percentiles from the referent populations we used. Our dataset also lacked information on placental and amniotic fluid weight, which typically weigh 2-3 pounds combined,[101] as well as on plasma volume.

The risk of stillbirth among women with high GWG z-score appears to be driven by factors other than GWG. Associations between high GWG z-score and risk factors for stillbirth, such as preeclampsia, may be weak in our study sample. In addition, although excess GWG has been linked to many adverse maternal outcomes,[104-106,111] a GWG level that is harmful for the mother may not always be harmful for the fetus.[101]

Although we did not detect statistical interaction between GWG z-score and pre-pregnancy BMI category, our findings differed slightly by pre-pregnancy BMI category in stratified analyses. Our sensitivity analyses also suggested that the association between high GWG z-score and stillbirth may differ between class 1 obese and morbidly obese women. However, precision was limited in sensitivity analyses. We also lacked an adequate sample size to further stratify morbidly obese women into classes 2 and 3 obese

women. Future research using larger sample sizes of morbidly obese women could be informative.

A systematic review of GWG and perinatal outcomes identified only four studies that assessed GWG and stillbirth.[49] All previous studies were restricted to stillbirths ≥28 weeks (in concordance with the World Health Organization's definition[153]); however, stillbirths at 20-27 weeks constitute half of stillbirths in the U.S.[147] Furthermore, two studies excluded intrapartum stillbirths,[51,140] two did not account for GA in adjusted analyses,[154,155] and one excluded women with gestational diabetes or hypertensive disorders[51], which are plausible consequences of GWG.[101] Despite these methodological differences, our finding of an overall null association between high GWG z-score and stillbirth was in concordance with three of these four previous studies.[51,140,154] However, our stratified analyses suggested a possible association between high GWG z-score and stillbirth among overweight and morbidly obese women. Our observation showing increased risk of stillbirth at low levels of GWG z-score is consistent with trends from three previous reports[51,140,155] (although Confidence Intervals from some prior studies overlapped the null[51,140]).

Analyzing the association between GWG and stillbirth is challenging given the relatively low incidence of stillbirth, need for high-quality data, and importance of properly accounting for GA. In a cohort study, survival analysis is one possible approach to evaluating the association between GWG and stillbirth, while accounting for GA. However, prospective studies are impractical and require incredibly large sample sizes for rare outcomes such as stillbirth. In our case-control study of stillbirth, we standardized for GA using the GWG z-score,[156,157,175] which is straightforward to calculate.

Our analytic methods have limitations. We used GWG at delivery. However, GWG should ideally be measured shortly before fetal death occurs. In addition, the GWG z-scores in our study, as derived from Hutcheon et al.'s cohort,[156,157] may not be entirely independent of gestational duration. A recent study using Consortium for Safe Labor data found that GWG z-scores remained slightly correlated with GA when Hutcheon et al.'s z-score formulas were applied in their study population.[174] This issue may arise if the relation between GWG and GA differs between Hutcheon et al.'s cohort and the study population of interest (this could lead to misspecification of the GWG—GA relation in the study population in question).[174] There is evidence that the SCRN study population differs from both Hutcheon et al.'s cohort and the FGLS cohort (evidenced by the non-zero mean GWG z-scores among SCRN control mothers). If GWG z-scores in our study remain correlated with GA, results for low GWG z-score and stillbirth could be biased up and away from the null. Additional prospective studies on the relation between GWG z-score and stillbirth are needed from other, diverse study populations.

Another limitation was our lack of data on maternal or fetal weight at the time of fetal death. However, we excluded macerated stillbirths, who may have notable discrepancies between fetal weight at death and delivery, in sensitivity analyses. Thirteen percent of eligible live births and 14.7% of eligible stillbirths in our study had missing information on GWG or pre-pregnancy BMI. However, in sensitivity analyses, we used maternal weight at last prenatal visit as an estimate of delivery weight for over 55% of observations missing delivery weight, and results were unchanged. We did not control for gestational diabetes, although a gestational diabetes diagnosis could plausibly influence women's GWG in late pregnancy. This was a purposeful decision, as gestational

diabetes may be an intermediate between GWG and stillbirth. Another potential weakness is an inability to control for all potential confounders due to limited sample size or lack of information on these factors (e.g., physical activity[264]). Lastly, our results may not be generalizable to women with non-singleton pregnancies or preexisting diabetes.

Our study has many strengths. To our knowledge, it is the first analysis of GWG and stillbirth to utilize the GWG z-score; to include stillbirths at 20-27 weeks; and to examine differences by obesity severity. We also conducted extensive sensitivity analyses evaluating how the timing and cause of fetal death, maceration level, choice of z-score referent population, and numerous other factors influenced results. We excluded women with preexisting diabetes, who have unique nutritional needs during pregnancy.[253] Furthermore, SCRN sampled women from geographically and demographically diverse catchment areas and did not restrict to academic or tertiary care hospitals.[243] SCRN's source population is also well-enumerated, with analysis weights that account for study design and probability of participation.[243] Finally, SCRN's comprehensive data collection process[243] provided detailed information on maternal covariates as well as timing and cause of fetal death. Investigators have recently advocated for the widespread use of the GWG z-score in research (and ultimately, clinical) settings across diverse populations.[156,157,175] The GWG z-score's predictive ability for stillbirth is likely limited due to the relatively modest aORs observed in our study. However, the z-score may prove useful for stillbirth in combination with other clinical measures, such as estimated fetal size. FGLS standards may be more broadly applicable to external datasets than Hutcheon et al.'s standards. FGLS standards were developed from a multinational, multiethnic cohort study, in which the US was one of eight countries included; in contrast, the study

population in Hutcheon et al.'s cohort was concentrated in the Pittsburgh, Pennsylvania, US area. In addition, the sample size was larger in the FGLS cohort (N=4,313 normal weight women, versus N=648 normal weight women in Hutcheon et al.'s study population). However, FGLS measures are only available for normal weight women. In addition, although the GWG distribution in our study differed from both GWG z-score referent populations, the GWG distribution in our study was more closely aligned with Hutcheon et al.'s referent population than with the FGLS. Results from our analyses suggest that low GWG z-score—using either standard—may be a marker of poor fetal health.

CONCLUSIONS

Gaining below the 35th percentile of GWG z-score may increase the risk of stillbirth by up to 45% among normal weight, overweight, and obese women.

LIST OF ABBREVIATIONS

Adjusted Odds Ratio (aOR)

Body mass index (BMI)

Confidence Interval (CI)

Crude Odds Ratio (cOR)

Fetal Growth Longitudinal Study (FGLS)

Gestational age (GA)

Gestational weight gain (GWG)

DECLARATIONS

Ethics approval and consent to participate: This study was reviewed and approved by

the Institutional Review Boards of each of the participating sites (Brown University, Emory University, University of Texas Health Science Center at San Antonio, University of Texas Medical Branch at Galveston, University of Utah) and by the data coordinating center (RTI International) (IRB #: IRB00000764).

Consent for publication: Not applicable.

Availability of data and materials: The datasets generated and/or analyzed during the current study are in the process of being made available in the National Institute of Child Health and Human Development (NICHD) Data and Specimen Hub (DASH) repository [https://dash.nichd.nih.gov/Resource/LinksToOtherArchives].

Competing Interests: No competing interests declared.

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Table 3-1. Frequencies of Maternal Characteristics by Case-Control Status

	Stillbirths (N=426)		Live births (N=1,459)		
	N	**Weighted %**	**N**	**Weighted %**	**P-value[a]**
Maternal age at delivery, years					
<20	52	12.5	178	10.8	0.0940
20-34	306	70.3	1093	75.9	
35-39	52	13.0	162	11.4	
≥40	16	4.2	26	2.0	
Maternal race/ethnicity					
White, non-Hispanic	166	36.6	538	44.6	0.0010
Black, non-Hispanic	71	17.9	243	10.4	
Hispanic	158	38.8	573	36.9	
Other	31	6.7	105	8.1	
Mother born in the United States					
Yes	331	78.2	1,150	79.8	0.4825
No	95	21.8	309	20.2	
Maternal education, grade					
0-11 (none/primary/some secondary)	95	22.1	300	18.7	0.1247
12 (completed secondary)	119	28.9	412	26.6	
≥13 (college)	212	49.0	747	54.7	
Marital status/cohabitating					
Not married or cohabitating	92	22.4	248	14.1	0.0013
Cohabitating	106	24.5	377	25.0	
Married	228	53.2	834	60.9	
Health insurance/method of payment					
No insurance	17	3.9	54	3.5	0.3398
Any public/private assistance	223	53.7	794	49.9	

VA/commercial health insurance/HMO[b]	186	42.4	611	46.6	
Trimester prenatal care began					
First	288	67.0	979	71.7	0.0008
Second	100	23.4	371	22.5	
Third	14	3.5	74	4.6	
No Prenatal Care	24	6.1	35	1.2	
Family income in the last 12 months					
Only public/private assistance	28	6.8	84	5.5	0.6576
Assistance and personal income	155	37.3	609	38.4	
Only personal income	243	55.9	766	56.1	
WIC enrollment[c]					
Yes	145	34.8	582	36.9	0.4510
No	281	65.2	877	63.1	
Average cigarettes/day during the 3 months prior to pregnancy					
Did not smoke	350	82.2	1,258	86.5	0.1181
<10	39	9.3	103	6.4	
≥10	37	8.5	98	7.1	
Alcohol consumption in the 3 months prior to pregnancy					
Did not drink	249	58.7	877	56.6	0.7658
Drank, no bingeing	96	22.1	310	22.9	
Binged	81	19.3	272	20.5	
Lifetime drug use					
Never	281	66.6	1,046	69.8	0.0992
Yes, without Addiction	127	29.4	374	28.2	
Yes, with addiction	18	4.1	39	2.0	
Pregnancy history					
Primiparous; never pregnant or only elective terminations	154	35.6	438	29.8	<0.0001

Primiparous with previous losses <20 weeks	40	9.5	78	5.0	
Multiparous with no previous losses/stillbirths	135	31.4	657	47.3	
Multiparous with previous losses <20 weeks	68	16.4	250	16.5	
Multiparous with previous stillbirth	29	7.2	36	1.3	
Pre-pregnancy Body Mass Index					
Normal weight (BMI 18.5 - < 25.0 kg/m^2)	179	41.7	728	52.4	0.0013
Overweight (BMI 25.0 - < 30.0 kg/m^2)	112	26.2	369	24.5	
Class 1 Obese (BMI 30.0 - <35.0 kg/m^2)	68	16.2	199	12.4	
Morbidly Obese (BMI ≥35 kg/m^2)	67	15.9	163	10.8	
Clinical history of hypertension					
Yes	36	8.8	85	4.8	0.0112
No	390	91.2	1,374	95.2	
Clinical history of thyroid disorder					
Yes	15	3.2	49	3.2	0.9782
No	411	96.8	1,410	96.8	
Gestational age at delivery, weeks					
20-23	118	28.4	75	0.3	<0.0001
24-27	80	18.5	75	0.6	
28-31	60	12.9	57	0.9	
32-36	84	20.6	110	7.8	
≥37	84	19.5	1,142	90.5	

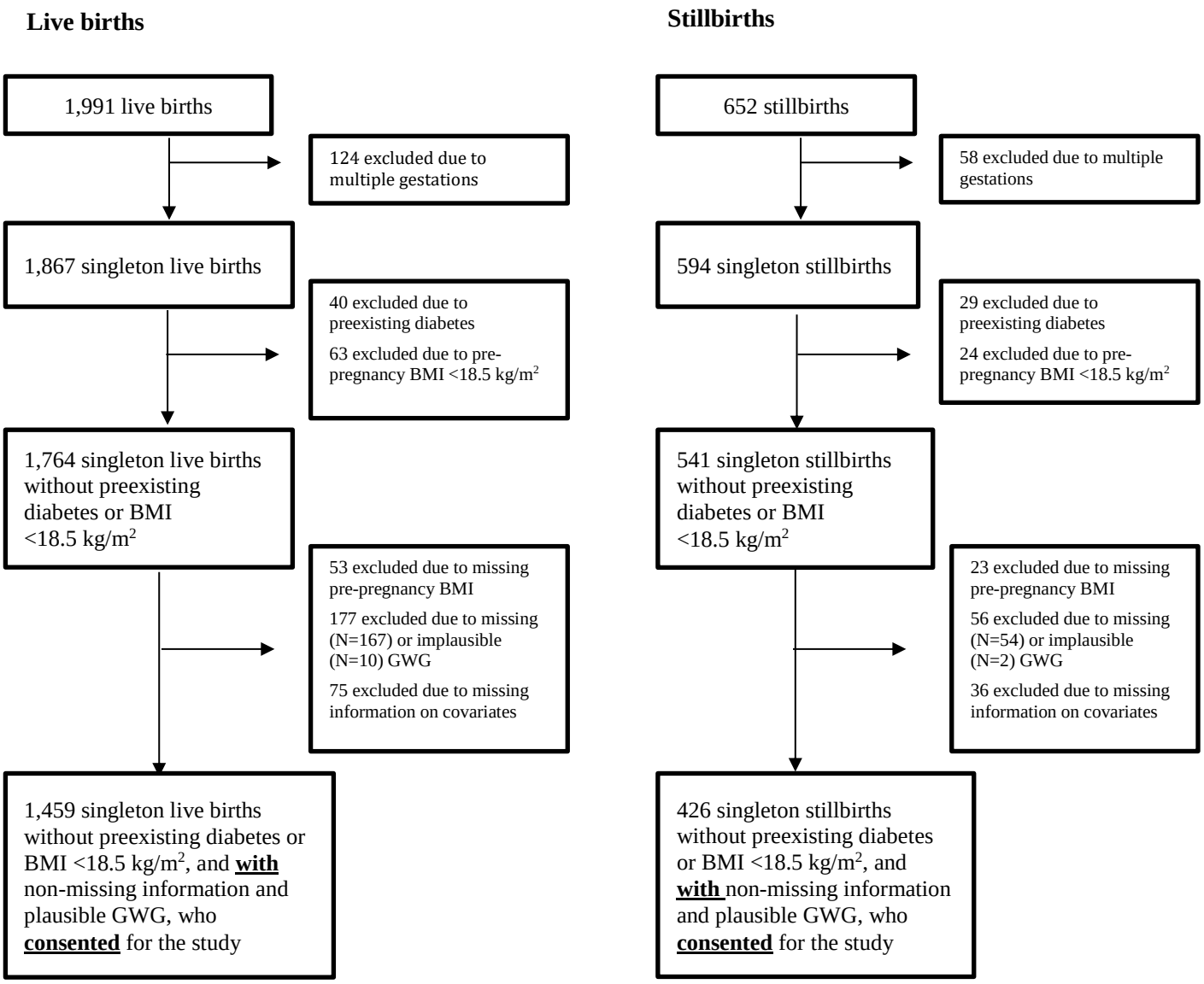
[a]χ^2 test of independence.
[b]VA, Veterans Affairs; HMO, Health Maintenance Organization.
[c]Special Supplemental Nutrition Program for Women, Infants, and Children.

Table 3-2. Distributions of Total GWG and GWG Z-score by Case-Control Status[a]

	Analysis Sample				
	Stillbirths (N=426)		**Live births (N=1,459)**		
Total GWG, lb	**Mean**	**SE**	**Mean**	**SE**	**P-value[b]**
Total sample (All BMI Categories)	18.59	0.87	30.89	0.45	<.0001
Normal weight (BMI 18.5 - <25.0 kg/m^2)	21.73	1.19	33.77	0.54	<.0001
Overweight (BMI 25.0 - <30.0 kg/m^2)	21.85	1.89	30.89	0.87	<.0001
Class 1 Obese (BMI 30.0 - <35.0 kg/m^2)	15.02	2.05	26.22	1.36	<.0001
Morbidly Obese (BMI ≥35.0 kg/m^2)	8.65	1.90	22.19	1.90	<.0001
GWG Z-score					
(Hutcheon et al. standards)	**Mean**	**SE**	**Mean**	**SE**	**P-value[b]**
Total sample (All BMI Categories)	-0.42	0.08	-0.17	0.03	0.0025
Normal weight (BMI 18.5 - <25.0 kg/m^2)	-0.63	0.14	-0.20	0.05	0.0034
Overweight (BMI 25.0 - <30.0 kg/m^2)	-0.27	0.13	-0.25	0.06	0.9030
Class 1 Obese (BMI 30.0 - <35.0 kg/m^2)	-0.37	0.14	-0.16	0.08	0.1833
Morbidly Obese (BMI ≥35.0 kg/m^2)	-0.15	0.13	0.10	0.08	0.0838
GWG Z-score					
(Fetal Growth Longitudinal Study Standards)	**Mean**	**SE**	**Mean**	**SE**	**P-value[b]**
Normal weight (BMI 18.5 - <25.0 kg/m^2)	-0.05	0.20	0.34	0.05	0.06

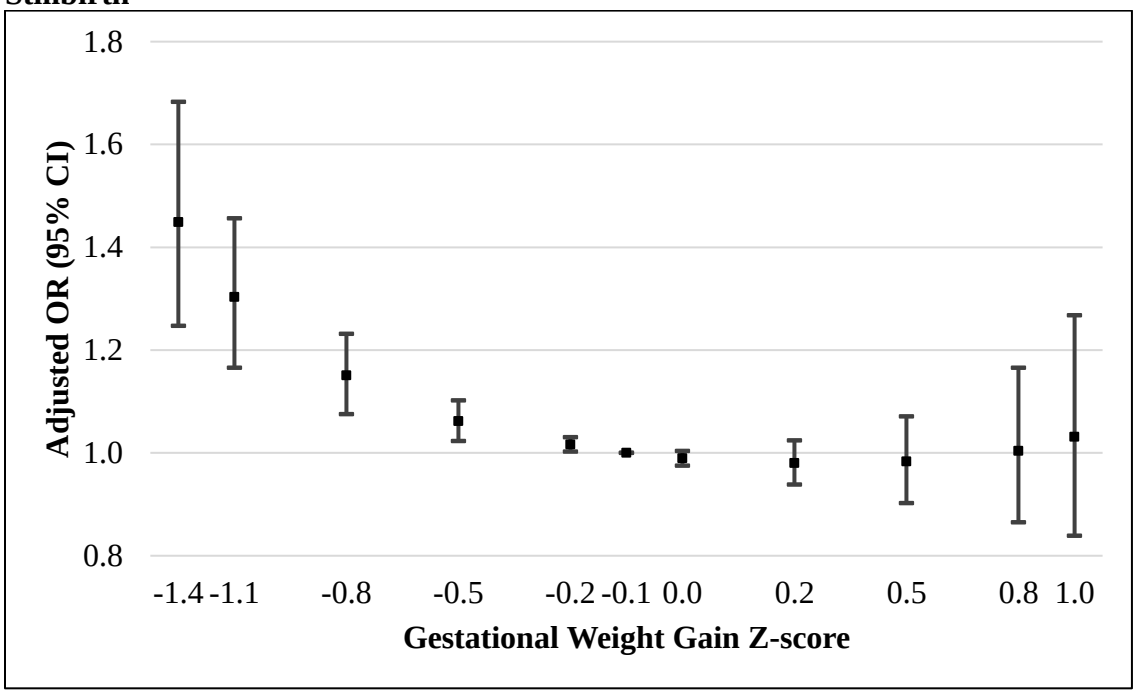
[a]Frequencies, means, and standard errors are weighted, but sample sizes are unweighted.
[b]2-sample t-test.

Figure 3-1. Study Exclusions by Case-Control Status



Description: This figure depicts how many women were excluded at each successive step of sample selection. We excluded women with multiple gestations, preexisting diabetes mellitus, pre-pregnancy BMI <18.5 kg/m^2, missing or implausible GWG, and missing pre-pregnancy BMI or covariates.

Figure 3-2. Adjusted Odds Ratios for Gestational Weight Gain Z-score and Stillbirth[a,b]

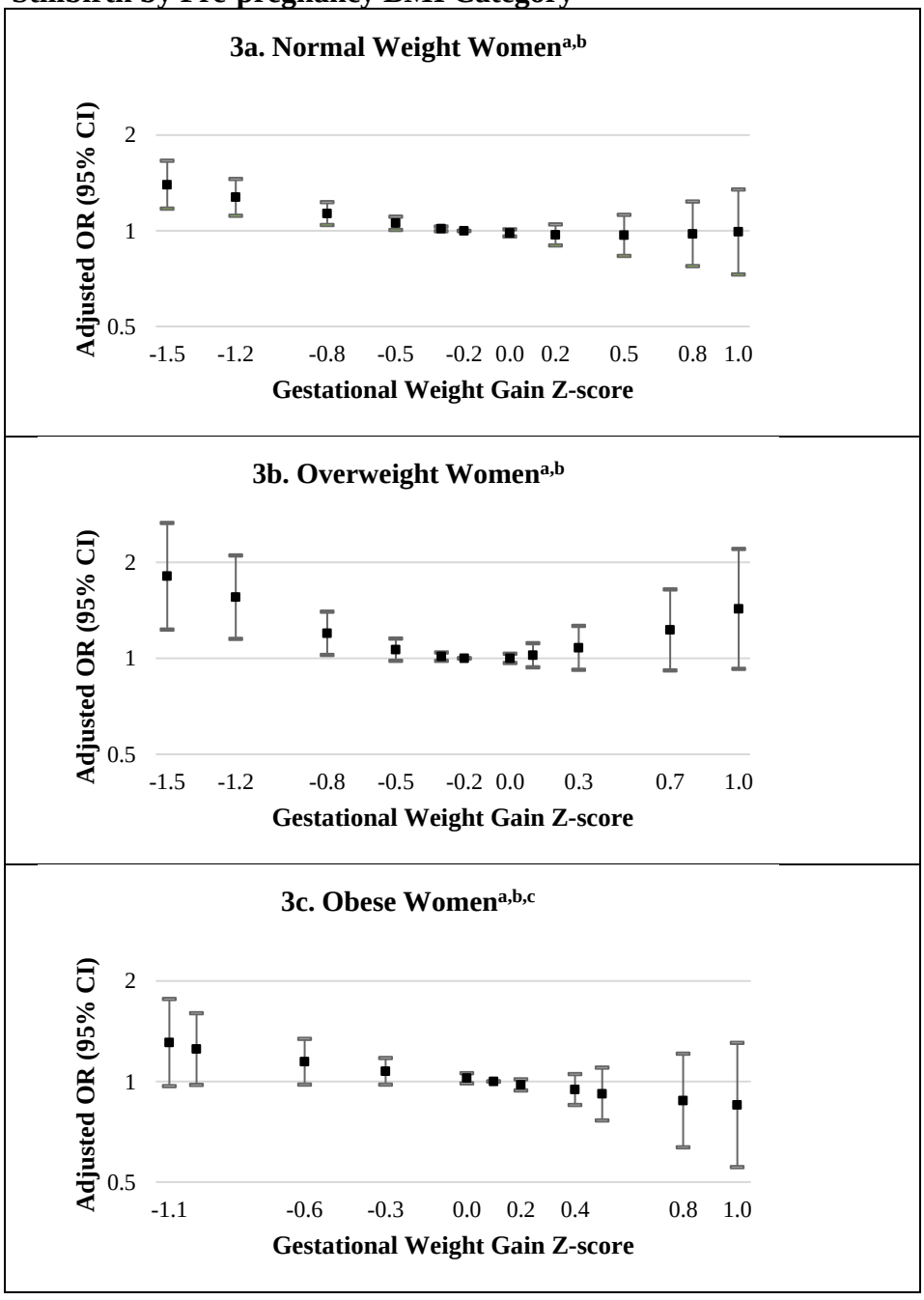


Description: Adjusted odds ratios for the association between GWG Z-score and stillbirth.

[a]The 10th, 15th, 25th, 35th, 45th, 55th, 65th, 75th, 85th, and 90th percentiles of GWG z-score were compared to the 50th percentile (referent).

[b]Adjusted for maternal age at delivery, maternal race/ethnicity, mother born in the United States, maternal education, marital status/cohabitating, health insurance type, trimester prenatal care began, family income in the last 12 months, WIC enrollment, average cigarettes/day during the 3 months prior to pregnancy, alcohol consumption in the 3 months prior to pregnancy, lifetime drug use, pregnancy history, pre-pregnancy BMI category, history of hypertension, and history of thyroid disorder.

Figure 3-3. Adjusted Odds Ratios for Gestational Weight Gain Z-score and Stillbirth by Pre-pregnancy BMI Category

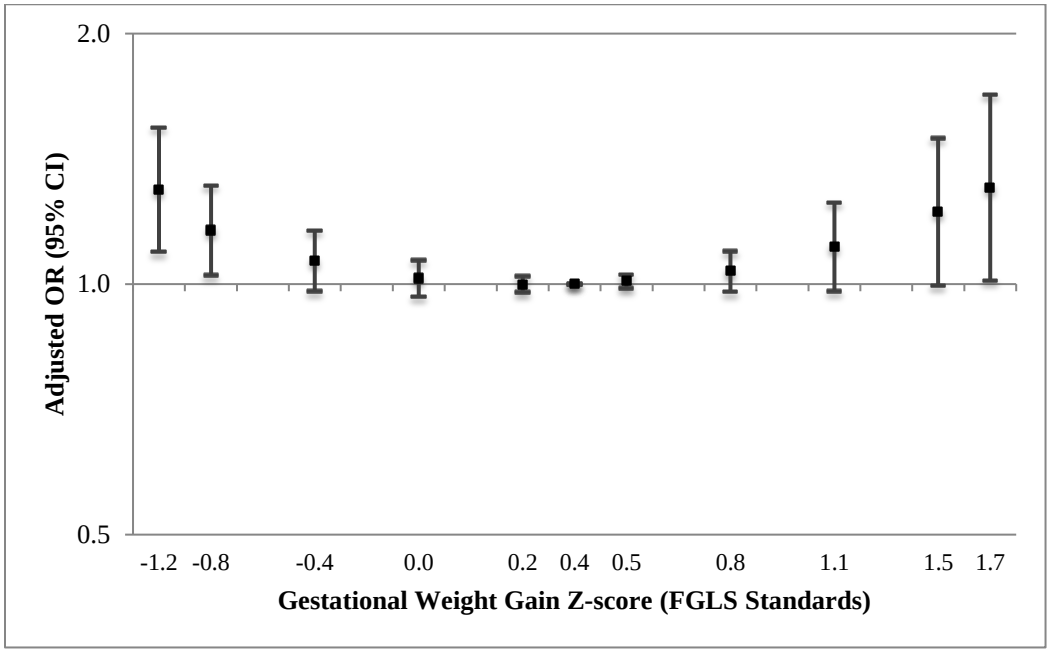


Description: This figure displays adjusted odds ratios for the association between GWG Z-score and stillbirth, stratified by pre-pregnancy BMI category (normal weight **[Figure 3-3a**], overweight **[Figure 3-3b**], obese **[Figure 3-3c**]).

[a]The 10th, 15th, 25th, 35th, 45th, 55th, 65th, 75th, 85th, and 90th percentiles of gestational weight gain z-score were compared to the 50th percentile (referent).

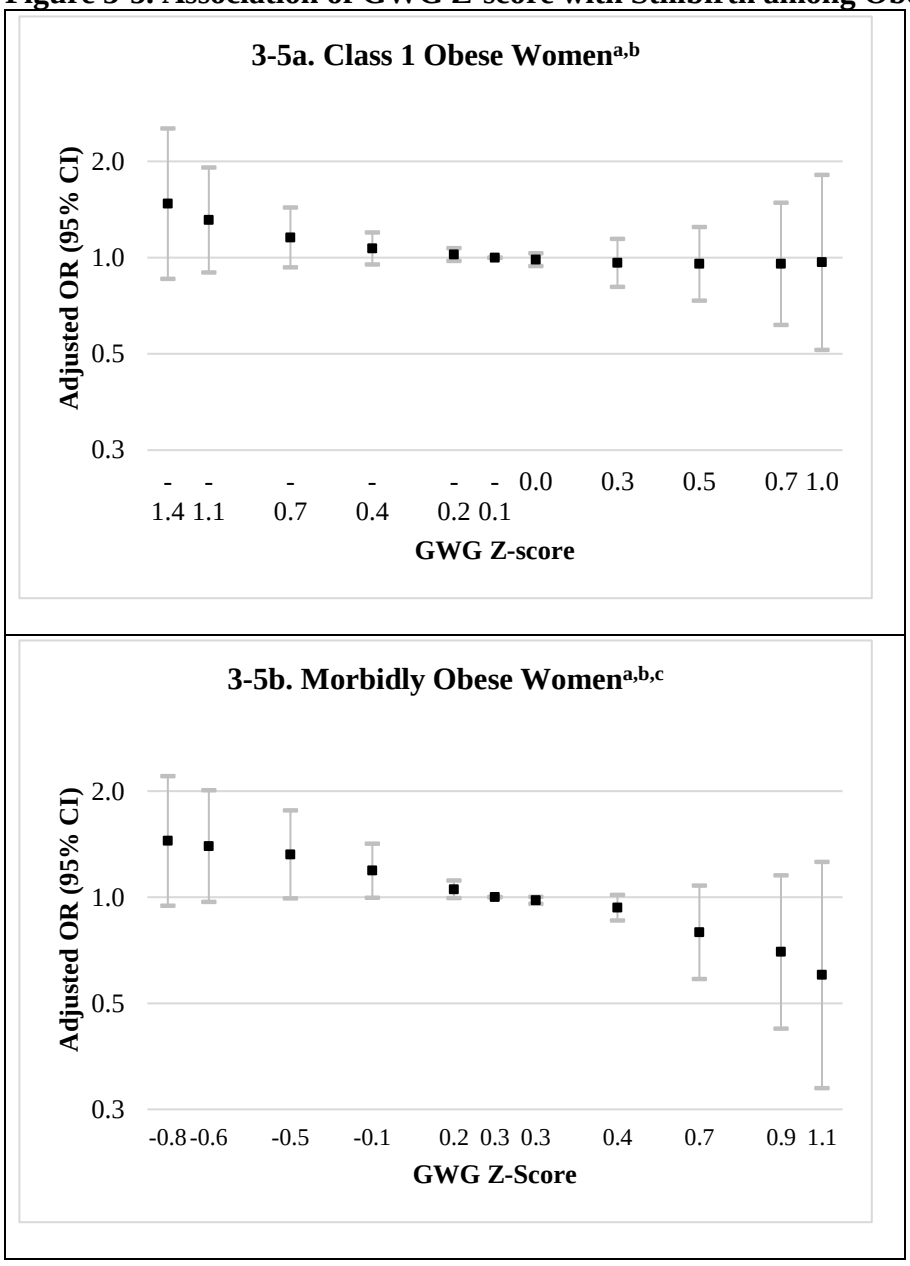
[b]Adjusted for maternal age at delivery, maternal race/ethnicity, mother born in the United States, maternal education, marital status/cohabitating, health insurance type, trimester prenatal care began, family income in the last 12 months, WIC enrollment, average cigarettes/day during the 3 months prior to pregnancy, alcohol consumption in the 3 months prior to pregnancy, lifetime drug use, pregnancy history, history of hypertension, and history of thyroid disorder.
[c]Also adjusted for obesity class (1, 2, 3).

Figure 3-4. Adjusted Odds Ratios for GWG Z-score and Stillbirth among Normal Weight Women using Fetal Growth Longitudinal Study (FGLS) Standards[a,b]



Description: This figure displays adjusted odds ratios for the association between GWG Z-score and stillbirth among normal weight women. The GWG z-score was calculated using Fetal Growth Longitudinal Study standards.
[a]The 10th, 15th, 25th, 35th, 45th, 55th, 65th, 75th, 85th, and 90th percentiles of gestational weight gain z-score were compared to the 50th percentile (referent=0.41).
[b]Adjusted for maternal age at delivery, maternal race/ethnicity, mother born in the United States, maternal education, marital status/cohabitating, health insurance type, trimester prenatal care began, family income in the last 12 months, WIC enrollment, average cigarettes/day during the 3 months prior to pregnancy, alcohol consumption in the 3 months prior to pregnancy, lifetime drug use, pregnancy history, history of hypertension, and history of thyroid disorder.

Figure 3-5. Association of GWG Z-score with Stillbirth among Obese Women



[a]The 10th, 15th, 25th, 35th, 45th, 55th, 65th, 75th, 85th, and 90th percentiles of gestational weight gain z-score were compared to the 50th percentile (referent).
[b]Adjusted for maternal age at delivery, maternal race/ethnicity, mother born in the United States, maternal education, marital status/cohabitating, health insurance type, trimester prenatal care began, family income in the last 12 months, WIC enrollment, average cigarettes/day during the 3 months prior to pregnancy, alcohol consumption in the 3 months prior to pregnancy, lifetime drug use, pregnancy history, history of hypertension, and history of thyroid disorder.
[c]Also adjusted for obesity class.

SUPPLEMENTARY TABLES

Supplementary Table 3-1. Unadjusted and Adjusted Odds Ratios for GWG Z-score among All Pre-pregnancy BMI Categories

Percentile Contrast[a]	Z-score Contrast[a]	Unadjusted OR [95% CI]	Adjusted OR [95% CI][b]	Adjusted OR [95% CI] using GA at death for stillbirths[b]
10th vs. 50th	**-1.43 vs. -0.10**	1.39 [1.22, 1.60]	1.45 [1.25, 1.68]	1.33 [1.15, 1.54]
15th vs. 50th	**-1.14 vs. -0.10**	1.26 [1.14, 1.39]	1.30 [1.17, 1.46]	1.22 [1.09, 1.36]
25th vs. 50th	**-0.77 vs. -0.10**	1.12 [1.05, 1.19]	1.15 [1.08, 1.23]	1.10 [1.03, 1.17]
35th vs. 50th	**-0.46 vs. -0.10**	1.04 [1.01, 1.08]	1.06 [1.02, 1.10]	1.03 [1.00, 1.07]
45th vs. 50th	**-0.22 vs. -0.10**	1.01 [1.00, 1.02]	1.02 [1.00, 1.03]	1.01 [0.99, 1.02]
50th vs. 50th	**-0.10 vs. -0.10**	1.00 [1.00, 1.00]	1.00 [1.00, 1.00]	1.00 [1.00, 1.00]
55th vs. 50th	**0.02 vs. -0.10**	1.00 [0.98, 1.01]	0.99 [0.98, 1.00]	1.00 [0.98, 1.01]
65th vs. 50th	**0.22 vs. -0.10**	1.00 [0.96, 1.04]	0.98 [0.94, 1.02]	1.01 [0.96, 1.05]
75th vs. 50th	**0.46 vs. -0.10**	1.02 [0.94, 1.10]	0.98 [0.90, 1.07]	1.03 [0.95, 1.12]
85th vs. 50th	**0.77 vs. -0.10**	1.07 [0.93, 1.23]	1.00 [0.87, 1.17]	1.08 [0.94, 1.25]
90th vs. 50th	**1.02 vs. -0.10**	1.12 [0.93, 1.36]	1.03 [0.84, 1.27]	1.14 [0.93, 1.38]

Description: This table displays the unadjusted and adjusted odds ratios for the association between GWG z-score and stillbirth.
[a]Percentiles of GWG z-score. -0.10 is the median (50th percentile) GWG z-score. Selected percentiles of GWG z-score were compared to the 50th percentile referent.
[b]Adjusted for maternal age at delivery, maternal race/ethnicity, mother born in the United States, maternal education, marital status/cohabitating, health insurance type, trimester prenatal care began, family income in the last 12 months, WIC enrollment, average cigarettes/day during the 3 months prior to pregnancy, alcohol consumption in the 3 months prior to pregnancy, lifetime drug use, pregnancy history, pre-pregnancy BMI category, history of hypertension, and history of thyroid disorder.

Supplementary Table 3-2. Unadjusted and Adjusted Odds Ratios for GWG Z-score among Normal Weight Women

Percentile Contrast[a]	GWG Z-score Contrast[a]	Unadjusted OR [95% CI]	Adjusted OR [95% CI][b]
10th vs. 50th	**-1.48 vs. -0.17**	1.51 [1.35, 1.68]	1.40 [1.29, 1.51]
15th vs. 50th	**-1.21 vs. -0.17**	1.34 [1.20, 1.49]	1.27 [1.18, 1.38]
25th vs. 50th	**-0.81 vs. -0.17**	1.15 [1.03, 1.29]	1.13 [1.05, 1.23]
35th vs. 50th	**-0.51 vs. -0.17**	1.06 [0.95, 1.18]	1.06 [0.98, 1.14]
45th vs. 50th	**-0.28 vs. -0.17**	1.01 [0.91, 1.13]	1.01 [0.94, 1.10]
50th vs. 50th	**-0.17 vs. -0.17**	1.00 [0.90, 1.12]	1.00 [0.92, 1.08]
55th vs. 50th	**-0.02 vs. -0.17**	0.99 [0.89, 1.10]	0.98 [0.91, 1.06]
65th vs. 50th	**0.21 vs. -0.17**	0.99 [0.88, 1.10]	0.97 [0.90, 1.05]
75th vs. 50th	**0.50 vs. -0.17**	1.01 [0.90, 1.12]	0.97 [0.90, 1.05]
85th vs. 50th	**0.79 vs. -0.17**	1.05 [0.94, 1.17]	0.98 [0.90, 1.06]
90th vs. 50th	**1.02 vs. -0.17**	1.09 [0.98, 1.22]	0.99 [0.92, 1.07]

Description: This table displays the unadjusted and adjusted odds ratios for the association between GWG z-score and stillbirth in normal weight women

[a]Percentiles of GWG z-score. -0.17 is the median GWG z-score among normal weight women. Selected percentiles of GWG z-score were compared to the 50th percentile referent.

[b]Adjusted for maternal age at delivery, maternal race/ethnicity, mother born in the United States, maternal education, marital status/cohabitating, health insurance type, trimester prenatal care began, family income in the last 12 months, WIC enrollment, average cigarettes/day during the 3 months prior to pregnancy, alcohol consumption in the 3 months prior to pregnancy, lifetime drug use, pregnancy history, history of hypertension, and history of thyroid disorder.

Supplementary Table 3-3. Unadjusted and Adjusted Odds Ratios for GWG Z-score among Overweight Women

Percentile Contrast[a]	GWG Z-score Contrast[a]	Unadjusted OR [95% CI]	Adjusted OR [95% CI][b]
10th vs. 50th	**-1.46 vs. -0.17**	1.39 [1.01, 1.89]	1.81 [1.23, 2.66]
15th vs. 50th	**-1.25 vs. -0.17**	1.26 [0.99, 1.61]	1.56 [1.15, 2.11]
25th vs. 50th	**-0.8 vs. -0.17**	1.08 [0.95, 1.23]	1.20 [1.03, 1.40]
35th vs. 50th	**-0.51 vs. -0.17**	1.02 [0.95, 1.08]	1.07 [0.98, 1.15]
45th vs. 50th	**-0.3 vs. -0.17**	1.00 [0.97, 1.02]	1.01 [0.98, 1.04]
50th vs. 50th	**-0.17 vs. -0.17**	1.00 [1.00, 1.00]	1.00 [1.00, 1.00]
55th vs. 50th	**-0.05 vs. -0.17**	1.01 [0.99, 1.04]	1.00 [0.97, 1.03]
65th vs. 50th	**0.14 vs. -0.17**	1.05 [0.98, 1.12]	1.02 [0.94, 1.12]
75th vs. 50th	**0.35 vs. -0.17**	1.11 [0.98, 1.26]	1.08 [0.92, 1.26]
85th vs. 50th	**0.67 vs. -0.17**	1.27 [1.27, 1.60]	1.23 [0.92, 1.65]
90th vs. 50th	**0.97 vs. -0.17**	1.46 [1.04, 2.05]	1.43 [0.93, 2.20]

Description: This table displays the unadjusted and adjusted odds ratios for the association between GWG z-score and stillbirth in overweight women.
[a]Percentiles of GWG z-score. -0.17 is the median GWG z-score among overweight women. Selected percentiles of GWG z-score were compared to the 50th percentile referent.
[b]Adjusted for maternal age at delivery, maternal race/ethnicity, mother born in the United States, maternal education, marital status/cohabitating, health insurance type, trimester prenatal care began, family income in the last 12 months, WIC enrollment, average cigarettes/day during the 3 months prior to pregnancy, alcohol consumption in the 3 months prior to pregnancy, lifetime drug use, pregnancy history, history of hypertension, and history of thyroid disorder.

Supplementary Table 3-4. Unadjusted and Adjusted Odds Ratios for GWG Z-score among All Obese Women

Percentile Contrast[a]	GWG Z-score Contrast[a]	Unadjusted OR [95% CI]	Adjusted OR [95% CI][b]
10th vs. 50th	**-1.15 vs. 0.07**	1.29 [1.00, 1.67]	1.31 [0.97, 1.77]
15th vs. 50th	**-0.96 vs. 0.07**	1.24 [1.01, 1.53]	1.25 [0.98, 1.60]
25th vs. 50th	**-0.58 vs. 0.07**	1.15 [1.01, 1.31]	1.15 [0.98, 1.34]
35th vs. 50th	**-0.28 vs. 0.07**	1.08 [1.00, 1.16]	1.07 [0.98, 1.18]
45th vs. 50th	**-0.05 vs. 0.07**	1.03 [1.00, 1.06]	1.02 [0.99, 1.06]
50th vs. 50th	**0.07 vs. 0.07**	1.00 [1.00, 1.00]	1.00 [1.00, 1.00]
55th vs. 50th	**0.19 vs. 0.07**	0.98 [0.94, 1.01]	0.98 [0.94, 1.02]
65th vs. 50th	**0.37 vs. 0.07**	0.94 [0.86, 1.03]	0.95 [0.85, 1.05]
75th vs. 50th	**0.54 vs. 0.07**	0.90 [0.77, 1.06]	0.92 [0.77, 1.10]
85th vs. 50th	**0.82 vs. 0.07**	0.85 [0.65, 1.13]	0.88 [0.64, 1.21]
90th vs. 50th	**1.01 vs. 0.07**	0.82 [0.56, 1.19]	0.85 [0.55, 1.31]

Description: This table displays the unadjusted and adjusted odds ratios for the association between GWG z-score and stillbirth in obese women.
[a]Percentiles of GWG z-score. 0.07 is the median GWG z-score among obese women. Selected percentiles of GWG z-score were compared to the 50th percentile referent.
[b]Adjusted for maternal age at delivery, maternal race/ethnicity, mother born in the United States, maternal education, marital status/cohabitating, health insurance type, trimester prenatal care began, family income in the last 12 months, WIC enrollment, average cigarettes/day during the 3 months prior to pregnancy, alcohol consumption in the 3 months prior to pregnancy, lifetime drug use, pregnancy history, obesity class, history of hypertension, and history of thyroid disorder.

Supplementary Table 3-5. Adjusted Odds Ratios for GWG Z-score among Class 1 Obese and Morbidly Obese Women

	Class 1 Obese Women		Morbidly Obese Women	
Percentile Contrast[a]	**GWG Z-score Contrast[a]**	**Adjusted OR [95% CI][b]**	**GWG Z-score Contrast[c]**	**Adjusted OR [95% CI][b,d]**
10th vs. 50th	**-1.43 vs. -0.09**	1.47 (0.86, 2.54)	**-0.78 vs. 0.26**	1.44 (0.95, 2.21)
15th vs. 50th	**-1.11 vs. -0.09**	1.31 (0.90, 1.91)	**-0.65 vs. 0.26**	1.40 (0.97, 2.01)
25th vs. 50th	**-0.73 vs. -0.09**	1.16 (0.93, 1.43)	**-0.46 vs. 0.26**	1.32 (0.99, 1.76)
35th vs. 50th	**-0.43 vs. -0.09**	1.07 (0.95, 1.20)	**-0.14 vs. 0.26**	1.19 (1.00, 1.42)
45th vs. 50th	**-0.22 vs. -0.09**	1.02 (0.98, 1.07)	**0.15 vs. 0.26**	1.05 (0.99, 1.11)
50th vs. 50th	**-0.09 vs. -0.09**	1.00 (1.00, 1.00)	**0.26 vs. 0.26**	1.00 (1.00, 1.00)
55th vs. 50th	**0.03 vs. -0.09**	0.98 (0.94, 1.03)	**0.30 vs. 0.26**	0.98 (0.96, 1.00)
65th vs. 50th	**0.30 vs. -0.09**	0.96 (0.81, 1.14)	**0.39 vs. 0.26**	0.93 (0.86, 1.01)
75th vs. 50th	**0.46 vs. -0.09**	0.96 (0.73, 1.25)	**0.67 vs. 0.26**	0.79 (0.59, 1.08)
85th vs. 50th	**0.73 vs. -0.09**	0.96 (0.62, 1.49)	**0.88 vs. 0.26**	0.70 (0.42, 1.15)
90th vs. 50th	**0.98 vs. -0.09**	0.97 (0.51, 1.81)	**1.12 vs. 0.26**	0.60 (0.29, 1.26)

[a]Percentiles of GWG z-score. -0.09 is the median GWG z-score among class 1 obese women. Selected GWG z-score percentiles were compared to the 50th percentile referent.
[b]Adjusted for maternal age at delivery, maternal race/ethnicity, mother born in the United States, maternal education, marital status/cohabitating, health insurance type, trimester prenatal care began, family income in the last 12 months, WIC enrollment, average cigarettes/day during the 3 months prior to pregnancy, alcohol consumption in the 3 months prior to pregnancy, lifetime drug use, pregnancy history, history of hypertension, and history of thyroid disorder.
[c]Percentiles of GWG z-score. 0.26 is the median GWG z-score among morbidly obese women. Selected GWG z-score percentiles were compared to the 50th percentile referent.
[d]Also adjusted for obesity class.

CHAPTER 4, TERM ELECTIVE INDUCTION OF LABOR AND OBSTETRIC OUTCOMES AMONG OBESE WOMEN

ABSTRACT

Purpose: Assess whether term elective labor induction in obese women reduces the odds of cesarean delivery and maternal morbidity compared to expectant management.

Materials and Methods: Using 2007-2011 California linked vital records and hospital discharge data for obese women (N=219,360), we compared elective labor induction in each week of term gestation (37-41) to expectant management. We restricted to singleton, non-anomalous deliveries in cephalic presentation and to women without a prior cesarean delivery or chronic disease. Outcomes included cesarean delivery, operative vaginal delivery, postpartum hemorrhage, severe perineal lacerations, and severe maternal morbidity, analyzed using multivariable models stratified by parity.

Results: Elective labor induction between 37 and 40 weeks reduced the odds of cesarean delivery, with adjusted odds ratios (aORs) ranging from 0.62 to 0.85 and increasing with gestational age ($p<0.003$). The adjusted odds of operative vaginal delivery were slightly elevated among electively induced women. Among nulliparous (39-40 weeks) and parous women (38-40 weeks), elective labor induction reduced the odds of postpartum hemorrhage (aORs from 0.65 to 0.79, $p<0.04$) and severe maternal morbidity (aORs from 0.72 to 0.84, $p<0.004$).

Conclusions: Term elective labor induction may reduce the risk of cesarean delivery, postpartum hemorrhage, and severe maternal morbidity among obese women.

INTRODUCTION

Over 20% of U.S. women enter pregnancy obese (pre-pregnancy body mass index [BMI] ≥30 kg/m^2).[2] Obese gravidas are at high risk of adverse pregnancy outcomes.[9,22] This risk persists even in the absence of other chronic diseases.[9] Consequently, obese women have an increased need for labor induction and other obstetric interventions compared to non-obese women.[9,22,182]

Historically, elective induction of labor (eIOL, labor induction without medical indication) was thought to increase the risk of cesarean delivery (CD). Recent studies comparing eIOL to expectant management, rather than to spontaneous labor in the index week (which is not a viable obstetric intervention[183]), have challenged these assumptions.[145,183] However, most recent studies have not specifically examined the impact of eIOL among obese women. Thus, among obese gravidas, it is unknown whether eIOL to prompt earlier delivery or expectant management results in lower risks of CD and other adverse pregnancy outcomes at each gestational age.[89]

Many health care facilities recently prohibited elective deliveries at <39 weeks due to higher rates of infant complications at early gestational ages.[185] Despite evidence that obesity is a risk factor for stillbirth[17,49] and maternal morbidity,[7,17,22] obesity is not a standard indication for earlier delivery. Delaying delivery in obese women could increase the risk of stillbirth or maternal medical conditions such as preeclampsia.[89] On the other hand, delaying delivery could decrease the risk of neonatal morbidity/mortality[185] and avoid the complications of failed IOL.[192]

A recent analysis examined the association between term eIOL and perinatal outcomes among obese Californian women in 2007.[187] However, this study lacked the

statistical power to detect differences in rare outcomes. Our study expands upon this analysis by including five years of data (2007-2011); by examining additional maternal outcomes, including severe maternal morbidity (SMM) and length of postpartum hospital stay; and by assessing effect measure modification by obesity class.

The aim of our study was to determine, beginning at 37 weeks' gestation, whether eIOL or expectant management results in lower risks of cesarean, operative vaginal delivery, and maternal complications among obese women. We hypothesized that eIOL would reduce the odds of cesarean and maternal complications without increasing the odds of operative vaginal delivery.

MATERIALS AND METHODS

DATA SOURCE

In this retrospective cohort study, we used the California Linked Patient Discharge Data/Birth Cohort File for years 2007-2011.[257] To create this dataset, the California Office for Statewide Health Planning and Development (OSHPD) linked vital records with maternal and infant hospital discharge data for deliveries in California, plus out-of-state deliveries to California residents. Over 95% of deliveries were successfully linked.[257] Deliveries occurring in different years to the same woman were not linked in this data source. We used hospital discharge data from the delivery visit, which included ICD-9-CM diagnostic and procedure codes. Medical diagnoses and procedures (including induction of labor, categorical study outcomes, and diagnoses used as study exclusion criteria) were coded as present if detected in either vital records or discharge data. This approach improves the sensitivity of detecting maternal and pregnancy complications while negligibly impacting specificity.[258-260] Maternal postpartum hospital stay was

defined using hospital discharge data only.

Our study was approved by the California Committee for the Protection of Human Subjects, the California OSHPD, and the Emory University Institutional Review Board. Because our dataset was de-identified, informed consent was not required.

STUDY EXCLUSION CRITERIA

We excluded deliveries with pre-pregnancy BMI <30 kg/m^2, gestational age <37 weeks, multiple gestations, previous CD, non-cephalic presentation, major fetal anomaly, missing data, or medical conditions known before term that influence mode of delivery (e.g., gestational diabetes) (**Figure 4-1**).

Body mass index was calculated from pre-pregnancy height and weight as reported on vital records. Gestational age in weeks was based on the best obstetric estimate. Parity was defined as the number of prior pregnancies reaching ≥20 weeks' gestation.

EXPOSURE DEFINITION

We assessed the association between eIOL and maternal outcomes separately for each week of term gestation (37 through 41 weeks). Exposure was defined as elective IOL (labor induction without medical indication) during the week in question. Medical indications for IOL were derived from the Joint Commission's list of conditions that may justify delivery <39 weeks.[187,218] Indications included premature rupture of membranes, maternal conditions (e.g., gestational hypertension), and others (detailed in **Table 4-A1**).

The unexposed group consisted of expectantly managed women (those who delivered by any method—including eIOL, spontaneous labor, or cesarean delivery without labor—in later weeks). In studies of obstetric decision-making, expectant

management is a more appropriate comparison group for eIOL than spontaneous labor *during the index week*. At any given time point, a clinician may choose between obstetric intervention to prompt earlier delivery (e.g., eIOL) and expectant management (watchful waiting). Spontaneous labor itself is not an intervention that can be influenced by obstetricians.[183]

STATISTICAL ANALYSIS

Data analysis was conducted in SAS Version 9.4 (Cary, NC). All models were stratified by parity (nulliparous, parous). Among each parity category, we used five models, one for each gestational week from 37 through 41 weeks, to evaluate the relation between eIOL in that week (versus expectant management) and each outcome. For each comparison (e.g., eIOL during week 37 versus delivery ≥38 weeks), spontaneous or medically indicated deliveries that occurred during the same week as the exposed delivered (e.g., week 37) were excluded from the given analysis.

We used multivariable, multinomial logistic regression to model the association between eIOL and mode of delivery (CD, operative vaginal delivery [forceps or vacuum], and non-operative vaginal delivery). We used multivariable logistic regression to model the associations of eIOL with postpartum hemorrhage, severe (third-or-fourth degree) perineal lacerations, and SMM (a composite outcome of postpartum hemorrhage, severe perineal lacerations, unplanned surgical procedure, uterine rupture, maternal intensive care unit admission, maternal sepsis, and endometritis). We ran models for severe perineal lacerations among all deliveries as well as among vaginal deliveries only, as women undergoing cesarean are generally not at risk of this outcome.

We log-transformed maternal postpartum hospital stay (in days), which was not normally distributed, and modeled its association with eIOL using multivariable linear regression.

For all categorical outcomes, we assessed multiplicative interaction between eIOL and obesity class using likelihood ratio tests ($p<0.20$). We assessed additive interaction between eIOL and obesity class using the Relative Excess Risk of Interaction[263] for dichotomous outcomes (including CD and operative vaginal delivery, modeled separately). For postpartum hospital stay, we assessed additive interaction between eIOL and obesity class using Type 3 likelihood ratio tests of the interaction terms ($p<0.20$).

Models were adjusted for maternal age, education, race/ethnicity, and obesity class; first-trimester prenatal care initiation; source of payment for delivery; birth year; weekday delivery; delivery at a teaching hospital; and hospital obstetric volume. These covariates were selected *a priori* based on evidence of their associations with eIOL and the outcomes;[145,187] we did not adjust for potential intermediates of the association between eIOL and maternal outcomes. Data on maternal sociodemographic characteristics, prenatal care initiation, and weekday delivery came from vital records. Information on remaining covariates came from discharge data.

SENSITIVITY ANALYSES

Our dataset did not include information on whether certain intrapartum complications, such as fetal distress, occurred prior to labor (in which case they would be indications for IOL) or during labor. In sensitivity analyses, we varied our assumptions about the timing of these complications (**Table 4-A1**).

In the main analyses, our expectant management definition ensured that the unexposed group represented delayed delivery relative to our exposed group. In sensitivity analyses, we expanded the expectant management group to include spontaneous deliveries occurring during the same week as the exposed were induced,[145] which may include deliveries occurring earlier in the week than some of the electively induced deliveries.

RESULTS

We excluded 2,403,567 of 2,622,927 deliveries due to previously outlined criteria; most of these exclusions were due to pre-pregnancy BMI <30 kg/m^2 (**Figure 4-1**). Our final study sample consisted of 219,360 term live births.

Electively induced obese women were more likely than expectantly managed obese women to be parous, non-Hispanic white, and ≥25 years of age (**Table 4-1**). In addition, they were more likely to have initiated prenatal care in the first trimester, to deliver in 2007 or 2008 (for eIOL <39 weeks only), to deliver on a weekday, and to deliver in a community hospital. The distributions of maternal education, insurance status, hospital obstetric volume, and obesity severity also varied by exposure category.

The risks of cesarean delivery, postpartum hemorrhage, and SMM, as well as the length of postpartum stay, increased with gestational age among both electively induced and expectantly managed groups (**Table 4-2**). At ≥41 weeks, nearly 50% of pregnancies to obese nulliparas ended in CD, and nearly 10% of obese nulliparas experienced severe maternal morbidity. Operative vaginal delivery decreased throughout gestation among both exposed and unexposed groups (**Table 4-2**). Between 2007 and 2011, CD, postpartum hemorrhage, SMM, and length of postpartum hospital stay increased, while

operative vaginal delivery decreased (data not shown). All outcomes were more frequent among nulliparas.

In both nulliparous and parous women, the crude frequencies of CD, postpartum hemorrhage, and SMM were lower, and the length of postpartum hospital stay was shorter, among electively induced women (**Table 4-2**).

We found no evidence of multiplicative interaction between eIOL and obesity class. With respect to cesarean delivery, additive interaction models suggested that the benefits of eIOL may increase with obesity severity among nulliparas. However, many additive interaction findings did not reach statistical significance (data not shown).

Point estimates were only minimally impacted by adjusting for covariates (**Table 4-A2**). In adjusted models, eIOL between 37 and 40 weeks was associated with reduced odds of CD among obese nulliparous and parous women (**Figure 4-2a**). Among obese nulliparas, associations between eIOL and CD appeared most protective at early gestational ages (e.g., adjusted odds ratio [aOR] and 95% Confidence Interval [CI] for 37 weeks: 0.62 [0.51, 0.76]; aOR [95% CI] for 40 weeks: 0.85 [0.80, 0.90]). The odds of operative vaginal delivery were slightly elevated among electively induced obese women (**Figure 4-2b**).

Elective IOL was associated with decreased odds of postpartum hemorrhage among both nulliparous (39-41 weeks) and parous obese women (38-40 weeks; **Figure 4-2c**). The odds of postpartum hemorrhage were reduced up to 35% in women undergoing eIOL. Elective IOL was not associated with severe perineal lacerations (**Figure 4-2d**); conclusions were unchanged after restricting to vaginal deliveries (**Table 4-A3**).

Between 39 and 40 weeks among obese nulliparas and from 38 through 40 weeks among obese parous women, eIOL was associated with decreased odds of SMM (**Figure 4-2e**). The odds of SMM were reduced up to 28% in electively induced obese women. Elective IOL between 38 and 40 weeks was associated with a reduced length of postpartum hospital stay among obese nulliparous women but was not associated with postpartum stay among obese parous women (**Figure 4-2f**).

After altering our assumptions about the timing of intrapartum complications, associations between eIOL and cesarean appeared more strongly protective, with aORs ranging from 0.38 to 0.58 (**Table 4-A4**). In contrast to the main analyses, eIOL was also associated with reduced odds of operative vaginal delivery (all obese women) and reduced length of postpartum stay (obese parous women).

After expanding our expectant management group to include spontaneous deliveries occurring during the index week, the frequency of non-operative vaginal delivery increased among expectantly managed obese women, particularly between 39 and 41 weeks. In adjusted analyses, the association between eIOL and CD remained protective at 37 and 38 weeks (**Table 4-A5**). However, eIOL between 39 and 41 weeks was associated with increased odds of cesarean (e.g., aOR [95% CI] for eIOL at 40 weeks among nulliparas: 1.84 [1.74, 1.95]). Associations between eIOL and maternal postpartum stay changed direction (from protective to harmful) in sensitivity analyses. Other outcomes were relatively unaffected.

DISCUSSION

In this study, term eIOL was associated with decreased odds of cesarean delivery, postpartum hemorrhage, and severe maternal morbidity among obese women. Likewise,

elective IOL was associated with a modestly reduced postpartum hospital stay (≤-0.1 days) among obese nulliparas. In contrast, eIOL slightly increased the odds of operative vaginal delivery. Elective IOL was not associated with severe perineal lacerations. Our findings agree with a recent modeling study, which found that routine IOL at 39 weeks would reduce CD risk and health care costs among obese women.[238] Similarly, a clinical protocol involving routine IOL by 40 weeks' gestation was recently found to reduce the rate of CD among obese women in a Pennsylvania health system, as compared to rates of CD before the protocol was initiated.[239]

In contrast to our study, Lee et al. generally found no association between eIOL and operative vaginal delivery. However, associations for CD and postpartum hemorrhage were in the same direction as in our study.[187] Point estimates among parous women were closer to the null in our investigation, and precision was improved due to the inclusion of five years of data. Other studies on IOL among obese women possess notable limitations. A 2014 hospital-based retrospective cohort study by Wolfe et al. found that eIOL at 39 or 40 weeks, as compared to expectant management ≥39 weeks, increased the risk of CD among obese nulliparas with an unfavorable cervix.[240] Although Wolfe et al. accessed medical records, they did not assess eIOL <39 weeks, include parous women, or adjust for covariates.[240] Furthermore, they did not stratify analyses by gestational week at induction. This could mask differences between eIOL at 39 versus 40 weeks' gestation.[240]

Elective IOL to prompt earlier delivery may prevent risk factors for CD and maternal morbidity that increase throughout gestation, such as macrosomia[145,187] and preeclampsia.[183] In contrast, the association between eIOL and increased operative

vaginal delivery could be due to side effects of IOL (greater need for epidural,[37] fetal distress,[211] prolonged labor) that increase the need for forceps or vacuum delivery. Because eIOL is associated with reduced risk of macrosomia,[145,187] we hypothesized that it would be associated with reduced risk of perineal lacerations. However, any protective association between eIOL and perineal lacerations due to the prevention of macrosomia may have been counteracted by the association between eIOL and increased operative vaginal delivery.

When we expanded our list of IOL indications to account for pregnancy complications with uncertain timing, a large number of high-risk women were removed from the eIOL group. This made eIOL appear more strongly protective. In a sensitivity analysis using the new expectant management classification (spontaneous deliveries during the index week plus all deliveries in later weeks), eIOL ≥39 weeks appeared harmful, rather than protective, with respect to CD and postpartum hospital stay. Stock et al. found a similar pattern upon revising their expectant management group in a study that was not restricted to obese women.[265] These sensitivity analysis results are also in the same direction as in Wolfe et al.'s study.[240] Notably, this sensitivity analysis could be biased up and past the null at ≥39 weeks.[197] During a given week, CD risk is lower in spontaneous than in induced deliveries. In this sensitivity analysis, all spontaneous deliveries during the index week were considered expectantly managed, even though they may have preceded the week's elective inductions. This could make eIOL appear artificially harmful. In contrast, our primary analyses may be biased away from the null, making eIOL appear artificially protective because the risk of CD increases with gestational age.[266] Despite the changes we observed for mode of delivery in this

sensitivity analysis, conclusions regarding maternal morbidity outcomes were not affected.

This is the second and largest study to compare eIOL at each week of term gestation to expectant management among obese women.[187] This study has many strengths.[187] Our dataset is sociodemographically diverse and population-based.[187] We also compared eIOL to expectant management, which is the choice that clinicians face.[183,187] Another strength of this study is our classification method for medical diagnoses and procedures, which improves sensitivity over using either data source alone.[258-260] Furthermore, we conducted sensitivity analyses evaluating assumptions related to the timing of intrapartum complications and the classification of expectant management.

Our study has limitations. Similarly to others,[145,187] we used Joint Commission guidelines[218] to define eIOL because this list is routinely used in obstetric decision-making. However, there is no single accepted list of indications for IOL. We lacked information on the timing of intrapartum complications; however, we evaluated our assumptions in sensitivity analyses. We also lacked accurate data on gestational age in days; as a result, we could not determine the relative timing of electively induced and spontaneous deliveries that occurred during the same week. To address this uncertainty, we evaluated two different expectant management definitions. It is possible that associations may vary by induction method,[267] but we lacked information on this variable. Unmeasured confounding by cervical status[241] (which is associated with the timing of induction,[193] as well as the probability of a successful vaginal delivery[241]) or other patient or provider preferences may be present. Our findings for CD may be conservative if

physicians who electively induce are more likely to proceed with cesarean without allowing sufficient time for labor to occur.[268] On the other hand, healthier women may be more likely to be electively induced, which could make eIOL look artificially protective.[145] To address this limitation, we adjusted for various sociodemographic and health characteristics (e.g., first-trimester prenatal care initiation) in our multivariable models. Maternal complications may be underreported in vital records and discharge data. However, the sensitivity for many diagnoses and procedures, including IOL, is high in linked datasets.[258] Finally, our results may not be generalizable to obese women with preexisting medical conditions or deliveries outside of California.

To fully inform obstetric management decisions, physicians must balance risks to the mother and the infant. Future research on the impact of eIOL on infant outcomes is needed in order to determine how the maternal benefits of eIOL <39 weeks may or may not be offset by an increased risk of infant complications. Our results suggest that eIOL may be most effective in limiting cesarean delivery among morbidly obese (versus non-morbidly obese) nulliparas. Nevertheless, additional research using larger sample sizes of morbidly obese women is warranted. A randomized, controlled trial would help further refine the estimated effects of eIOL among obese gravidas.

In conclusion, term elective IOL may be an effective method to reduce CD and maternal morbidity among obese women—particularly among obese nulliparas, where the frequency of CD is high. Additional research on neonatal outcomes is needed before elective IOL is routinely recommended before 39 weeks' gestation.

Table 4-1. Frequencies of Maternal Characteristics among Electively Induced and Expectantly Managed Women[a]										
	37 weeks		38 weeks		39 weeks		40 weeks		41 weeks	
Maternal characteristic	**eIOL (N=1,626)**	**Expectant Management (N=203,833)**	**eIOL (N=5,478)**	**Expectant Management (N=165,975)**	**eIOL (N=13,568)**	**Expectant Management (N=95,094)**	**eIOL (N=17,809)**	**Expectant Management (N=25,279)**	**eIOL (N=9,909)**	**Expectant Management (N=1,928)**
Parity										
Nulliparous (%)	30.5	38.3	29.5	39.4	29.1	42.8	39.6	49.3	50.1	50.2
Parous (%)	69.5	61.7	70.5	60.6	70.9	57.2	60.4	50.7	49.9	49.8
Obesity class										
1 (30.0- <35.0 kg/m^2) (%)	63.8	65.0	63.6	65.0	63.9	64.0	63.7	62.2	61.6	61.1
2 (35.0- <40.0 kg/m^2) (%)	25.0	23.4	23.8	23.4	23.7	24.0	24.1	24.7	25.2	24.2
3 (≥40.0 kg/m^2) (%)	11.2	11.6	12.6	11.6	12.4	12.0	12.2	13.1	13.3	14.7
Maternal age, years										
<20 (%)	6.6	8.1	6.2	8.3	6.4	8.6	8.0	9.1	8.9	9.4
20-24 (%)	23.6	27.0	25.0	27.2	25.4	27.8	28.1	28.5	28.1	31.0
25-29 (%)	33.0	30.8	32.4	30.8	32.0	30.6	30.5	30.0	30.4	29.8
30-34 (%)	23.0	21.9	23.6	21.8	22.9	21.6	21.7	21.4	21.9	19.9
35-39 (%)	11.3	10.0	10.6	9.8	10.9	9.4	9.7	9.0	8.8	7.9

≥40 (%)	2.5	2.2	2.2	2.1	2.4	2.0	2.1	2.1	2.0	1.9
Race/ethnicity										
Asian/Pacific Islander (%)	2.8	3.8	3.4	3.7	3.4	3.5	3.2	3.4	3.1	3.5
Hispanic (all races) (%)	63.6	63.4	59.0	63.1	58.8	61.8	61.8	56.8	55.4	54.6
Non-Hispanic Black (%)	6.5	6.5	6.0	6.5	5.3	6.8	5.9	7.4	7.4	8.3
Non-Hispanic White (%)	24.9	23.6	29.1	24.0	29.4	25.0	26.2	29.3	31.3	30.4
Other (%)	2.2	2.7	2.5	2.7	3.1	2.8	2.8	3.0	2.8	3.2
Maternal education										
Less than high school (%)	27.4	27.4	25.0	27.1	22.8	26.9	25.3	25.5	23.1	28.3
High school (%)	31.8	32.2	31.5	32.2	33.9	31.8	32.6	31.4	31.9	29.7
Some college (%)	30.1	28.0	31.2	28.0	31.1	28.2	29.7	28.9	30.3	29.4
≥College degree (%)	10.8	12.4	12.3	12.6	12.2	13.0	12.3	14.2	14.7	12.7
Payer for maternal delivery										
Private (%)	39.7	41.6	43.7	41.6	44.0	41.9	41.4	43.7	47.8	36.9
Public/none (%)	60.3	58.4	56.3	58.4	56.0	58.1	58.6	56.3	52.2	63.1
First trimester prenatal care initiation										
Yes (%)	83.8	81.0	82.9	80.7	84.0	79.3	80.7	75.9	77.5	68.0
No (%)	16.2	19.0	17.1	19.3	16.0	20.7	19.3	24.1	22.5	32.0

Year of delivery										
2007 (%)	23.1	19.1	23.7	19.0	18.5	19.8	19.9	20.3	19.5	25.7
2008 (%)	23.2	20.0	25.0	19.7	19.8	20.1	20.8	20.2	20.1	19.7
2009 (%)	21.0	20.4	21.0	20.5	20.5	19.9	19.9	19.9	20.0	19.3
2010 (%)	17.8	20.3	17.6	20.4	20.1	20.3	20.3	19.7	19.8	18.4
2011 (%)	14.9	20.2	12.7	20.5	21.1	19.9	19.1	19.8	20.6	17.0
Weekday birth										
Yes (%)	78.4	76.3	80.8	76.3	81.8	76.5	81.2	76.6	78.4	74.5
No (%)	21.6	23.7	19.2	23.7	18.2	23.5	18.8	23.4	21.6	25.5
Delivery at teaching hospital										
Yes (%)	8.4	9.1	5.4	9.2	4.4	9.9	6.0	11.7	10.4	11.2
No (%)	91.6	90.9	94.6	90.8	95.6	90.1	94.0	88.3	89.6	88.8
Obstetric volume, deliveries/year										
<1200 (%)	10.8	12.3	13.2	12.2	14.0	12.4	11.6	13.0	11.3	19.0
1200- <2400 (%)	31.4	29.1	29.7	29.1	29.2	30.0	28.7	29.5	27.6	30.6
2400- <3600 (%)	28.8	28.0	30.9	27.8	29.6	27.5	30.0	27.4	29.0	25.7
≥3600 (%)	29.0	30.6	26.2	30.8	27.2	30.1	29.7	30.1	32.2	24.6

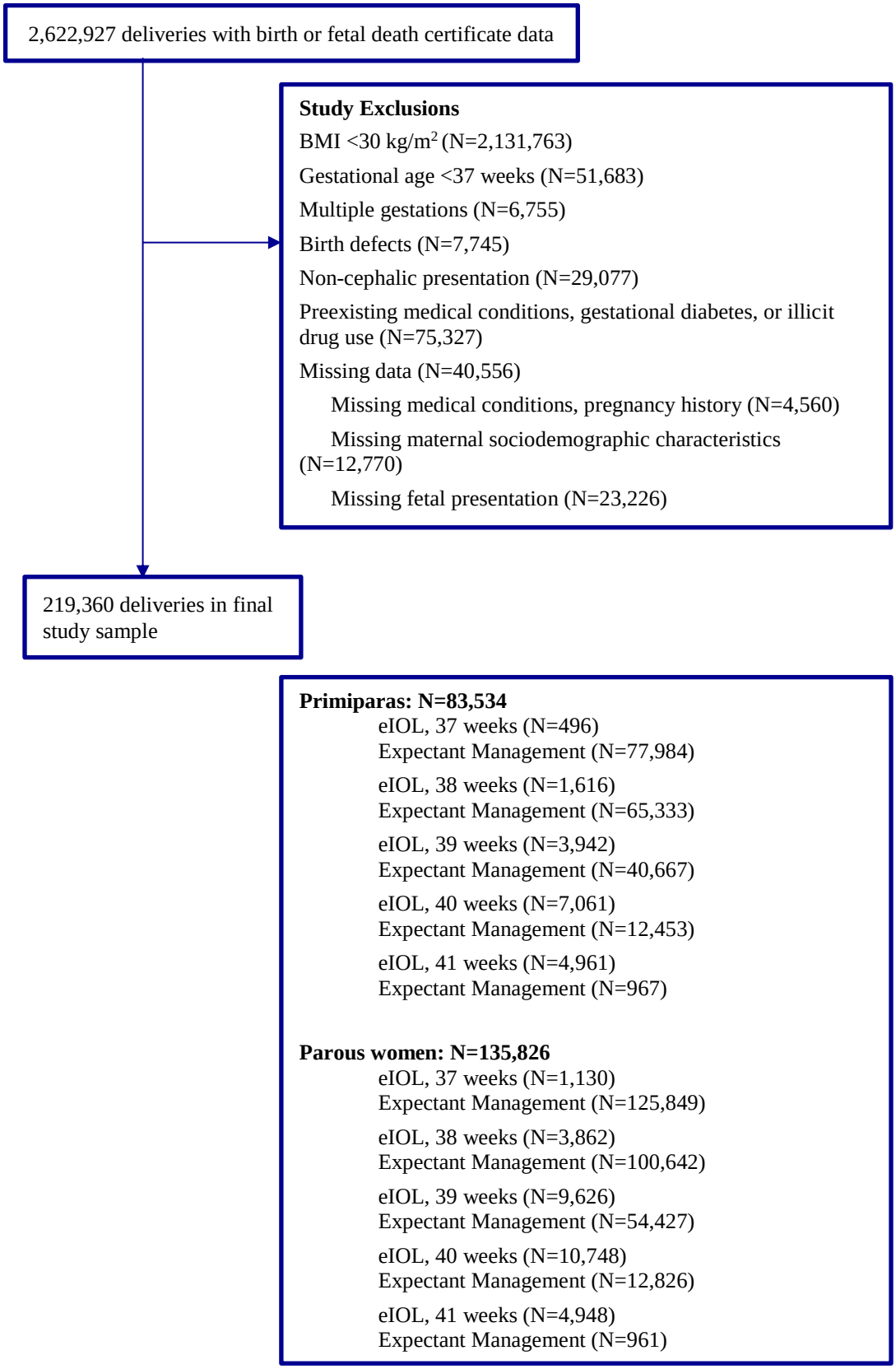
[a]eIOL, elective induction of labor. Table data are percentages (%) within exposure categories.

Table 4-2. Distribution of Maternal Outcomes among Electively Induced and Expectantly Managed Women[a]										
Nulliparous women (N=83,534)										
	37 weeks		**38 weeks**		**39 weeks**		**40 weeks**		**41 weeks**	
Outcome	**eIOL (N=496)**	**Expectant Management (N=77,984)**	**eIOL (N=1,616)**	**Expectant Management (N=65,333)**	**eIOL (N=3,942)**	**Expectant Management (N=40,667)**	**eIOL (N=7,061)**	**Expectant Management (N=12,453)**	**eIOL (N=4,961)**	**Expectant Management (N=967)**
Cesarean delivery (%)	28.0	37.9	31.9	38.9	35.9	41.0	41.8	46.2	45.5	49.4
Operative vaginal delivery (%)	9.3	7.4	9.9	7.3	8.9	7.1	7.8	6.8	7.4	6.1
Postpartum hemorrhage (%)	2.4	3.5	3.0	3.6	2.6	3.9	3.3	4.8	4.4	5.9
Severe perineal lacerations (%)	4.0	2.9	3.2	3.0	2.7	3.1	3.1	3.0	3.3	2.8
Severe maternal morbidity (%)[b]	6.5	6.9	6.7	7.1	5.6	7.6	6.8	8.5	8.2	9
Postpartum stay, mean (SE)	3.13 (0.9)	3.21 (0.9)	3.13 (0.9)	3.21 (0.9)	3.17 (0.9)	3.23 (0.9)	3.20 (0.9)	3.30 (1.0)	3.26 (1.0)	3.31 (0.9)
Ln(postpartum stay), mean (SE)	1.10 (0.3)	1.13 (0.3)	1.10 (0.3)	1.13 (0.3)	1.11 (0.3)	1.13 (0.3)	1.13 (0.3)	1.15 (0.3)	1.14 (0.3)	1.16 (0.3)
Parous women (N=135,826)										
	37 weeks		**38 weeks**		**39 weeks**		**40 weeks**		**41 weeks**	
Outcome	**eIOL (N=1,130)**	**Expectant Management (N=125,849)**	**eIOL (N=3,862)**	**Expectant Management (N=100,642)**	**eIOL (N=9,626)**	**Expectant Management (N=54,427)**	**eIOL (N=10,748)**	**Expectant Management (N=12,826)**	**eIOL (N=4,948)**	**Expectant Management (N=961)**
Cesarean delivery (%)	5.8	8.4	7.0	8.5	7.0	8.7[1]	8.3	10.0[1]	9.6	11.6

Operative vaginal delivery (%)	3.9	3.7	4.5	3.8	4.4	4.0[1]	4.9	3.8[1]	4.0	3.5
Postpartum hemorrhage (%)	2.5	2.6	1.7	2.7	2.3	3.0	2.5	3.9	4.1	4.3
Severe perineal lacerations (%)	0.7	0.8	0.8	0.9	1.0	0.9	1.1	0.8	0.9	0.7
Severe maternal morbidity (%)[b]	3.4	3.6	2.6	3.7	3.3	4.0	3.7	4.9	5.3	5.2
Postpartum stay, mean (SE)	2.69 (0.8)	2.66 (0.7)	2.64 (0.7)	2.66 (0.7)	2.63 (0.7)	2.64 (0.7)	2.64 (0.7)	2.67 (0.7)	2.65 (0.7)	2.70 (0.7)
Ln(postpartum stay), mean (SE)	0.96 (0.3)	0.95 (0.3)	0.94 (0.2)	0.94 (0.3)	0.93 (0.3)	0.94 (0.3)	0.94 (0.3)	0.95 (0.3)	0.94 (0.3)	0.96 (0.3)

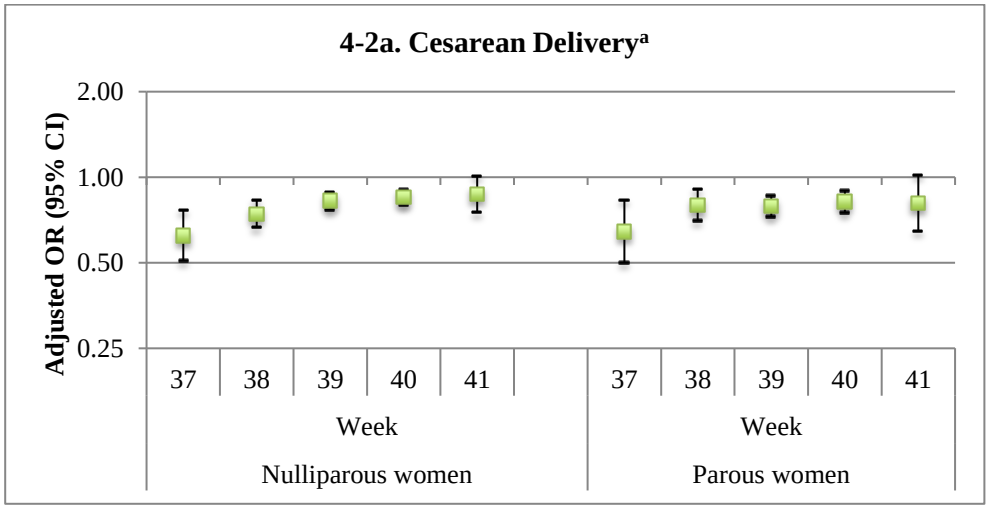
[a]eIOL, elective induction of labor.
[b]Of 10,529 women with severe maternal morbidity, 56.8% had postpartum hemorrhage, 31.9% had a severe perineal laceration, and the remaining 11.3% experienced multiple or rare complications.

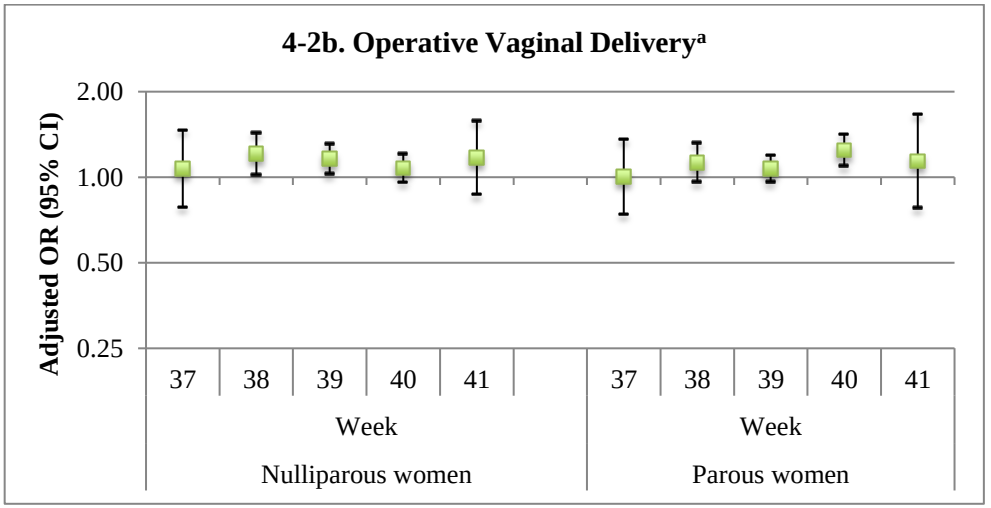
Figure 4-1. Study Exclusion Criteria[a]

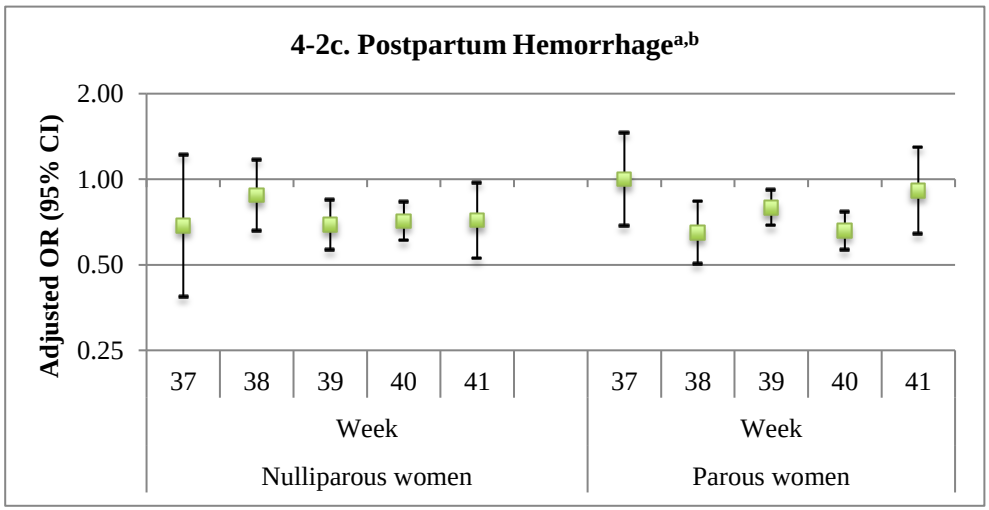


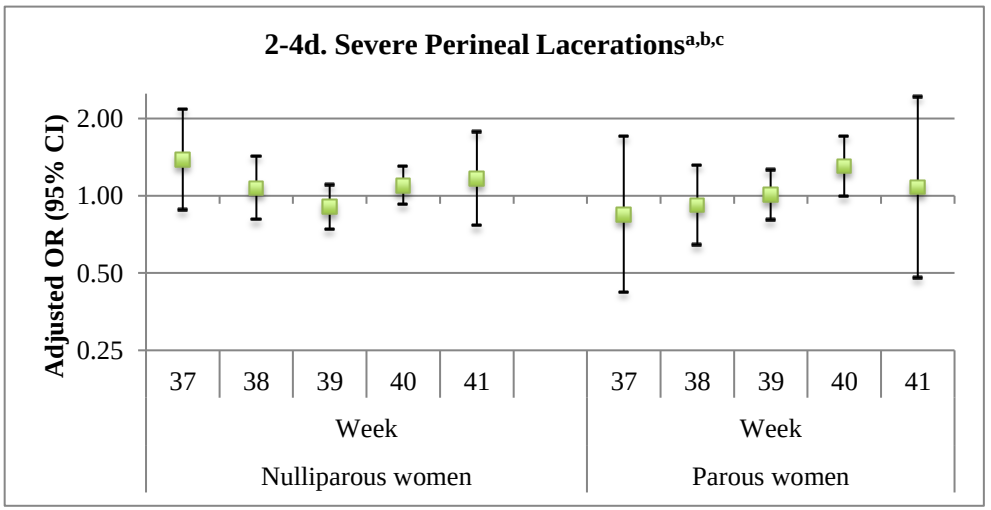
Description: This flow chart shows the exclusion criteria for our study and the final sample sizes of exposed and unexposed women. eIOL, elective induction of labor.
[a]These numbers (N) represent the number of women excluded at each successive step of study sample determination. E.g., 2,131,763 women were initially excluded due to pre-pregnancy BMI <30 kg/m^2. Subsequently, among remaining eligible women, 51,683 more were subsequently excluded due to gestational age <37 weeks (and so on). All stillbirths were ultimately excluded from the study sample due to preexisting conditions or missing data.

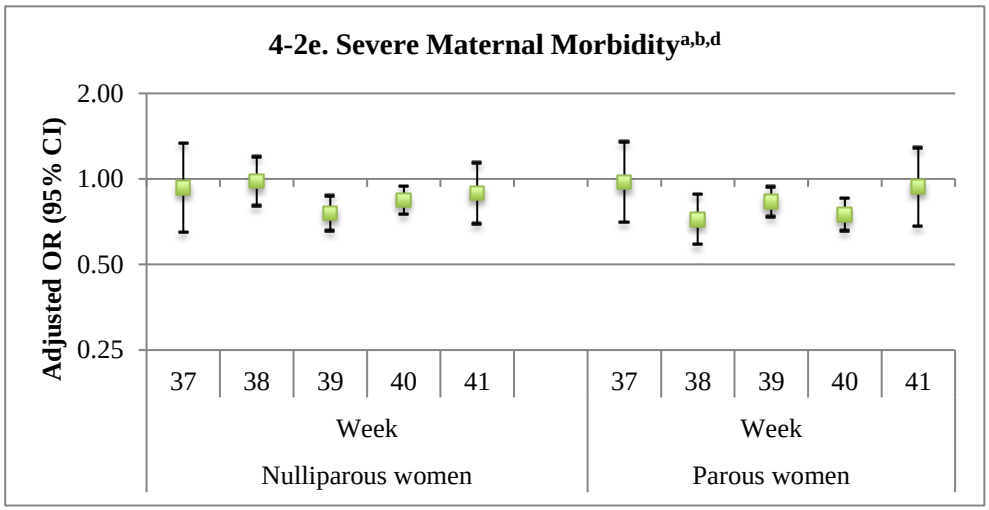
Figure 4-2. Adjusted Odds Ratios for Elective Induction of Labor (versus Expectant Management) and Obstetric Outcomes

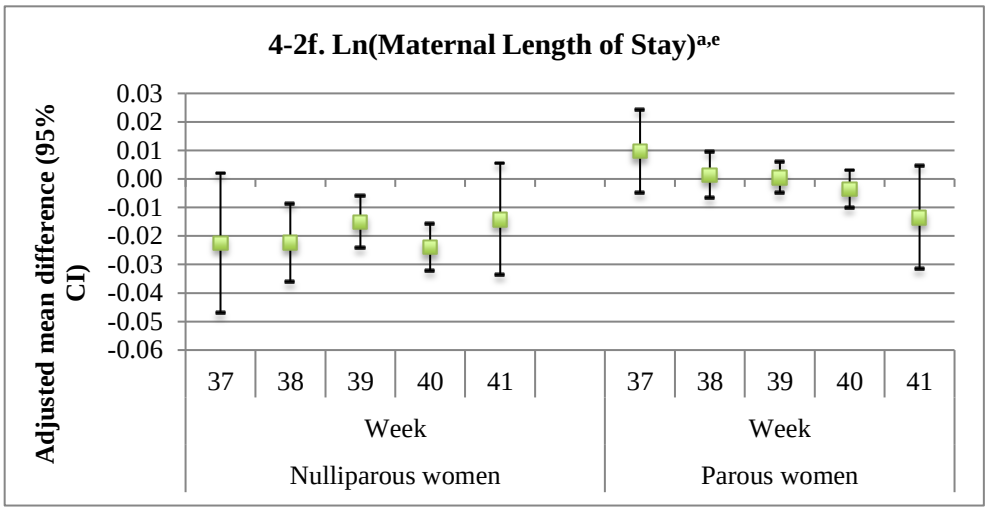












Description*:* Figures 2a through 2f display adjusted odds ratios for the association between term elective induction of labor (versus expectant management) and obstetric outcomes, stratified by parity. OR, Odds Ratio; CI, Confidence Interval.

[a]Models were adjusted for maternal age, maternal education, maternal race/ethnicity, first-trimester prenatal care initiation, principal source of payment for delivery, birth year, obesity class, weekday delivery, delivery at a teaching hospital, and hospital obstetric volume.

[b]Mode of delivery was a three-category outcome (cesarean delivery, operative vaginal delivery, non-operative vaginal delivery [referent]) that was modeled using multinomial logistic regression.

[c]Outcome was modeled using multivariable logistic regression.

[d]Among all deliveries. Additional models for severe perineal lacerations were run among vaginal deliveries only (Appendix Table A3).

[e]Severe maternal morbidity was a composite outcome that included postpartum hemorrhage, severe perineal laceration, unplanned surgical procedure, uterine rupture, maternal intensive care unit admission, maternal sepsis, and endometritis. Of 10,529 women with this outcome, 56.8% had postpartum hemorrhage, 31.9% had a severe perineal laceration, and the remaining 11.3% experienced multiple or rare complications.

[f]Outcome (log-transformed maternal postpartum hospital stay in days) was modeled using multivariable linear regression.

APPENDIX TABLES

Table 4-A1. Indications for Induction of Labor[a]

Condition	ICD-9 code
HIV	042, 079.53, V08
Coagulation disorders	286.0, 286.1, 286.2, 286.3, 286.4, 286.5, 286.7
Placenta previa	641.0,[b] 641.1,[b] 762.0[b]
Vasa previa	663.5[b]
Placental abruption	641.2,[c] 762.1[c]
Antepartum hemorrhage	641.8, 641.9
Preexisting hypertension	401,[b] 402,[b] 403,[b] 404,[b] 405,[b] 642.0,[b] 642.1,[b] 642.2,[b] 642.7[b]
Gestational hypertension	642.3
Preeclampsia/eclampsia	642.4, 642.5, 642.6, 642.7
Other hypertension	437.2, 642.9, 760.0
Liver/biliary tract disorder	570, 571.1, 571.2,[b] 571.5,[b] 571.6,[b] 572.2,[b] 572.4,[b] 646.7
Diabetes mellitus (preexisting or gestational)	249,[b] 250,[b] 357.2,[b] 362.0,[b] 648.0,[b] 648.8,[b] 775.0[b]
Renal disease	403,[b] 404,[b] 580, 581,[b] 582,[b] 583, 584, 585,[b] 586, 587, 642.1,[b] 646.2, V42.0[b]
Cardiovascular disease	394,[b] 395,[b] 396,[b] 397,[b] 398,[b] 402,[b] 404,[b] 410, 411, 412,[b] 413,[b] 414.0,[b] 414.1, 414.2,[b] 414.3,[b] 414.4,[b] 414.8,[b] 414.9,[b] 415, 416,[b] 417.0,[b] 417.1, 417.8,[b] 417.9,[b] 420, 421, 422,

	423,[b] 424,[b] 425,[b] 426,[b] 427.0,[b] 427.1,[b] 427.2,[b] 427.3,[b] 427.4,[b] 427.5, 427.6,[b] 427.8,[b] 427.9,[b] 428, 648.5,[b] 648.6,[b] 760.3[b]
Multiple gestations	651,[b] 652.6,[b] 761.5[b]
Major fetal abnormality	653.6,[b] 655.0,[b] 655.1,[b] 740.0,[b] 740.1,[b] 740.2,[b] 741.0,[b] 741.9,[b] 742.0,[b] 742.2,[b] 742.3,[b] 742.1,[b] 743.0,[b] 743.1,[b] 743.2,[b] 743.3[0,1,2,3,4],[b] 743.45,[b] 744.0,[b] 744.01[b],744.23[b] 745.0,[b] 745.1,[b] 745.2,[b] 745.3,[b] 746.01,[b] 746.02,[b] 746.1,[b] 746.2,[b] 746.3,[b] 746.7,[b] 747.0,[b] 747.10,[b] 747.41,[b] 748.0,[b] 748.5[b]
Fetal-maternal hemorrhage	656.0,[c] 772.0[c]
Isoimmunization	656.1, 656.2, 773.0,[b] 773.1, 773.2,[b] 773.3[b]
Intrauterine death	656.4,[d] 768.0,[d] V27.1[d]
Poor fetal growth	656.5, 764.0, 764.1, 764.9
Polyhydramnios	657.0, 761.3
Oligohydramnios	658.0, 761.2
Premature rupture of membranes	658.1, 761.1
Fetal distress or fetal heart rate abnormality <u>before</u> onset of labor	768.2, 763.81
Pregnancy with poor reproductive history	V23.5
Other fetal conditions affecting management of mother	655.3, 655.4, 655.5, 655.6, 655.8
Indications in sensitivity analysis only	
Fetal distress or fetal heart rate abnormality	656.3, 659.7, 763.83, 768.4

with unspecified time of onset	
Coagulation deficiency hemorrhage	641.31, 649.3
Amniotic infection/chorioamnionitis	658.41, 762.7

[a]We used vital records and hospital discharge data ICD-9 codes to classify indications. An indication was classified as present if detected in vital records or hospital discharge data.
[b]Considered an exclusion criteria for our study.
[c]Not classified as an indication in a sensitivity analysis that accounted for the uncertain timing of intrapartum complications.
[d]All stillbirths were excluded from this study due to exclusion criteria or missing data.

Table 4-A2. Crude Odds Ratios for Elective Induction of Labor versus Expectant Management and Obstetric Outcomes[a]					
Nulliparous women (N=83,534)					
Outcome	**eIOL, 37 weeks (N=496) vs. EM (N=77,984)**	**eIOL, 38 weeks (N=1,616) vs. EM (N=65,333)**	**eIOL, 39 weeks (N=3,942) vs. EM (N=40,667)**	**eIOL, 40 weeks (N=7,061) vs. EM (N=12,453)**	**eIOL, 41 weeks (N=4,961) vs. EM (N=967)**
Cesarean delivery	0.65 (0.53, 0.79)	0.76 (0.68, 0.85)	0.82 (0.77, 0.88)	0.84 (0.79, 0.89)	0.87 (0.75, 1.00)
Operative vaginal delivery	1.09 (0.80, 1.49)	1.25 (1.05, 1.48)	1.18 (1.05, 1.33)	1.07 (0.96, 1.20)	1.14 (0.85, 1.53)
Postpartum hemorrhage	0.68 (0.38, 1.21)	0.84 (0.63, 1.12)	0.65 (0.53, 0.80)	0.66 (0.57, 0.78)	0.73 (0.54, 0.99)
Severe perineal lacerations[b]	1.39 (0.89, 2.18)	1.06 (0.80, 1.41)	0.89 (0.73, 1.08)	1.06 (0.90, 1.26)	1.18 (0.78, 1.78)
Severe perineal lacerations[c]	1.21 (0.77, 1.90)	0.94 (0.70, 1.25)	0.82 (0.67, 1.00)	0.98 (0.83, 1.17)	1.13 (0.74, 1.73)
Severe maternal morbidity[d]	0.93 (0.65, 1.33)	0.95 (0.78, 1.16)	0.73 (0.63, 0.84)	0.80 (0.71, 0.89)	0.91 (0.71, 1.16)
Ln(postpartum hospital stay)	-0.02 (-0.05, 0.004)	-0.02 (-0.04, -0.01)	-0.02 (-0.03, -0.01)	-0.03 (-0.04, -0.02)	-0.02 (-0.04, 0.002)
Parous women (N=135,826)					
Outcome	**eIOL, 37 weeks (N=1,130) vs. EM (N=125,849)**	**eIOL, 38 weeks (N=3,862) vs. EM (N=100,642)**	**eIOL, 39 weeks (N=9,626) vs. EM (N=54,427)**	**eIOL, 40 weeks (N=10,748) vs. EM (N=12,826)**	**eIOL, 41 weeks (N=4,948) vs. EM (N=961)**
Cesarean delivery	0.67 (0.52, 0.86)	0.82 (0.72, 0.93)	0.79 (0.73, 0.86)	0.82 (0.75, 0.90)	0.81 (0.65, 1.01)
Operative vaginal delivery	1.04 (0.77, 1.40)	1.18 (1.01, 1.38)	1.10 (0.99, 1.23)	1.30 (1.14, 1.47)	1.12 (0.77, 1.62)
Postpartum hemorrhage	0.96 (0.66, 1.41)	0.62 (0.48, 0.79)	0.76 (0.66, 0.87)	0.64 (0.55, 0.74)	0.96 (0.68, 1.36)
Severe perineal lacerations[b]	0.84 (0.42, 1.69)	0.95 (0.67, 1.35)	1.06 (0.85, 1.33)	1.42 (1.09, 1.86)	1.28 (0.58, 2.84)
Severe perineal lacerations[c]	0.82 (0.41, 1.65)	0.94 (0.66, 1.34)	1.05 (0.84, 1.31)	1.37 (1.05, 1.80)	1.25 (0.56, 2.79)
Severe maternal morbidity[d]	0.95 (0.68, 1.31)	0.70 (0.57, 0.86)	0.81 (0.72, 0.92)	0.75 (0.66, 0.85)	1.01 (0.74, 1.38)
Ln(postpartum hospital stay)	0.01 (-0.01, 0.02)	-0.01 (-0.01, 0.003)	-0.01 (-0.01, -0.001)	-0.01 (-0.01, -0.001)	-0.02 (-0.04, -0.003)

[a]eIOL, elective induction of labor. EM, expectant management. Table data are crude odds ratios (95% confidence intervals). Mode of delivery was modeled using multinomial logistic regression. Ln(maternal hospital stay) was modeled using linear regression. Other outcomes were modeled using logistic regression.
[b]Among all deliveries.
[c]Among vaginal deliveries only.
[d]Composite outcome including postpartum hemorrhage, severe perineal laceration, unplanned surgical procedure, uterine rupture, maternal intensive care unit admission, maternal sepsis, and endometritis.

Table 4-A3. Adjusted Odds Ratios for Elective Induction of Labor versus Expectant Management and Obstetric Outcomes[a]					
Nulliparous women (N=83,534)					
Outcome	**eIOL, 37 weeks (N=496) vs. EM (N=77,984)**	**eIOL, 38 weeks (N=1,616) vs. EM (N=65,333)**	**eIOL, 39 weeks (N=3,942) vs. EM (N=40,667)**	**eIOL, 40 weeks (N=7,061) vs. EM (N=12,453)**	**eIOL, 41 weeks (N=4,961) vs. EM (N=967)**
Cesarean delivery	0.62 (0.51, 0.76)	0.74 (0.66, 0.83)	0.82 (0.77, 0.88)	0.85 (0.80, 0.90)	0.87 (0.75, 1.01)
Operative vaginal delivery	1.07 (0.78, 1.46)	1.21 (1.02, 1.43)	1.16 (1.03, 1.31)	1.08 (0.96, 1.21)	1.17 (0.87, 1.58)
Postpartum hemorrhage	0.68 (0.39, 1.22)	0.88 (0.66, 1.17)	0.69 (0.56, 0.85)	0.71 (0.61, 0.83)	0.72 (0.53, 0.97)
Severe perineal lacerations[b]	1.38 (0.88, 2.17)	1.07 (0.81, 1.42)	0.90 (0.74, 1.10)	1.10 (0.92, 1.30)	1.16 (0.77, 1.77)
Severe perineal lacerations[c]	1.18 (0.75, 1.86)	0.94 (0.70, 1.25)	0.83 (0.68, 1.01)	1.02 (0.85, 1.21)	1.08 (0.70, 1.67)
Severe maternal morbidity[d]	0.93 (0.65, 1.33)	0.98 (0.81, 1.19)	0.76 (0.66, 0.87)	0.84 (0.75, 0.94)	0.89 (0.70, 1.14)
Ln(postpartum hospital stay)	-0.02 (-0.05, 0.002)	-0.02 (-0.04, -0.01)	-0.02 (-0.02, -0.01)	-0.02 (-0.03, -0.02)	-0.01 (-0.03, 0.01)
Parous women (N=135,826)					
Outcome	**eIOL, 37 weeks (N=1,130) vs. EM (N=125,849)**	**eIOL, 38 weeks (N=3,862) vs. EM (N=100,642)**	**eIOL, 39 weeks (N=9,626) vs. EM (N=54,427)**	**eIOL, 40 weeks (N=10,748) vs. EM (N=12,826)**	**eIOL, 41 weeks (N=4,948) vs. EM (N=961)**
Cesarean delivery	0.64 (0.50, 0.83)	0.80 (0.70, 0.90)	0.79 (0.72, 0.86)	0.82 (0.75, 0.90)	0.81 (0.65, 1.02)
Operative vaginal delivery	1.00 (0.74, 1.36)	1.13 (0.96, 1.32)	1.07 (0.96, 1.19)	1.24 (1.09, 1.41)	1.14 (0.78, 1.66)
Postpartum hemorrhage	1.00 (0.68, 1.45)	0.65 (0.50, 0.83)	0.79 (0.69, 0.92)	0.66 (0.56, 0.77)	0.91 (0.64, 1.29)
Severe perineal lacerations[b]	0.85 (0.42, 1.70)	0.92 (0.64, 1.31)	1.01 (0.81, 1.26)	1.30 (0.99, 1.71)	1.08 (0.48, 2.43)
Severe perineal lacerations[c]	0.82 (0.41, 1.64)	0.91 (0.63, 1.29)	1.00 (0.80, 1.25)	1.25 (0.96, 1.64)	1.06 (0.47, 2.38)
Severe maternal morbidity[d]	0.97 (0.70, 1.35)	0.72 (0.59, 0.88)	0.83 (0.74, 0.94)	0.75 (0.66, 0.85)	0.94 (0.68, 1.29)
Ln(postpartum hospital stay)	0.01 (-0.005, 0.02)	0.001 (-0.01, 0.01)	0.001 (-0.005, 0.01)	-0.004 (-0.01, 0.003)	-0.01 (-0.03, 0.005)

[a]eIOL, elective induction of labor. EM, expectant management. Table data are adjusted odds ratios (95% confidence intervals). These data are also presented graphically in Figures 2-3. Mode of delivery was modeled using multivariable, multinomial logistic regression. Ln(maternal hospital stay) was modeled using multivariable linear regression. Other outcomes were modeled using multivariable logistic regression. Models were adjusted for maternal age, education, and

race/ethnicity; first-trimester prenatal care initiation, payment source of payment for delivery, birth year, obesity class, weekday delivery, delivery at a teaching hospital, and hospital obstetric volume.
[b]Among all deliveries.
[c]Among vaginal deliveries only.
[d]Composite outcome including postpartum hemorrhage, severe perineal laceration, unplanned surgical procedure, uterine rupture, maternal intensive care unit admission, maternal sepsis, and endometritis.

Table 4-A4. Adjusted Odds Ratios, Elective Labor Induction versus Expectant Management and Obstetric Outcomes, Accounting for Uncertain Timing of Intrapartum Indications[a,b]					
Nulliparous women (N=83,534)					
Outcome	**eIOL, 37 weeks (N= 372) vs. EM (N= 77,984)**	**eIOL, 38 weeks (N= 1,176) vs. EM (N= 65,333)**	**eIOL, 39 weeks (N= 2,912) vs. EM (N= 40,667)**	**eIOL, 40 weeks (N= 4,965) vs. EM (N= 12,453)**	**eIOL, 41 weeks (N= 3,232) vs. EM (N= 967)**
Cesarean delivery	0.38 (0.30, 0.49)	0.50 (0.43, 0.57)	0.58 (0.54, 0.63)	0.55 (0.51, 0.59)	0.52 (0.45, 0.61)
Operative vaginal delivery	0.60 (0.39, 0.92)	0.88 (0.72, 1.09)	0.80 (0.69, 0.93)	0.76 (0.66, 0.87)	0.91 (0.67, 1.24)
Postpartum hemorrhage	0.69 (0.36, 1.34)	0.84 (0.60, 1.19)	0.71 (0.57, 0.90)	0.74 (0.62, 0.88)	0.73 (0.53, 1.01)
Severe perineal lacerations[c]	1.21 (0.70, 2.12)	1.20 (0.87, 1.64)	0.96 (0.77, 1.21)	1.20 (0.99, 1.45)	1.35 (0.88, 2.08)
Severe perineal lacerations[d]	0.92 (0.53, 1.61)	0.93 (0.67, 1.28)	0.80 (0.64, 1.00)	0.95 (0.78, 1.15)	1.03 (0.66, 1.62)
Severe maternal morbidity[e]	0.91 (0.59, 1.38)	1.00 (0.80, 1.26)	0.79 (0.67, 0.93)	0.87 (0.77, 0.99)	0.91 (0.70, 1.18)
Ln(postpartum hospital stay)	-0.05 (-0.08, -0.03)	-0.05 (-0.06, -0.03)	-0.04 (-0.05, -0.03)	-0.06 (-0.07, -0.05)	-0.07 (-0.09, -0.04)
Parous women (N=135,826)					
Outcome	**eIOL, 37 weeks (N=988) vs. EM (N=125,849)**	**eIOL, 38 weeks (N=3,339) vs. EM (N=100,642)**	**eIOL, 39 weeks (N=8,346) vs. EM (N=54,427)**	**eIOL, 40 weeks (N=9,065) vs. EM (N=12,826)**	**eIOL, 41 weeks (N=4,061) vs. EM (N=961)**
Cesarean delivery	0.45 (0.32, 0.61)	0.47 (0.39, 0.55)	0.46 (0.41, 0.51)	0.43 (0.38, 0.48)	0.38 (0.29, 0.48)
Operative vaginal delivery	0.81 (0.57, 1.15)	0.75 (0.62, 0.92)	0.67 (0.59, 0.77)	0.78 (0.67, 0.90)	0.62 (0.41, 0.93)
Postpartum hemorrhage	0.87 (0.56, 1.34)	0.65 (0.49, 0.85)	0.79 (0.68, 0.92)	0.64 (0.54, 0.75)	0.84 (0.58, 1.20)
Severe perineal lacerations[c]	0.84 (0.40, 1.78)	0.94 (0.64, 1.37)	0.97 (0.76, 1.24)	1.23 (0.93, 1.64)	0.97 (0.42, 2.22)
Severe perineal lacerations[d]	0.81 (0.38, 1.70)	0.90 (0.61, 1.31)	0.94 (0.73, 1.19)	1.16 (0.87, 1.54)	0.89 (0.39, 2.04)
Severe maternal morbidity[e]	0.89 (0.61, 1.28)	0.72 (0.58, 0.89)	0.82 (0.72, 0.93)	0.71 (0.62, 0.82)	0.86 (0.62, 1.19)
Ln(postpartum hospital stay)	0.003 (-0.01, 0.02)	-0.01 (-0.02, -0.001)	-0.01 (-0.01, -0.003)	-0.02 (-0.03, -0.01)	-0.04 (-0.06, -0.02)

[a]eIOL, elective induction of labor. EM, expectant management. In this analysis, placental abruption and fetal-maternal hemorrhage were not considered indications for IOL. Coagulation deficiency, amniotic infection, and fetal distress/fetal heart rate abnormalities with unspecified time of onset were considered indications for IOL.
[b]Table data are adjusted odds ratios (95% confidence intervals). Delivery mode was modeled using multivariable, multinomial logistic regression. Ln(maternal hospital stay) was modeled using multivariable linear regression. Other outcomes were modeled using multivariable logistic regression. Models were adjusted for maternal age, education, and race/ethnicity; first-trimester prenatal care initiation; payment source; birth year; obesity class; weekday delivery; delivery at a teaching hospital; and hospital obstetric volume.
[c]Among all deliveries.
[d]Among vaginal deliveries only.
[e]Composite outcome including postpartum hemorrhage, severe perineal laceration, unplanned surgical procedure, uterine rupture, maternal intensive care unit admission, maternal sepsis, and endometritis.

Table 4-A5. Adjusted Odds Ratios for Elective Labor Induction versus Expectant Management and Obstetric Outcomes using New Expectant Management Classification[a,b]					
Nulliparous women (N=83,534)					
Outcome	**eIOL, 37 weeks (N=496) vs. EM (N=80,953)**	**eIOL, 38 weeks (N=1,616) vs. EM (N=72,145)**	**eIOL, 39 weeks (N=3,942) vs. EM (N=53,650)**	**eIOL, 40 weeks (N=7,061) vs. EM (N=25,502)**	**eIOL, 41 weeks (N=4,961) vs. EM (N=4,363)**
Cesarean delivery	0.65 (0.53, 0.80)	0.84 (0.75, 0.94)	1.14 (1.07, 1.23)	1.84 (1.74, 1.95)	2.52 (2.30, 2.77)
Operative vaginal delivery	1.08 (0.79, 1.47)	1.22 (1.03, 1.45)	1.18 (1.05, 1.33)	1.17 (1.05, 1.29)	1.16 (0.99, 1.35)
Postpartum hemorrhage	0.69 (0.39, 1.23)	0.88 (0.66, 1.18)	0.71 (0.58, 0.86)	0.79 (0.69, 0.92)	0.79 (0.65, 0.96)
Severe perineal lacerations[c]	1.37 (0.87, 2.15)	1.06 (0.80, 1.40)	0.84 (0.69, 1.03)	0.88 (0.76, 1.02)	0.81 (0.65, 1.00)
Severe perineal lacerations[d]	1.19 (0.76, 1.88)	0.97 (0.73, 1.29)	0.87 (0.71, 1.06)	1.09 (0.93, 1.27)	1.11 (0.89, 1.39)
Severe maternal morbidity[e]	0.93 (0.65, 1.34)	0.98 (0.81, 1.20)	0.75 (0.65, 0.87)	0.85 (0.76, 0.94)	0.85 (0.73, 0.98)
Ln(postpartum hospital stay)	-0.02 (-0.04, 0.01)	-0.01 (-0.03, 0.002)	0.01 (0.003, 0.02)	0.04 (0.03, 0.05)	0.07 (0.06, 0.08)
Parous women (N=135,826)					
Outcome	**eIOL, 37 weeks (N=1,130) vs. EM (N=133,055)**	**eIOL, 38 weeks (N=3,862) vs. EM (N=118,708)**	**eIOL, 39 weeks (N=9,626) vs. EM (N=85,915)**	**eIOL, 40 weeks (N=10,748) vs. EM (N=39,494)**	**eIOL, 41 weeks (N=4,948) vs. EM (N=6,553)**
Cesarean delivery	0.68 (0.53, 0.87)	0.92 (0.81, 1.04)	1.16 (1.07, 1.27)	1.97 (1.81, 2.14)	2.73 (2.32, 3.20)
Operative vaginal delivery	1.01 (0.75, 1.37)	1.17 (1.00, 1.37)	1.14 (1.03, 1.27)	1.32 (1.19, 1.46)	1.08 (0.89, 1.31)
Postpartum hemorrhage	1.01 (0.69, 1.47)	0.67 (0.52, 0.86)	0.88 (0.77, 1.02)	0.84 (0.73, 0.96)	1.16 (0.95, 1.40)
Severe perineal lacerations[c]	0.85 (0.42, 1.72)	0.95 (0.66, 1.35)	1.06 (0.85, 1.31)	1.18 (0.96, 1.46)	1.16 (0.77, 1.75)
Severe perineal lacerations[d]	0.83 (0.41, 1.67)	0.94 (0.66, 1.34)	1.07 (0.86, 1.34)	1.21 (0.98, 1.49)	1.25 (0.83, 1.87)
Severe maternal morbidity[e]	0.98 (0.71, 1.36)	0.74 (0.61, 0.91)	0.91 (0.81, 1.03)	0.90 (0.81, 1.01)	1.18 (0.99, 1.40)
Ln(postpartum hospital stay)	0.01 (-0.004, 0.03)	0.005 (-0.003, 0.01)	0.01 (0.004, 0.01)	0.02 (0.02, 0.03)	0.02 (0.01, 0.03)

[a]eIOL, elective induction of labor. EM, expectant management. We expanded the expectant management group to include spontaneously laboring women who delivered during the same week as the exposed were induced.
[b]Table data are adjusted odds ratios (95% confidence intervals). Mode of delivery was modeled using multivariable, multinomial logistic regression. Ln(maternal hospital stay) was modeled using multivariable linear regression. Other outcomes were modeled using multivariable logistic regression. Models were adjusted for maternal age, maternal education, maternal race/ethnicity, initiation of prenatal care in the first trimester, principal source of payment for delivery, birth year, obesity class, weekday delivery, delivery at a teaching hospital, and hospital obstetric volume.
[c]Among all deliveries.
[d]Among vaginal deliveries only.
[e]Composite outcome including postpartum hemorrhage, severe perineal laceration, unplanned surgical procedure, uterine rupture, maternal intensive care unit admission, maternal sepsis, and endometritis.

CHAPTER 5, TERM ELECTIVE INDUCTION OF LABOR AND INFANT OUTCOMES AMONG OBESE WOMEN

ABSTRACT

Objective: Evaluate whether term elective induction of labor, as compared to expectant management, reduces adverse outcomes among offspring of obese women.

Methods: We conducted a retrospective study of 219,360 singleton, non-anomalous deliveries to obese women using the 2007-2011 California Linked Patient Discharge Data/Birth Cohort File. Women with preexisting disease, a prior cesarean delivery, or non-cephalic presentation were excluded. For each term gestational week (37-41), we used multivariable logistic regression models, stratified by parity, to assess whether elective labor induction or expectant management was associated with lower risks of infant mortality (≤1 year) and morbidity (macrosomia, chorioamnionitis, respiratory distress syndrome, meconium aspiration syndrome, shoulder dystocia, brachial plexus injury, infant hospital stay >5 days).

Results: Elective labor induction at 37 weeks was associated with increased infant mortality among obese parous women (adjusted odds ratio [OR]: 3.48, 95% Confidence Interval [CI] 1.42, 8.50). Among all women, term elective labor induction was associated with reduced odds of meconium aspiration syndrome (e.g., in nulliparas, adjusted OR at 39 weeks: 0.56 [95% CI 0.48, 0.67]), chorioamnionitis (e.g., in nulliparas, adjusted OR at 39 weeks: 0.56 [95% CI 0.36, 0.88]), macrosomia, and infant stay >5 days. Among parous women, elective induction was associated with reduced odds of brachial plexus injury (adjusted OR, 40 weeks: 0.46 [95% CI 0.26, 0.83]) and shoulder dystocia.

Conclusions: In obese women, elective labor induction <39 weeks should not be recommended owing to the increased risk of infant death. However, elective labor induction between 39 and 41 weeks may reduce neonatal morbidity without increasing infant mortality.

INTRODUCTION

Maternal obesity (pre-pregnancy body mass index ≥30 kg/m^2) increases the risk of adverse obstetric,[9] fetal,[17,49] and infant[9,49] outcomes. Despite the high U.S. prevalence of pre-pregnancy obesity (20.5%[2]) and the myriad of complications associated with this condition, a uniform standard of care for obese gravidas does not currently exist.

Obese women are more likely to have their labor induced than non-obese women.[8,9,17,23] However, the risks and benefits of labor induction have not been thoroughly evaluated among obese gravidas. In particular, there has been limited research on the impact of term elective induction of labor, as compared to expectant management, on neonatal outcomes among obese women.

Infants of obese gravidas are at elevated risk of macrosomia,[8,17] shoulder dystocia,[8] brachial plexus injury,[186] meconium aspiration syndrome,[8] and stillbirth,[17,49] all of which increase with gestational age.[145,187,188] It is plausible that these infant complications could be prevented through elective induction of labor and earlier delivery. Other investigators have shown that delivery <39 weeks benefits the infants of certain high-risk women, such as those with diabetes[189,190] or severe preeclampsia.[191] However, the potential negative side effects of elective labor induction and earlier delivery (including unplanned cesarean delivery and neonatal respiratory morbidity, respectively) must also be considered.[192,193]

A recent study suggested that elective labor induction <39 weeks may reduce the risks of chorioamnionitis, macrosomia, and shoulder dystocia among infants of obese women.[187] However, this study did not examine meconium aspiration syndrome, infant hospital stay, or infant death. This study also lacked statistical power to detect differences

in respiratory distress syndrome (RDS).

Our objective was to assess whether term elective induction of labor, as compared to expectant management, reduced the risks of adverse outcomes among infants of obese women. We hypothesized that elective labor induction would: 1) increase the odds of respiratory distress syndrome (RDS) and infant mortality before 39 weeks' gestation; 2) decrease the odds of RDS and infant mortality from 39-41 weeks' gestation; and 3) reduce the odds of other infant complications between 37-41 weeks' gestation.

MATERIALS AND METHODS

For this retrospective cohort study, we used the 2007-2011 California Linked Patient Discharge Data/Birth Cohort File.[257] This dataset included linked vital records, maternal hospital discharge records, and infant hospital discharge records for all California deliveries, as well as out-of-state births to California residents. Deliveries occurring to the same woman but in different years were not linked in this dataset. Hospital discharge data from the delivery visit contained ICD-9-CM procedure and diagnostic codes. We used ICD-9-CM procedure and diagnostic codes from both vital records and hospital discharge data to classify induction of labor, pregnancy characteristics, and infant outcomes.

Obese women with singleton, term deliveries in cephalic presentation were included if they did not have preexisting medical complications (including gestational diabetes, which would have been diagnosed prior to 37 weeks), a prior cesarean delivery, or an infant with a major congenital anomaly (**Figure 5-1**). Gestational age was defined by best obstetric estimate. Parity was defined as the number of previous pregnancies reaching ≥20 weeks' gestation. Pre-pregnancy body mass index was derived using vital

records data.

We evaluated infant outcomes at each term (37-41) gestational week by comparing exposed women (those who underwent induction without medical indication in the given week) with unexposed women (expectantly managed women who delivered at a later gestational week). The expectant management group consisted of all women who delivered in later weeks, regardless of delivery method or labor onset type. Medical indications for labor induction (which were used to classify inductions as elective versus non-elective) were defined using recent Joint Commission guidelines[187,218] (see **Table 5-S1** [Supplemental Digital Content] for a list of conditions in this study).

Study outcomes included infant mortality (death in first year of life), extended infant hospital stay (>5 days), macrosomia (birthweight ≥4000 grams), chorioamnionitis, meconium aspiration syndrome, respiratory distress syndrome (RDS), shoulder dystocia, and brachial plexus injury.

STATISTICAL ANALYSIS

We modeled crude and adjusted associations between elective labor induction and infant outcomes using logistic regression. In multivariable analyses, we adjusted for maternal sociodemographic characteristics (age, race/ethnicity, education, obesity severity, payment source for delivery, first-trimester prenatal care initiation), delivery characteristics (weekday [versus weekend] delivery, birth year), and hospital characteristics (hospital type [community or teaching], annual obstetric volume). Hospital type, obstetric volume, payment source, and birth year were classified using hospital discharge data. Other variables were classified using vital records.

We calculated crude and adjusted odds ratios comparing elective labor induction

in each individual week (37-41) to expectant management, stratifying by parity (nulliparous, parous). Specifically, each model compared electively induced deliveries during the given week to all deliveries in later weeks. In each model, spontaneous and medically indicated deliveries that occurred during the index week were excluded. We assessed additive and multiplicative interaction between elective labor induction and obesity class using the Relative Excess Risk of Interaction[263] and likelihood ratio tests ($p<0.20$), respectively. In supplementary analyses of shoulder dystocia and brachial plexus injury, we restricted our sample to vaginal deliveries only.

In sensitivity analyses, we revised our list of indications for labor induction (see **Table 5-S1** [Supplemental Digital Content]). We added certain intrapartum complications to the list of indications (coagulation deficiency hemorrhage, amniotic infection, fetal distress with unspecified time of onset, and fetal heart rate abnormalities with unspecified time of onset) and removed others (placental abruption and fetal-maternal hemorrhage). These complications could either be medical indications for labor induction or consequences of labor induction, depending on their timing. In additional sensitivity analyses, we revised the expectant management group to: spontaneous deliveries during the index week plus all deliveries in later weeks.[145]

We used SAS Version 9.4 (Cary, NC) for data analysis. This study was approved by the Emory University Institutional Review Board, the California Committee for the Protection of Human Subjects, and the California Office for Statewide Health Planning and Development. Informed consent was not necessary due to the de-identified nature of the dataset.

RESULTS

Out of 2,622,927 California deliveries occurring between 2007-2011, we excluded 2,403,567 ineligible births, most of which had pre-pregnancy BMI <30 kg/m^2 (**Figure 5-1**). A total of 219,360 term deliveries to obese women remained eligible for analysis.

The frequencies of maternal sociodemographic characteristics varied by exposure status, gestational age, and parity (**Table 5-1**). Compared to expectantly managed obese women, electively induced obese women were less likely to deliver in a teaching hospital, more likely to deliver on a weekday, and more likely to have initiated prenatal care in the first trimester. Electively induced parous women were more likely to be non-Hispanic white and privately insured than expectantly managed parous women.

The frequencies of infant outcomes varied between electively induced and expectantly managed obese women (**Table 5-2**). Extended infant stay was more frequent among electively induced obese women at 37 weeks. Similarly, at 37 weeks, infant death was more common in electively induced than in expectantly managed obese parous women (0.4% versus 0.1%). In contrast, the frequencies of macrosomia, chorioamnionitis, and meconium aspiration syndrome were lower in electively induced than in expectantly managed obese women. Chorioamnionitis, RDS, and meconium aspiration syndrome increased slightly from 2007-2011, while macrosomia, shoulder dystocia, and infant death decreased modestly (data not shown).

We detected no multiplicative interaction between obesity class and elective labor induction. Crude odds ratios (ORs; **Table 5-S2** [Supplemental Digital Content]) were similar in magnitude to adjusted ORs (**Figures 5-2 and 5-3; Table 5-S3** [Supplemental Digital Content]).

Elective induction of labor was associated with increased odds of infant death at 37 weeks in obese parous women (adjusted OR [95% Confidence Interval {CI}]=3.48 [1.42, 8.50]; **Figure 5-2a**). The odds of infant death were also elevated at 38 weeks in obese nulliparas (adjusted OR=2.39 [95% CI 0.87, 6.59]). Adjusted ORs dropped below 1 at 39 weeks. Models for infant death did not converge at 37 weeks (nulliparas) or 41 weeks (either parity).

At 37 weeks' gestation, the odds of extended infant hospital stay were higher among offspring of electively induced, versus expectantly managed, obese women (e.g., among nulliparas, adjusted OR [95% CI]= 1.45 [0.99, 2.13]; **Figure 5-2b**). In contrast, the adjusted odds of extended infant stay were reduced in electively induced obese women at 39-40 weeks.

The adjusted odds of other neonatal complications were generally lower in electively induced than in expectantly managed obese women. Elective induction of labor between 37 and 40 weeks was associated with reduced odds of macrosomia among all obese women (**Figure 5-2c**). Elective induction at 41 weeks was also associated with reduced odds of macrosomia among obese nulliparous women. Associations were strongest at early gestational ages (e.g., in nulliparas, the adjusted OR [95% CI] increased from 0.12 [0.06, 0.23] at 37 weeks to 0.76 [0.65, 0.90] at 41 weeks). Additive interaction models suggested that elective induction is more strongly associated with reduced risk of macrosomia in classes 2 and 3 (versus class 1) obese nulliparas; however, some of these findings were imprecise (data not shown).

Elective labor induction between 38 and 41 weeks was associated with reduced odds of chorioamnionitis among obese nulliparous women. The association was most

strongly protective at 39 weeks (adjusted OR [95% CI]=0.56 [0.48, 0.67], **Figure 5-2d**). Among obese parous women, elective labor induction was associated with reduced odds of chorioamnionitis at 39 and 40 weeks (adjusted ORs [95% CIs] at 39 and 40 weeks were 0.62 [0.47, 0.81] and 0.57 [0.44, 0.74], respectively).

Elective labor induction was associated with reduced odds of meconium aspiration syndrome; adjusted ORs between 38 and 41 weeks ranged from 0.31 to 0.55 among obese nulliparous women and from 0.39 to 0.43 among obese parous women (**Figure 5-3a**). At 37-38 weeks' gestation, the odds of RDS were modestly elevated among infants of electively induced obese women (e.g., in nulliparas, adjusted OR [95% CI] for elective induction at 37 weeks versus expectant management= 1.26 [0.71, 2.24]; **Figure 5-3b**).

At 41 weeks' gestation, the odds of shoulder dystocia were higher among electively induced, versus expectantly managed, obese nulliparous women (adjusted OR=1.71 [95% CI 0.88, 3.33]; **Figure 5-3c**). In contrast, among obese parous women, elective induction between 38 and 40 weeks was associated with lower odds of shoulder dystocia. Results were not meaningfully different in analyses restricted to vaginal deliveries.

Models for brachial plexus injury did not converge among nulliparas at 37 or 41 weeks. At 39 weeks, the odds of brachial plexus injury were reduced among electively induced, versus expectantly managed, obese nulliparous women; however, the estimate was imprecise (adjusted OR [95% CI]=0.40 [0.12, 1.26]; **Figure 5-3d**). Elective induction of labor was associated with lower odds of brachial plexus injury at 40-41 weeks in obese parous women (adjusted OR [95% CI] at 40 weeks=0.46 [0.26, 0.83].

Conclusions were unaltered after restricting to vaginal deliveries.

Results were mostly unchanged in sensitivity analyses that accounted for the uncertain timing of fetal distress and other intrapartum complications (**Table 5-S4** [Supplemental Digital Content]). Elective labor induction became associated with reduced odds of RDS at 40 weeks (both parities) and 41 weeks (nulliparas only) in sensitivity analyses.

Most conclusions were not affected upon revising the expectant management group to include spontaneous deliveries during the current week (**Table 5-S5** [Supplemental Digital Content]). However, some associations between elective induction ≥40 weeks and infant outcomes no longer appeared protective in sensitivity analyses. In addition, among nulliparas, elective induction at 41 weeks became associated with slightly increased odds of macrosomia.

COMMENTS

In this study, elective induction of labor <39 weeks was associated with increased risk of infant mortality, RDS, and extended infant stay among offspring of obese women. At 37-38 weeks' gestation, the odds of infant death were more than doubled in offspring of electively induced, versus expectantly managed, obese women. In contrast, elective induction between 39 and 41 weeks was associated with reduced risk of neonatal morbidity and no added risk of infant mortality. The odds of macrosomia, chorioamnionitis, and meconium aspiration syndrome (both parities), as well as shoulder dystocia and brachial plexus injury (parous women only), were lower in electively induced than in expectantly managed obese women.

Additive interaction models suggested that elective induction may be more

beneficial in preventing macrosomia among classes 2 and 3 (versus class 1) obese nulliparas. We did not observe additive or multiplicative interaction for other infant outcomes. However, our study may lack the power to detect interaction between levels of obesity and elective labor induction for rare infant outcomes.

This is an extension of the analysis conducted by Lee et al., who examined obese women in the 2007 California Linked dataset.[187] Similarly to our analysis, Lee et al. found that term elective induction of labor was associated with reduced risks of macrosomia and chorioamnionitis among offspring of obese women.[187] With five years' data (2007-2011), we were able to newly document both increased risk of infant death, RDS, and extended stay for deliveries <39 weeks, as well as several significant protective associations between elective labor induction and other major infant complications (e.g., meconium aspiration syndrome and brachial plexus injury). Additionally, we evaluated elective induction at 41 weeks' gestation.

Schuster et al. reported that a clinical protocol to induce obese women by their estimated due date slightly reduced neonatal intensive care unit (NICU) *length* of stay.[239] These findings have parallels to our study, in which eIOL ≥39 weeks was associated with reduced odds of extended infant stay. Schuster et al.'s clinical protocol was also associated with a slight increase in NICU *admission*, although these findings were not specific to obese women.[239] This clinical protocol was tested in a single healthcare system, and analysis was limited to-proxy indicators of neonatal morbidity (e.g., APGAR score, NICU admission).[239]

Similarly to our results showing a reduced risk of macrosomia among offspring of electively induced obese women, a small hospital-based study of obese nulliparas

reported lower mean birthweight among infants of electively induced women at 39-40 weeks' gestation.[240] However, unlike Wolfe et al.'s study,[240] who also reported higher risk of NICU admission and neonatal morbidity, we found that elective induction was associated with reduced neonatal morbidity at 39-40 weeks. Several factors may explain these differing results. Wolfe et al. assessed different neonatal morbidity outcomes than we did. They also combined all elective inductions in weeks 39-40.[240] In contrast, we evaluated elective induction separately at each term gestational week. Thus, our method may more closely represent "real-time" obstetric-decision making.

Elective induction of labor may prevent infant complications that increase with gestational age, such as macrosomia[145,187] and meconium aspiration syndrome.[188] Reduced risk of macrosomia may drive the observed reduction in shoulder dystocia, brachial plexus injury, and extended infant stay among electively induced women in our study. Elective induction may also prevent premature rupture of membranes, and consequently, chorioamnionitis.[208] However, fetal lung maturity may be compromised by delivering before 39 weeks' gestation.[193] This may explain the elevated odds of infant death and RDS that we observed at early term gestations.

Our study has many strengths. We included a large sample size of almost 220,000 deliveries. This allowed us to examine rare outcomes, including infant mortality, which were not previously evaluated. Our analysis also produced more precise estimates than prior investigations. We used expectant management as the comparison group. Many prior studies of obstetric decision-making have compared elective labor induction to spontaneous labor. However, spontaneous labor is not a true clinical management option, as it is not under a physician's control. In contrast, expectant management is a valid

clinical alternative to labor induction. Thus, it is a more appropriate comparison group in studies of obstetric decision-making.[183] Another strength is our comparison of elective labor induction to expectant management for each week of term gestation, unlike some previous analyses. In contrast to earlier studies, we assessed elective labor induction at 41 weeks' gestation. In addition, we used both hospital discharge data and vital records to classify medical complications. This increases the sensitivity of detection, while only negligibly impacting specificity, compared to using either data source alone.[258-260] Our dataset is large, diverse, and population-based with high rates of record linkage.[257] Finally, we tested the robustness of our assumptions in several sensitivity analyses.

Limitations in this study included inability to evaluate stillbirth, as all fetal deaths were excluded during sample selection due to preexisting maternal conditions or missing data. Our results may only be generalizable to obese Californian women without preexisting disease. There could be residual confounding in our study, as our dataset did not contain information on factors such as cervical status,[241] maternal discomfort,[193] or provider preferences.[193] Electively induced women may be healthier than expectantly managed women[145] (e.g., electively induced women in our study were more likely than expectantly managed women to initiate prenatal care in the first trimester). Under this scenario, protective associations could be biased away from the null.[145] However, we adjusted for first-trimester prenatal care initiation, obesity class, maternal age, and other health-related factors in multivariable models. Finally, although medical complications may be underreported in administrative data, linked datasets are accurate for many complications and procedures.[258-260]

Our findings agree with current recommendations against elective delivery <39

weeks' gestation.[193] Additional research using larger sample sizes of morbidly obese women may help determine whether a uniform policy on elective induction is appropriate for all obese women. In addition, future studies should consider utilizing a randomized, controlled trial design to reduce unobserved confounding. Future analyses of stillbirth are also essential. In conclusion, elective labor induction between 39 and 41 weeks' gestation may be an effective method to reduce neonatal morbidity among offspring of obese women.

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See next page for tables and figures.

Table 5-1. Frequencies of Maternal Characteristics among Electively Induced and Expectantly Managed Obese Women, Stratified by Parity[a]										
Nulliparous women (N=83,534)										
	37 weeks		**38 weeks**		**39 weeks**		**40 weeks**		**41 weeks**	
Maternal characteristic	**Elective Induction (N=496)**	**Expectant Management (N=77,984)**	**Elective Induction (N=1,616)**	**Expectant Management (N=65,333)**	**Elective Induction (N=3,942)**	**Expectant Management (N=40,667)**	**Elective Induction (N=7,061)**	**Expectant Management (N=12,453)**	**Elective Induction (N=4,961)**	**Expectant Management (N=967)**
Obesity class										
1 (BMI 30.0-<35.0 kg/m^2) (%)	63.7	64.7	63.4	64.5	64.8	63.5	64.3	61.9	62.0	60.8
2 (BMI 35.0-<40.0 kg/m^2) (%)	26.2	23.5	24.1	23.6	23.5	24.1	23.9	24.8	24.8	24.5
3 (BMI ≥40.0 kg/m^2) (%)	10.1	11.8	12.6	11.9	11.7	12.4	11.8	13.4	13.3	14.7
Maternal age, years										
<20 (%)	16.5	17.2	17.0	17.3	17.6	16.9	17.1	15.9	15.4	16.4
20-24 (%)	31.7	36.0	36.2	36.0	37.3	36.1	38.6	35.1	35.2	37.5
25-29 (%)	29.4	26.0	27.3	26.0	26.6	25.9	25.0	26.0	26.3	24.4
30-34 (%)	15.9	14.1	13.7	14.2	12.5	14.7	13.5	15.7	16.2	14.7
35-39 (%)	5.2	5.5	4.8	5.4	4.7	5.4	4.7	5.9	5.5	5.4
≥40 (%)	1.2	1.2	1.0	1.1	1.3	1.1	1.0	1.3	1.3	1.6
Race/ethnicity										
Asian/Pacific Islander (%)	3.4	4.1	4.3	4.0	4.1	3.7	3.3	3.3	3.0	2.9
Hispanic (all races) (%)	59.5	56.5	55.9	56.3	56.1	55.0	57.9	50.3	48.7	48.2
Non-Hispanic Black (%)	6.7	7.4	7.3	7.4	5.6	7.7	6.4	8.1	8.2	8.6
Non-Hispanic White (%)	27.8	28.7	30.1	29.1	30.9	30.3	29.2	34.9	36.9	37.1
Other (%)	2.6	3.2	2.4	3.3	3.2	3.4	3.2	3.4	3.1	3.2
Maternal education										
Less than high school (%)	17.7	18.7	18.1	18.5	18.1	18.3	18.2	17.4	15.8	19.8
High school (%)	31.9	33.0	33.7	33.0	34.7	32.5	34.0	31.6	31.7	30.3

Some college (%)	33.3	31.3	33.2	31.2	31.8	31.7	32.0	32.1	33.1	32.5
≥4-year college degree (%)	17.1	17.1	14.9	17.3	15.5	17.5	15.8	18.9	19.4	17.5
Payer for maternal delivery										
Private (%)	47.6	47.6	45.6	47.6	46.3	48.0	44.8	50.2	53.8	45.0
Public/none (%)	52.4	52.4	54.4	52.4	53.7	52.0	55.2	49.8	46.2	55.0
First trimester prenatal care initiation										
Yes (%)	84.5	82.5	83.5	82.2	85.1	81.2	82.0	78.7	80.0	73.0
No (%)	15.5	17.5	16.5	17.8	14.9	18.8	18.0	21.3	20.0	27.0
Year of delivery										
2007 (%)	22.4	18.4	22.9	18.3	18.8	18.9	19.5	19.1	18.6	24.2
2008 (%)	21.6	19.6	24.7	19.3	20.5	19.6	20.4	19.6	19.4	18.3
2009 (%)	20.0	20.8	20.4	20.9	21.0	20.1	19.7	20.5	20.7	21.0
2010 (%)	19.8	20.7	17.2	20.8	19.5	21.0	20.7	20.2	20.0	18.2
2011 (%)	16.3	20.5	14.8	20.7	20.1	20.4	19.6	20.6	21.4	18.3
Weekday birth										
Yes (%)	76.6	75.4	76.9	75.5	78.7	75.7	79.3	75.7	76.8	72.6
No (%)	23.4	24.6	23.1	24.5	21.3	24.3	20.7	24.3	23.2	27.4
Delivery at teaching hospital										
Yes (%)	8.3	8.9	5.7	9.0	4.9	9.5	5.8	10.9	9.7	11.3
No (%)	91.7	91.1	94.3	91.0	95.1	90.5	94.2	89.1	90.3	88.7
Obstetric volume, deliveries/year										
<1200 (%)	9.7	11.9	10.7	11.9	12.0	12.2	10.1	13.4	11.8	20.2
1200- <2400 (%)	30.4	28.9	29.7	28.9	28.7	29.5	28.8	29.0	27.3	29.0
2400- <3600 (%)	28.0	28.0	32.3	27.8	30.6	27.6	29.9	27.1	28.4	24.3
≥3600 (%)	31.9	31.2	27.3	31.4	28.7	30.7	31.2	30.4	32.5	26.6
Parous women (N=135,826)										

Maternal characteristic	Elective Induction (N=1,130)	Expectant Management (N=125,849)	Elective Induction (N=3,862)	Expectant Management (N=100,642)	Elective Induction (N=9,626)	Expectant Management (N=54,427)	Elective Induction (N=10,748)	Expectant Management (N=12,826)	Elective Induction (N=4,948)	Expectant Management (N=961)
Obesity class										
1 (BMI 30.0-<35.0 kg/m^2) (%)	63.8	65.3	63.7	65.2	63.5	64.4	63.4	62.5	61.2	61.4
2 (BMI 35.0-<40.0 kg/m^2) (%)	24.5	23.3	23.7	23.3	23.8	24.0	24.2	24.7	25.6	23.9
3 (BMI ≥40.0 kg/m^2) (%)	11.7	11.4	12.6	11.4	12.6	11.6	12.4	12.8	13.2	14.7
Maternal age, years										
<20 (%)	2.3	2.5	1.7	2.5	1.9	2.5	2.0	2.4	2.3	2.4
20-24 (%)	20.1	21.5	20.3	21.5	20.5	21.7	21.1	22.1	20.9	24.3
25-29 (%)	34.6	33.8	34.5	33.9	34.2	34.0	34.0	33.8	34.4	35.3
30-34 (%)	26.1	26.8	27.7	26.7	27.2	26.8	27.0	26.8	27.6	25.2
35-39 (%)	13.9	12.7	13.0	12.7	13.5	12.4	13.1	12.0	12.0	10.5
≥40 (%)	3.0	2.8	2.7	2.7	2.8	2.6	2.8	2.8	2.7	2.3
Race/ethnicity										
Asian/Pacific Islander (%)	2.6	3.7	3.0	3.6	3.1	3.4	3.1	3.6	3.2	4.2
Hispanic (all races) (%)	65.4	67.6	60.3	67.5	59.9	66.9	64.4	63.2	62.1	61.1
Non-Hispanic Black (%)	6.5	6.0	5.5	6.0	5.2	6.2	5.6	6.7	6.5	8.0
Non-Hispanic White (%)	23.6	20.4	28.6	20.6	28.8	21.1	24.3	23.9	25.7	23.6
Other (%)	1.9	2.4	2.5	2.4	3.0	2.4	2.6	2.6	2.5	3.1
Maternal education										
Less than high school (%)	31.6	32.8	27.8	32.7	24.8	33.4	30.0	33.3	30.4	36.8
High school (%)	31.8	31.7	30.6	31.8	33.6	31.3	31.7	31.2	32.0	29.0
Some college (%)	28.7	26.0	30.4	25.9	30.7	25.7	28.2	25.7	27.6	26.2
≥4-year college degree (%)	8.0	9.5	11.2	9.6	10.9	9.6	10.0	9.7	10.0	7.9

Payer for maternal delivery										
Private (%)	36.3	37.8	42.9	37.8	43.0	37.3	39.2	37.3	41.8	28.8
Public/none (%)	63.7	62.2	57.1	62.2	57.0	62.7	60.8	62.7	58.2	71.2
First trimester prenatal care initiation										
Yes (%)	83.5	80.1	82.7	79.7	83.5	77.8	79.8	73.1	75.1	63.1
No (%)	16.5	19.9	17.3	20.3	16.5	22.2	20.2	26.9	24.9	36.9
Year of delivery										
2007 (%)	23.4	19.5	24.0	19.4	18.4	20.5	20.1	21.5	20.5	27.2
2008 (%)	23.9	20.2	25.1	19.9	19.5	20.5	21.0	20.7	20.8	21.0
2009 (%)	21.5	20.2	21.3	20.3	20.3	19.7	20.1	19.4	19.2	17.6
2010 (%)	16.9	20.0	17.7	20.1	20.4	19.8	20.1	19.3	19.6	18.6
2011 (%)	14.3	20.1	11.9	20.3	21.5	19.6	18.7	19.1	19.9	15.6
Weekday birth										
Yes (%)	79.1	76.8	82.5	76.8	83.0	77.0	82.4	77.4	79.9	76.5
No (%)	20.9	23.2	17.5	23.2	17.0	23.0	17.6	22.6	20.1	23.5
Delivery at teaching hospital										
Yes (%)	8.5	9.3	5.2	9.3	4.3	10.2	6.2	12.4	11.1	11.0
No (%)	91.5	90.7	94.8	90.7	95.7	89.8	93.8	87.6	88.9	89.0
Obstetric volume, deliveries/year										
<1200 (%)	11.2	12.6	14.3	12.5	14.8	12.5	12.6	12.6	10.8	17.9
1200- <2400 (%)	31.8	29.3	29.7	29.3	29.5	30.3	28.6	29.9	27.9	32.3
2400- <3600 (%)	29.2	27.9	30.3	27.8	29.2	27.5	30.0	27.7	29.5	27.2
≥3600 (%)	27.8	30.2	25.7	30.4	26.5	29.7	28.8	29.7	31.8	22.7

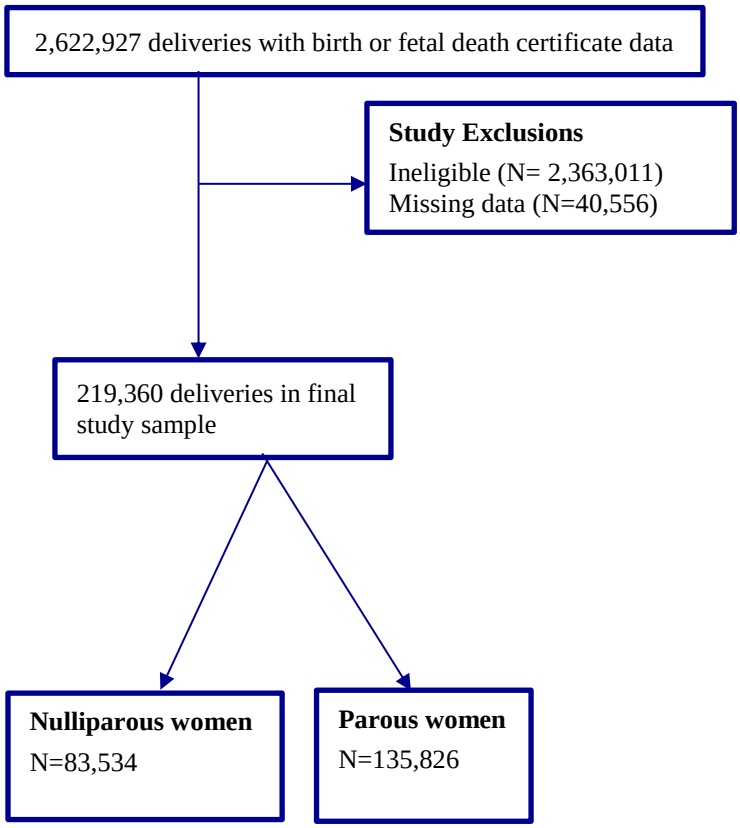
[a]Elective Induction, elective induction of labor. Table data are percentages (%) within exposure categories.

Table 5-2. Distribution of Infant Outcomes among Electively Induced and Expectantly Managed Obese Women[a]										
Nulliparous women (N=83,534)										
	37 weeks		**38 weeks**		**39 weeks**		**40 weeks**		**41 weeks**	
Outcome	**Elective Induction (N=496)**	**Expectant Management (N=77,984)**	**Elective Induction (N=1,616)**	**Expectant Management (N=65,333)**	**Elective Induction (N=3,942)**	**Expectant Management (N=40,667)**	**Elective Induction (N=7,061)**	**Expectant Management (N=12,453)**	**Elective Induction (N=4,961)**	**Expectant Management (N=967)**
Infant death (%)	0.0	0.1	0.2	0.1	0.0	0.1	0.1	0.1	0.1	0.0
Infant stay >5 days (%)[b]	5.6	3.9	3.1	3.9	3.2	4.2	3.7	4.5	3.8	5.3
Macrosomia (≥4000 g) (%)	1.6	12.0	7.1	13.3	9.3	15.9	14.5	20.4	20.7	25.1
Chorioamnionitis (%)	5.2	5.9	3.7	6.2	3.8	6.9	5.0	8.3	7.9	9.4
Meconium aspiration syndrome (%)	0.2	0.7	0.2	0.8	0.5	1.0	0.4	1.3	0.9	2.0
Respiratory distress (%)	2.4	2.0	2.4	2.0	1.9	2.2	1.9	2.4	2.0	2.7
Shoulder dystocia (%)	1.6	1.4	1.4	1.4	1.6	1.4	1.6	1.4	1.8	1.0
Brachial plexus injury (%)	0.0	0.2	0.1	0.2	0.1	0.2	0.2	0.2	0.2	0.2
Parous women (N=135,826)										
	37 weeks		**38 weeks**		**39 weeks**		**40 weeks**		**41 weeks**	
Outcome	**Elective Induction (N=1,130)**	**Expectant Management (N=125,849)**	**Elective Induction (N=3,862)**	**Expectant Management (N=100,642)**	**Elective Induction (N=9,626)**	**Expectant Management (N=54,427)**	**Elective Induction (N=10,748)**	**Expectant Management (N=12,826)**	**Elective Induction (N=4,948)**	**Expectant Management (N=961)**
Infant death (%)	0.4	0.1	0.2	0.1	0.1	0.1	0.1	0.1	0.1	0.2
Infant stay >5 days (%)[b]	2.5	1.7	1.7	1.7	1.2	1.7	1.4	1.7	1.6	1.5
Macrosomia (≥4000 g) (%)	5.4	15.1	9.7	17.0	13.7	20.7	20.1	26.4	27.1	28.1
Chorioamnionitis (%)	0.9	0.9	0.7	0.9	0.6	1.1	0.8	1.5	1.6	1.0
Meconium aspiration syndrome (%)	0.2	0.3	0.1	0.3	0.2	0.4	0.2	0.6	0.4	1.1
Respiratory distress (%)	1.3	1.1	1.4	1.1	1.1	1.1	1.1	1.4	1.1	1.5
Shoulder dystocia (%)	1.7	2.2	1.6	2.4	2.1	2.9	2.8	3.6	3.8	4.3

Brachial plexus injury (%)	0.3	0.2	0.1	0.2	0.2	0.2	0.2	0.3	0.2	0.7

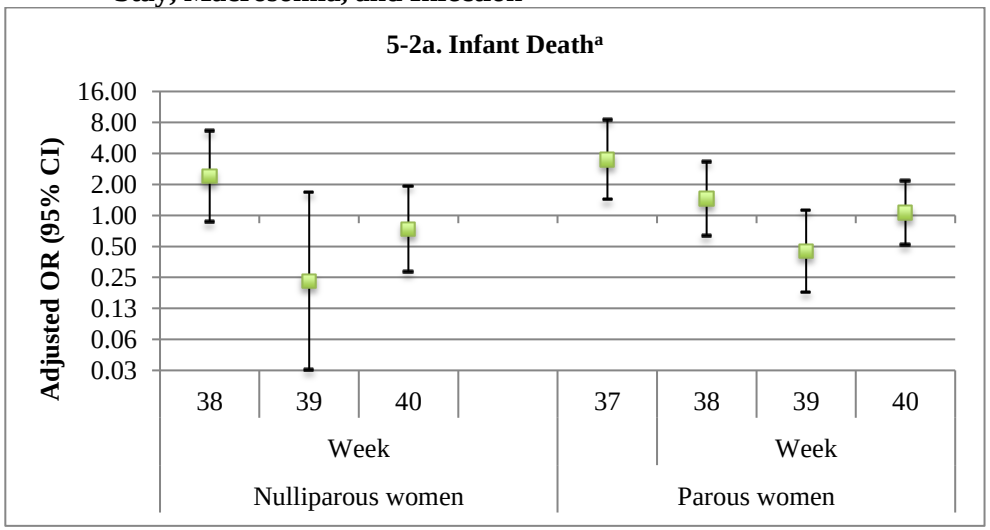
[a]All frequencies were calculated among the entire sample (all deliveries).
[b]N=21 nulliparous women and N=27 parous women were missing data on length of infant stay.

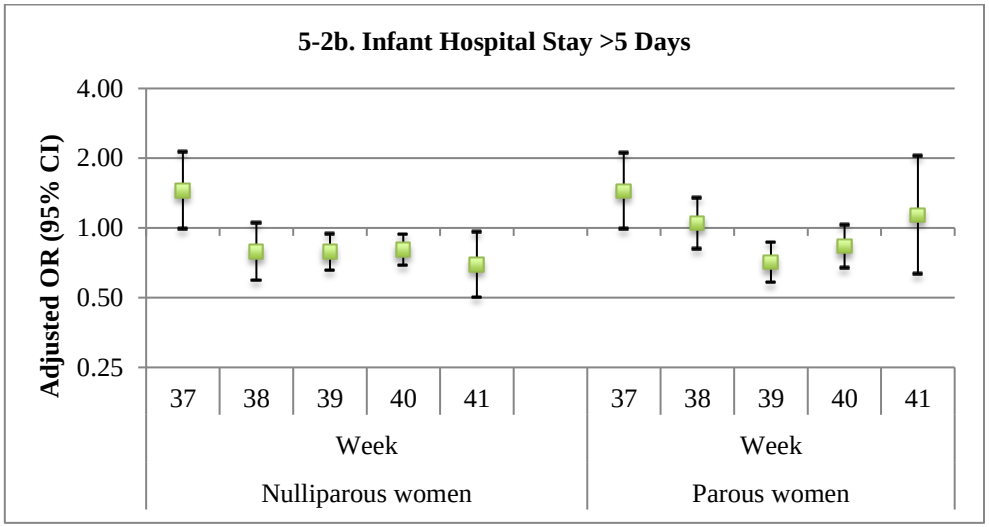
Figure 5-1. Study Exclusion Criteria[a]

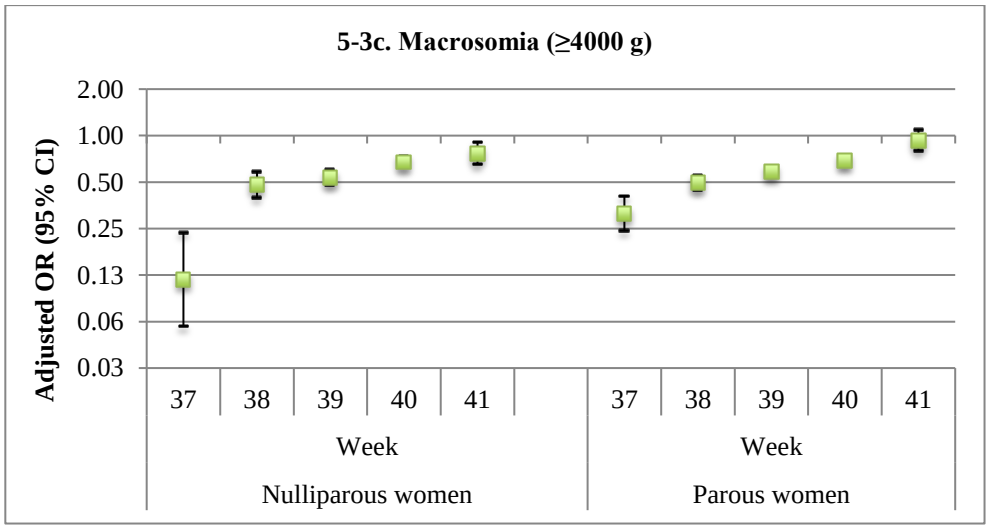


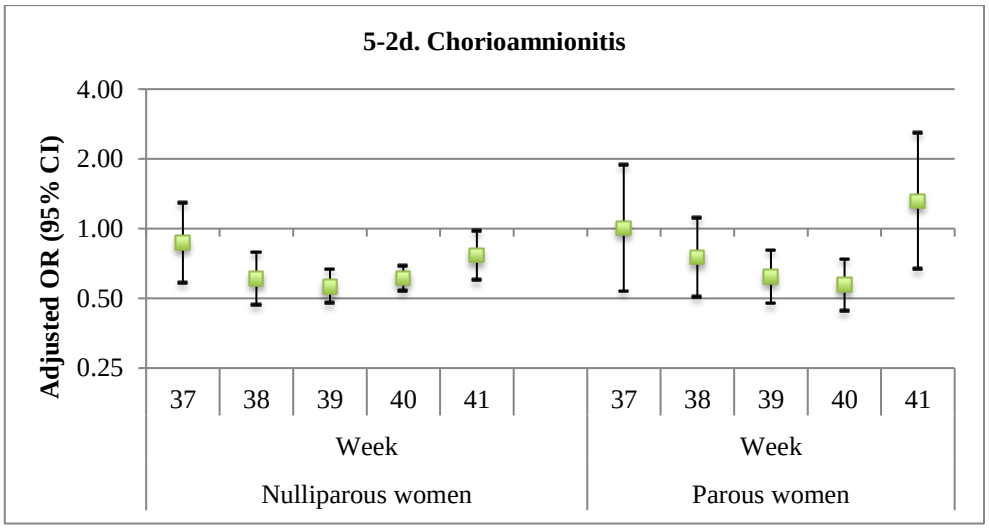
Description: This flow chart shows the exclusion criteria for our study.
[a]These numbers (N) represent the number of women excluded due to study ineligibility (e.g., preexisting maternal conditions, birth defects, previous cesarean, multiple gesations) and missing data. Numbers do not overlap.

Figure 5-2. Adjusted Odds Ratios for Elective Labor Induction, as compared to Expectant Management, and Infant Mortality, Hospital Stay, Macrosomia, and Infection[a]







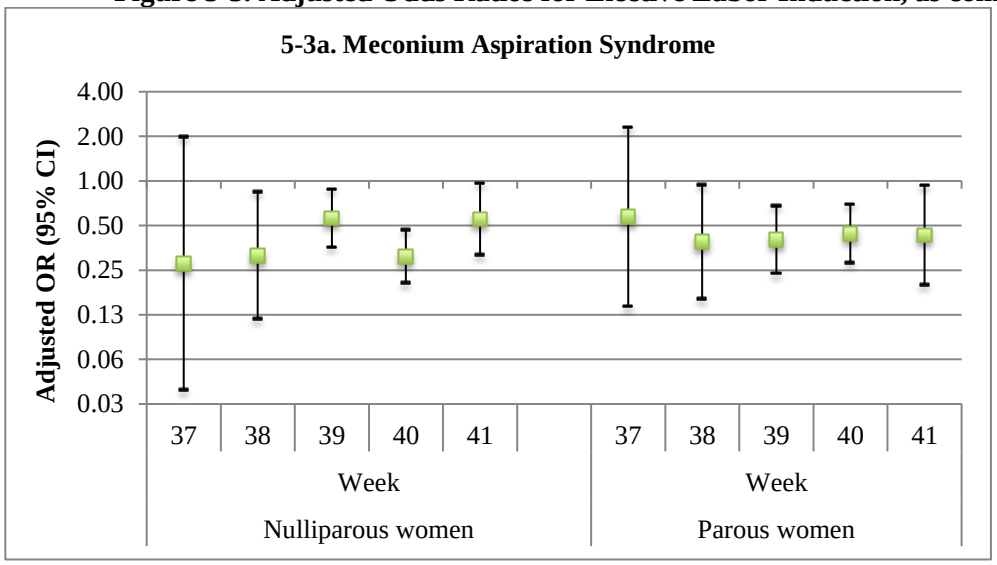


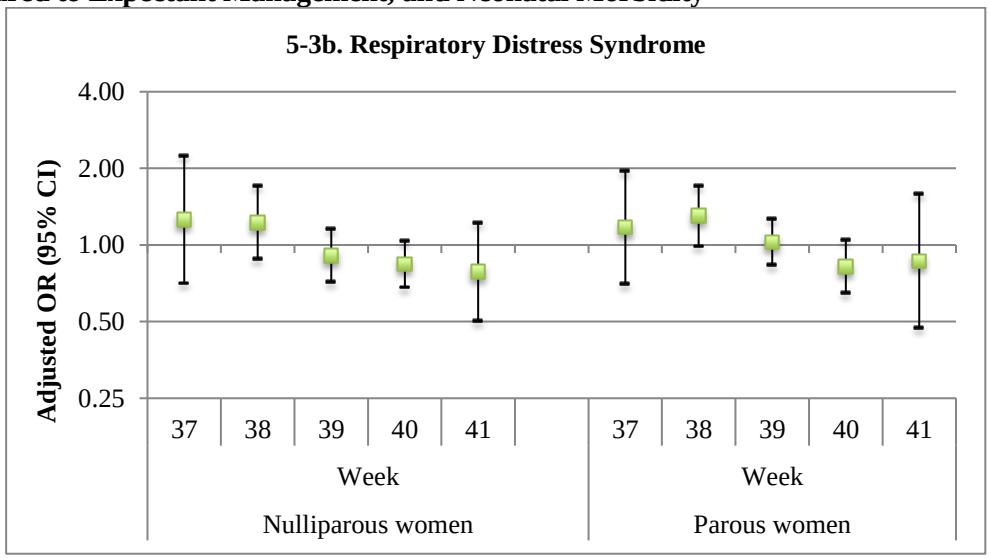
Description*:* Figures 5-2a through 5-2d display adjusted odds ratios, stratified by parity, for the associations between term elective induction of labor (versus expectant management) and infant mortality, infant hospital stay >5 days, macrosomia, and chorioamnionitis among obese women. OR, Odds Ratio; CI, Confidence Interval.

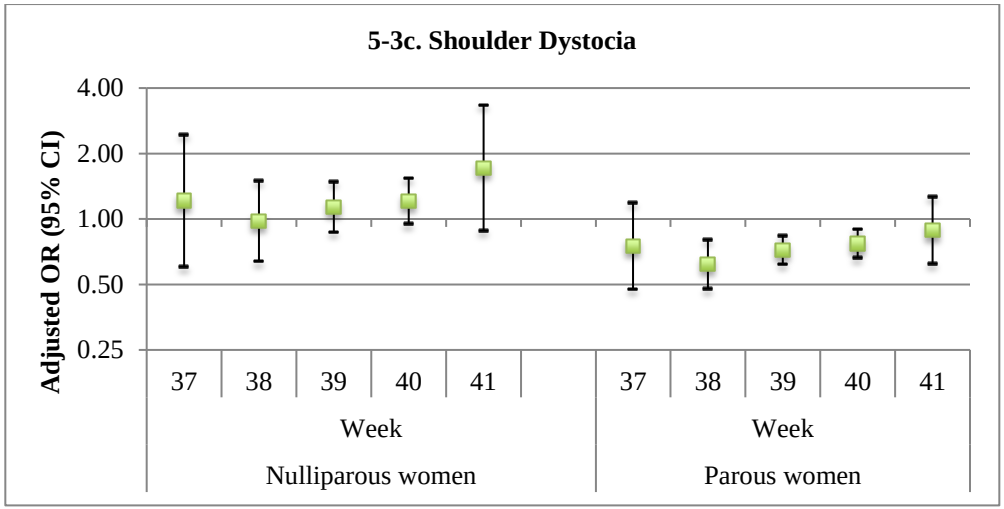
[a]Models were adjusted for maternal sociodemographic characteristics (age, race/ethnicity, education, obesity severity, payment source for delivery, first-trimester prenatal care initiation), delivery characteristics (weekday delivery, birth year), and hospital characteristics (hospital type [community or teaching], annual obstetric volume).

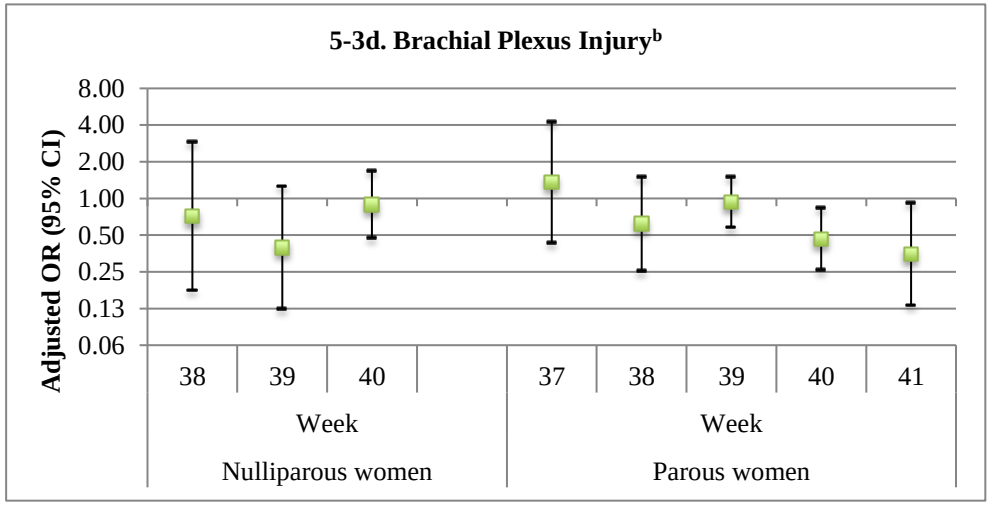
[b]Models for infant death did not converge at 37 weeks (nulliparas) or 41 weeks (either parity).

Figure 5-3. Adjusted Odds Ratios for Elective Labor Induction, as compared to Expectant Management, and Neonatal Morbidity[a]









Description*:* Figures 5-3a through 5-3d display adjusted odds ratios, stratified by parity, for the associations between term elective induction of labor (versus expectant management) and meconium aspiration syndrome, respiratory distress syndrome, shoulder dystocia, and brachial plexus injury. OR, Odds Ratio; CI, Confidence Interval.

[a]Models were adjusted for maternal sociodemographic characteristics (age, race/ethnicity, education, obesity severity, payment source for delivery, first-trimester prenatal care initiation), delivery characteristics (weekday delivery, birth year), and hospital characteristics (hospital type [community or teaching], annual obstetric volume).

[b]Models for brachial plexus injury did not converge among nulliparas at 37 or 41 weeks.

Table 5-S1. Indications for Induction of Labor[a]

Condition	**ICD-9 code**
HIV	042, 079.53, V08
Coagulation disorders	286.0, 286.1, 286.2, 286.3, 286.4, 286.5, 286.7
Placenta previa	641.0,[b] 641.1,[b] 762.0[b]
Vasa previa	663.5[b]
Placental abruption	641.2,[c] 762.1[c]
Antepartum hemorrhage	641.8, 641.9
Preexisting hypertension	401,[b] 402,[b] 403,[b] 404,[b] 405,[b] 642.0,[b] 642.1,[b] 642.2,[b] 642.7[b]
Gestational hypertension	642.3
Preeclampsia/eclampsia	642.4, 642.5, 642.6, 642.7
Other hypertension	437.2, 642.9, 760.0
Liver/biliary tract disorder	570, 571.1, 571.2,[b] 571.5,[b] 571.6,[b] 572.2,[b] 572.4,[b] 646.7
Diabetes mellitus (preexisting or gestational)	249,[b] 250,[b] 357.2,[b] 362.0,[b] 648.0,[b] 648.8,[b] 775.0[b]
Renal disease	403,[b] 404,[b] 580, 581,[b] 582,[b] 583, 584, 585,[b] 586, 587, 642.1,[b] 646.2, V42.0[b]
Cardiovascular disease	394,[b] 395,[b] 396,[b] 397,[b] 398,[b] 402,[b] 404,[b] 410, 411, 412,[b] 413,[b] 414.0,[b] 414.1, 414.2,[b]

	414.3,[b] 414.4,[b] 414.8,[b] 414.9,[b] 415, 416,[b] 417.0,[b] 417.1, 417.8,[b] 417.9,[b] 420, 421, 422, 423,[b] 424,[b] 425,[b] 426,[b] 427.0,[b] 427.1,[b] 427.2,[b] 427.3,[b] 427.4,[b] 427.5, 427.6,[b] 427.8,[b] 427.9,[b] 428, 648.5,[b] 648.6,[b] 760.3[b]
Multiple gestations	651,[b] 652.6,[b] 761.5[b]
Major fetal abnormality	653.6,[b] 655.0,[b] 655.1,[b] 740.0,[b] 740.1,[b] 740.2,[b] 741.0,[b] 741.9,[b] 742.0,[b] 742.2,[b] 742.3,[b] 742.1,[b] 743.0,[b] 743.1,[b] 743.2,[b] 743.3[0,1,2,3,4],[b] 743.45,[b] 744.0,[b] 744.01[b],744.23[b] 745.0,[b] 745.1,[b] 745.2,[b] 745.3,[b] 746.01,[b] 746.02,[b] 746.1,[b] 746.2,[b] 746.3,[b] 746.7,[b] 747.0,[b] 747.10,[b] 747.41,[b] 748.0,[b] 748.5[b]
Fetal-maternal hemorrhage	656.0,[c] 772.0[c]
Isoimmunization	656.1, 656.2, 773.0,[b] 773.1, 773.2,[b] 773.3[b]
Intrauterine death	656.4,[d] 768.0,[d] V27.1[d]
Poor fetal growth	656.5, 764.0, 764.1, 764.9
Polyhydramnios	657.0, 761.3
Oligohydramnios	658.0, 761.2
Premature rupture of membranes	658.1, 761.1
Fetal distress or fetal heart rate abnormality <u>before</u> onset of labor	768.2, 763.81

Pregnancy with poor reproductive history	V23.5
Other fetal conditions affecting management of mother	655.3, 655.4, 655.5, 655.6, 655.8
Indications in sensitivity analysis only	
Fetal distress or fetal heart rate abnormality with unspecified time of onset	656.3, 659.7, 763.83, 768.4
Coagulation deficiency hemorrhage	641.31, 649.3
Amniotic infection/chorioamnionitis	658.41, 762.7

[a]We used vital records and hospital discharge data ICD-9 codes to classify indications. An indication was classified as present if detected in vital records or hospital discharge data.
[b]Considered an exclusion criteria for our study.
[c]Not classified as an indication in a sensitivity analysis that accounted for the uncertain timing of intrapartum complications.
[d]All stillbirths were excluded from this study due to exclusion criteria or missing data.

Table 5-S2. Crude Odds Ratios for Elective Induction of Labor versus Expectant Management and Infant Outcomes [a]					
Nulliparous women (N=83,534)					
Outcome	**Elective Induction, 37 weeks (N=496) vs. Expectant Management (N=77,984)**	**Elective Induction, 38 weeks (N=1,616) vs. Expectant Management (N=65,333)**	**Elective Induction, 39 weeks (N=3,942) vs. Expectant Management (N=40,667)**	**Elective Induction, 40 weeks (N=7,061) vs. Expectant Management (N=12,453)**	**Elective Induction, 41 weeks (N=4,961) vs. Expectant Management (N=967)**
Infant Death	0.00 (0.00, Infinity)	2.45 (0.89, 6.74)	0.21 (0.03, 1.56)	0.71 (0.27, 1.82)	71652.20 (0.00, 3.45E+235)
Infant stay >5 days[b]	1.46 (1.00, 2.14)	0.79 (0.59, 1.04)	0.77 (0.64, 0.93)	0.81 (0.70, 0.94)	0.71 (0.52, 0.97)
Macrosomia (≥4000 g)	0.12 (0.06, 0.24)	0.49 (0.41, 0.60)	0.54 (0.48, 0.61)	0.66 (0.61, 0.72)	0.78 (0.66, 0.92)
Chorioamnionitis	0.88 (0.59, 1.30)	0.59 (0.45, 0.76)	0.54 (0.45, 0.63)	0.58 (0.51, 0.66)	0.83 (0.65, 1.05)
Meconium aspiration syndrome	0.27 (0.04, 1.93)	0.30 (0.11, 0.80)	0.52 (0.33, 0.81)	0.29 (0.19, 0.44)	0.46 (0.27, 0.78)
Respiratory distress	1.23 (0.69, 2.19)	1.18 (0.85, 1.63)	0.86 (0.67, 1.09)	0.79 (0.65, 0.98)	0.75 (0.49, 1.16)
Shoulder dystocia[c]	1.19 (0.59, 2.40)	0.98 (0.64, 1.51)	1.11 (0.85, 1.45)	1.16 (0.92, 1.47)	1.77 (0.92, 3.41)
Shoulder dystocia[d]	1.08 (0.54, 2.19)	0.89 (0.57, 1.37)	1.03 (0.78, 1.35)	1.08 (0.84, 1.38)	1.54 (0.79, 2.98)
Brachial plexus injury[c]	0.00 (0.00, Infinity)	0.73 (0.18, 2.95)	0.40 (0.13, 1.27)	0.94 (0.50, 1.77)	1.17 (0.26, 5.24)
Brachial plexus injury[d]	0.00 (0.00, I)	0.69 (0.17, 2.80)	0.40 (0.12, 1.26)	0.84 (0.44, 1.61)	1.09 (0.24, 4.87)
Parous women (N=135,826)					
Outcome	**Elective Induction, 37 weeks (N=1,130) vs. Expectant Management (N=125,849)**	**Elective Induction, 38 weeks (N=3,862) vs. Expectant Management (N=100,642)**	**Elective Induction, 39 weeks (N=9,626) vs. Expectant Management (N=54,427)**	**Elective Induction, 40 weeks (N=10,748) vs. Expectant Management (N=12,826)**	**Elective Induction, 41 weeks (N=4,948) vs. Expectant Management (N=961)**

Infant death	3.49 (1.43, 8.52)	1.44 (0.63, 3.27)	0.48 (0.19, 1.19)	1.12 (0.55, 2.26)	0.49 (0.09, 2.50)
Infant stay >5 days[b]	1.45 (0.99, 2.11)	1.00 (0.77, 1.28)	0.67 (0.55, 0.82)	0.82 (0.66, 1.01)	1.07 (0.60, 1.90)
Macrosomia (≥4000 g)	0.32 (0.25, 0.41)	0.53 (0.47, 0.59)	0.61 (0.57, 0.65)	0.70 (0.66, 0.74)	0.95 (0.82, 1.11)
Chorioamnionitis	0.98 (0.52, 1.83)	0.72 (0.49, 1.07)	0.60 (0.46, 0.78)	0.55 (0.43, 0.71)	1.52 (0.79, 2.95)
Meconium aspiration syndrome	0.57 (0.14, 2.31)	0.38 (0.16, 0.92)	0.38 (0.23, 0.65)	0.42 (0.27, 0.65)	0.35 (0.17, 0.73)
Respiratory distress	1.20 (0.72, 2.01)	1.29 (0.98, 1.69)	0.99 (0.81, 1.22)	0.81 (0.64, 1.02)	0.76 (0.42, 1.37)
Shoulder dystocia[c]	0.76 (0.48, 1.19)	0.64 (0.49, 0.82)	0.73 (0.63, 0.84)	0.75 (0.65, 0.87)	0.88 (0.62, 1.24)
Shoulder dystocia[d]	0.74 (0.47, 1.17)	0.63 (0.49, 0.82)	0.72 (0.62, 0.83)	0.75 (0.64, 0.87)	0.85 (0.60, 1.20)
Brachial plexus injury[c]	1.38 (0.44, 4.31)	0.63 (0.26, 1.53)	0.94 (0.59, 1.51)	0.46 (0.26, 0.83)	0.33 (0.13, 0.84)
Brachial plexus injury[d]	1.34 (0.43, 4.20)	0.62 (0.25, 1.50)	0.93 (0.58, 1.49)	0.46 (0.26, 0.81)	0.32 (0.13, 0.82)

[a]Table data are crude odds ratios (95% confidence intervals).

[b]N=21 nulliparous women and N=27 parous women were missing data on length of infant stay.

[c]Among all deliveries.

[d]Among vaginal deliveries only.

Table 5-S3. Adjusted Odds Ratios for Elective Induction of Labor versus Expectant Management and Infant Outcomes [a]					
Nulliparous women (N=83,534)					
Outcome	**Elective Induction, 37 weeks (N=496) vs. Expectant Management (N=77,984)**	**Elective Induction, 38 weeks (N=1,616) vs. Expectant Management (N=65,333)**	**Elective Induction, 39 weeks (N=3,942) vs. Expectant Management (N=40,667)**	**Elective Induction, 40 weeks (N=7,061) vs. Expectant Management (N=12,453)**	**Elective Induction, 41 weeks (N=4,961) vs. Expectant Management (N=967)**
Infant Death	0.00 (0.00, Infinity)	2.39 (0.87, 6.59)	0.23 (0.03, 1.67)	0.73 (0.28, 1.92)	Did not converge
Infant stay >5 days[b]	1.45 (0.99, 2.13)	0.79 (0.59, 1.05)	0.79 (0.66, 0.95)	0.80 (0.69, 0.94)	0.69 (0.50, 0.96)
Macrosomia (≥4000 g)	0.12 (0.06, 0.23)	0.48 (0.40, 0.58)	0.53 (0.48, 0.60)	0.68 (0.62, 0.73)	0.76 (0.65, 0.90)
Chorioamnionitis	0.87 (0.58, 1.29)	0.61 (0.47, 0.79)	0.56 (0.48, 0.67)	0.61 (0.54, 0.69)	0.76 (0.60, 0.98)
Meconium aspiration syndrome	0.28 (0.04, 1.97)	0.31 (0.12, 0.84)	0.56 (0.36, 0.88)	0.31 (0.21, 0.47)	0.55 (0.32, 0.97)
Respiratory distress syndrome	1.26 (0.71, 2.24)	1.23 (0.88, 1.70)	0.91 (0.71, 1.16)	0.84 (0.68, 1.04)	0.78 (0.50, 1.22)
Shoulder dystocia[c]	1.21 (0.60, 2.44)	0.98 (0.64, 1.50)	1.13 (0.87, 1.48)	1.20 (0.95, 1.53)	1.71 (0.88, 3.33)
Shoulder dystocia[d]	1.09 (0.54, 2.21)	0.87 (0.56, 1.35)	1.04 (0.79, 1.37)	1.12 (0.87, 1.44)	1.48 (0.75, 2.90)
Brachial plexus injury[c]	0.00 (0.00, Infinity)	0.71 (0.18, 2.89)	0.40 (0.12, 1.26)	0.98 (0.47, 1.68)	Did not converge
Brachial plexus injury[d]	0.00 (0.00, Infinity)	0.66 (0.16, 2.66)	0.38 (0.12, 1.19)	0.77 (0.40, 1.48)	Did not converge
Parous women (N=135,826)					
Outcome	**Elective Induction, 37 weeks (N=1,130) vs. Expectant Management (N=125,849)**	**Elective Induction, 38 weeks (N=3,862) vs. Expectant Management (N=100,642)**	**Elective Induction, 39 weeks (N=9,626) vs. Expectant Management (N=54,427)**	**Elective Induction, 40 weeks (N=10,748) vs. Expectant Management (N=12,826)**	**Elective Induction, 41 weeks (N=4,948) vs. Expectant Management (N=961)**
Infant death	3.48 (1.42, 8.50)	1.45 (0.64, 3.31)	0.45 (0.18, 1.12)	1.05 (0.52, 2.16)	Did not converge
Infant stay >5 days[b]	1.44 (0.99, 2.10)	1.05 (0.81, 1.35)	0.71 (0.58, 0.87)	0.83 (0.67, 1.03)	1.14 (0.63, 2.04)
Macrosomia (≥4000 g)	0.31 (0.24, 0.40)	0.50 (0.44, 0.55)	0.58 (0.55, 0.62)	0.69 (0.65, 0.73)	0.93 (0.79, 1.09)
Chorioamnionitis	1.00 (0.54, 1.88)	0.75 (0.51, 1.11)	0.62 (0.47, 0.81)	0.57 (0.44, 0.74)	1.32 (0.67, 2.58)

Meconium aspiration syndrome	0.57 (0.14, 2.30)	0.39 (0.16, 0.94)	0.40 (0.24, 0.68)	0.44 (0.28, 0.70)	0.43 (0.20, 0.93)
Respiratory distress syndrome	1.17 (0.70, 1.96)	1.30 (0.99, 1.71)	1.03 (0.83, 1.26)	0.82 (0.65, 1.04)	0.87 (0.47, 1.59)
Shoulder dystocia[c]	0.75 (0.48, 1.18)	0.62 (0.48, 0.80)	0.72 (0.62, 0.84)	0.77 (0.66, 0.90)	0.89 (0.62, 1.26)
Shoulder dystocia[d]	0.73 (0.47, 1.16)	0.61 (0.47, 0.79)	0.71 (0.61, 0.82)	0.76 (0.66, 0.89)	0.86 (0.60, 1.22)
Brachial plexus injury[c]	1.36 (0.43, 4.25)	0.62 (0.26, 1.51)	0.94 (0.58, 1.51)	0.46 (0.26, 0.83)	0.35 (0.13, 0.92)
Brachial plexus injury[d]	1.33 (0.42, 4.15)	0.61 (0.25, 1.48)	0.91 (0.57, 1.48)	0.45 (0.25, 0.81)	0.33 (0.13, 0.88)

[a]Table data are adjusted odds ratios (95% confidence intervals). Models were adjusted for maternal age, maternal education, maternal race/ethnicity, initiation of prenatal care in the first trimester, principal source of payment for delivery, birth year, obesity class, weekday delivery, delivery at a teaching hospital, and hospital obstetric volume.
[b]N=21 nulliparous women and N=27 parous women were missing data on length of infant stay.
[c]Among all deliveries.
[d]Among vaginal deliveries only.

Table 5-S4. Adjusted Odds Ratios for Elective Labor Induction versus Expectant Management and Infant Outcomes, Accounting for Uncertain Timing of Intrapartum Indications[a,b]					
Nulliparous women (N=83,534)					
Outcome	**Elective Induction, 37 weeks (N=372) vs. Expectant Management (N= 77,984)**	**Elective Induction, 38 weeks (N=1,176) vs. Expectant Management (N= 65,333)**	**Elective Induction,39 weeks (N=2,912) vs. Expectant Management (N= 40,667)**	**Elective Induction, 40 weeks (N=4,965) vs. Expectant Management (N= 12,453)**	**Elective Induction, 41 weeks (N=3,232) vs. Expectant Management (N= 967)**
Infant Death	0.00 (0.00, Infinity)	2.53 (0.79, 8.07)	0.32 (0.04, 2.32)	0.89 (0.32, 2.50)	Did not converge
Infant stay >5 days[e]	1.31 (0.82, 2.08)	0.59 (0.40, 0.86)	0.63 (0.50, 0.80)	0.58 (0.47, 0.70)	0.48 (0.34, 0.69)
Macrosomia (≥4000 g)	0.08 (0.03, 0.21)	0.49 (0.39, 0.61)	0.52 (0.45, 0.59)	0.71 (0.64, 0.77)	0.80 (0.67, 0.95)
Meconium aspiration syndrome	0.38 (0.05, 2.70)	0.11 (0.02, 0.78)	0.46 (0.26, 0.82)	0.18 (0.10, 0.34)	0.27 (0.13, 0.54)
Respiratory distress syndrome	1.27 (0.65, 2.47)	0.93 (0.60, 1.44)	0.77 (0.57, 1.04)	0.61 (0.46, 0.79)	0.49 (0.29, 0.82)
Shoulder dystocia[c]	1.00 (0.41, 2.43)	0.97 (0.59, 1.60)	1.20 (0.89, 1.61)	1.29 (0.99, 1.69)	1.90 (0.96, 3.75)
Shoulder dystocia[d]	0.81 (0.34, 1.98)	0.83 (0.50, 1.36)	1.03 (0.76, 1.40)	1.08 (0.83, 1.42)	1.39 (0.70, 2.78)
Brachial plexus injury[c]	0.00 (0.00, Infinity)	0.50 (0.07, 3.57)	0.18 (0.02, 1.27)	0.75 (0.35, 1.62)	Did not converge
Brachial plexus injury[d]	0.00 (0.00, Infinity)	0.41 (0.06, 2.94)	0.15 (0.02, 1.10)	0.54 (0.24, 1.20)	Did not converge
Parous women (N=135,826)					
Outcome	**Elective Induction, 37 weeks (N=988) vs. Expectant Management (N=125,849)**	**Elective Induction,38 weeks (N=3,339) vs. Expectant Management (N=100,642)**	**Elective Induction, 39 weeks (N=8,346) vs. Expectant Management (N=54,427)**	**Elective Induction, 40 weeks (N=9,065) vs. Expectant Management (N=12,826)**	**Elective Induction, 41 weeks (N=4,061) vs. Expectant Management (N=961)**
Infant Death	3.97 (1.62, 9.70)	1.38 (0.56, 3.41)	0.41 (0.15, 1.14)	1.17 (0.57, 2.43)	Did not converge
Infant stay >5 days[e]	1.25 (0.81, 1.93)	0.96 (0.72, 1.27)	0.63 (0.50, 0.79)	0.75 (0.59, 0.94)	0.95 (0.52, 1.75)
Macrosomia (≥4000 g)	0.32 (0.25, 0.42)	0.51 (0.46, 0.57)	0.59 (0.56, 0.63)	0.69 (0.65, 0.74)	0.94 (0.80, 1.11)
Meconium aspiration syndrome	0.34 (0.05, 2.39)	0.45 (0.19, 1.10)	0.28 (0.14, 0.55)	0.28 (0.16, 0.50)	0.35 (0.15, 0.82)

Respiratory distress syndrome	1.09 (0.61, 1.92)	1.15 (0.84, 1.57)	0.98 (0.78, 1.23)	0.65 (0.49, 0.85)	0.72 (0.38, 1.37)
Shoulder dystocia[c]	0.73 (0.44, 1.20)	0.62 (0.47, 0.82)	0.72 (0.61, 0.84)	0.76 (0.65, 0.89)	0.91 (0.63, 1.30)
Shoulder dystocia[d]	0.70 (0.43, 1.15)	0.60 (0.45, 0.79)	0.69 (0.58, 0.81)	0.72 (0.62, 0.85)	0.83 (0.58, 1.20)
Brachial plexus injury[c]	1.57 (0.50, 4.92)	0.72 (0.30, 1.75)	0.86 (0.51, 1.46)	0.48 (0.26, 0.89)	0.38 (0.14, 1.02)
Brachial plexus injury[d]	1.50 (0.48, 4.71)	0.68 (0.28, 1.66)	0.82 (0.48, 1.39)	0.45 (0.24, 0.84)	0.35 (0.13, 0.93)

[a]In this analysis, placental abruption and fetal-maternal hemorrhage were not considered indications for induction. Coagulation deficiency, amniotic infection (i.e., chorioamnionitis), and fetal distress/fetal heart rate abnormalities with unspecified time of onset were considered indications for induction. We could not analyze the chorioamnionitis outcome in this sensitivity analysis, as chorioamnionitis was considered an indication for induction. No women with chorioamnionitis were considered exposed (electively induced) in this sensitivity analysis.
[b]Table data are adjusted odds ratios (95% confidence intervals). Models were adjusted for maternal age, maternal education, maternal race/ethnicity, initiation of prenatal care in the first trimester, principal source of payment for delivery, birth year, obesity class, weekday delivery, delivery at a teaching hospital, and hospital obstetric volume.
[c]Among all deliveries.
[d]Among vaginal deliveries only.
[e]N=21 nulliparous women and N=27 parous women were missing data on length of infant stay.

Table 5-S5. Adjusted Odds Ratios for Elective Labor Induction versus Expectant Management and Infant Outcomes using New Expectant Management Definition[a,b]					
Nulliparous women (N=83,534)					
Outcome	**Elective Induction, 37 weeks (N=496) vs. Expectant Management (N=80,953)**	**Elective Induction, 38 weeks (N=1,616) vs. Expectant Management (N=72,145)**	**Elective Induction, 39 weeks (N=3,942) vs. Expectant Management (N=53,650)**	**Elective Induction, 40 weeks (N=7,061) vs. Expectant Management (N=25,502)**	**Elective Induction, 41 weeks (N=4,961) vs. Expectant Management (N=4,363)**
Infant Death	0.00 (0.00, Infinity)	2.54 (0.92, 6.99)	0.24 (0.03, 1.72)	0.66 (0.28, 1.59)	Did not converge
Infant stay >5 days[e]	1.45 (0.99, 2.13)	0.80 (0.60, 1.07)	0.85 (0.71, 1.03)	0.92 (0.80, 1.06)	0.90 (0.73, 1.11)
Macrosomia (≥4000 g)	0.12 (0.06, 0.24)	0.52 (0.43, 0.63)	0.64 (0.57, 0.71)	0.94 (0.87, 1.01)	1.19 (1.07, 1.32)
Chorioamnionitis	0.88 (0.59, 1.32)	0.63 (0.48, 0.81)	0.62 (0.52, 0.73)	0.72 (0.64, 0.81)	0.93 (0.80, 1.09)
Meconium aspiration syndrome	0.29 (0.04, 2.03)	0.34 (0.13, 0.90)	0.61 (0.39, 0.96)	0.37 (0.25, 0.55)	0.64 (0.44, 0.95)
Respiratory distress syndrome	1.26 (0.71, 2.25)	1.27 (0.91, 1.76)	0.97 (0.76, 1.23)	0.89 (0.74, 1.08)	0.80 (0.61, 1.06)
Shoulder dystocia[c]	1.21 (0.60, 2.44)	0.97 (0.63, 1.49)	1.07 (0.82, 1.39)	1.08 (0.88, 1.34)	1.19 (0.86, 1.65)
Shoulder dystocia[d]	1.11 (0.55, 2.26)	0.90 (0.58, 1.40)	1.09 (0.83, 1.42)	1.28 (1.03, 1.59)	1.57 (1.12, 2.21)
Brachial plexus injury[c]	0.00 (0.00, Infinity)	0.72 (0.18, 2.92)	0.41 (0.13, 1.29)	1.00 (0.56, 1.78)	Did not converge
Brachial plexus injury[d]	0.00 (0.00, Infinity)	0.69 (0.17, 2.80)	0.43 (0.14, 1.36)	1.17 (0.64, 2.12)	Did not converge
Parous women (N=135,826)					
Outcome	**Elective Induction, 37 weeks (N=1,130) vs. Expectant Management (N=133,055)**	**Elective Induction, 38 weeks (N=3,862) vs. Expectant Management (N=118,708)**	**Elective Induction, 39 weeks (N=9,626) vs. Expectant Management (N=85,915)**	**Elective Induction, 40 weeks (N=10,748) vs. Expectant Management (N=39,494)**	**Elective Induction, 41 weeks (N=4,948) vs. Expectant Management (N=6,553)**

Infant Death	3.27 (1.34, 7.99)	1.33 (0.58, 3.01)	0.45 (0.18, 1.10)	1.36 (0.74, 2.47)	Did not converge
Infant stay >5 days[e]	1.40 (0.96, 2.05)	1.04 (0.81, 1.34)	0.75 (0.61, 0.91)	0.85 (0.71, 1.01)	1.18 (0.86, 1.61)
Macrosomia (≥4000 g)	0.33 (0.25, 0.42)	0.55 (0.49, 0.61)	0.72 (0.68, 0.76)	0.95 (0.90, 1.00)	1.06 (0.98, 1.16)
Chorioamnionitis	1.01 (0.54, 1.89)	0.78 (0.53, 1.16)	0.71 (0.55, 0.93)	0.83 (0.66, 1.05)	1.57 (1.12, 2.20)
Meconium aspiration syndrome	0.59 (0.15, 2.38)	0.42 (0.17, 1.02)	0.44 (0.26, 0.74)	0.57 (0.38, 0.87)	0.73 (0.42, 1.26)
Respiratory distress syndrome	1.16 (0.70, 1.94)	1.34 (1.02, 1.77)	1.10 (0.90, 1.34)	1.05 (0.85, 1.29)	0.80 (0.57, 1.12)
Shoulder dystocia[c]	0.77 (0.49, 1.21)	0.66 (0.51, 0.85)	0.80 (0.69, 0.93)	0.91 (0.80, 1.03)	0.96 (0.79, 1.17)
Shoulder dystocia[d]	0.76 (0.48, 1.19)	0.66 (0.51, 0.85)	0.81 (0.70, 0.94)	0.95 (0.83, 1.08)	1.01 (0.83, 1.23)
Brachial plexus injury[c]	1.39 (0.44, 4.35)	0.65 (0.27, 1.58)	0.98 (0.62, 1.56)	0.59 (0.35, 1.01)	0.56 (0.28, 1.10)
Brachial plexus injury[d]	1.37 (0.44, 4.28)	0.65 (0.27, 1.57)	0.99 (0.62, 1.58)	0.62 (0.36, 1.05)	0.60 (0.30, 1.19)

[a]We expanded the expectant management definition to include spontaneously laboring women who delivered during the same week as the exposed were induced.
[b]Table data are adjusted odds ratios (95% confidence intervals). Models were adjusted for maternal age, maternal education, maternal race/ethnicity, initiation of prenatal care in the first trimester, principal source of payment for delivery, birth year, obesity class, weekday delivery, delivery at a teaching hospital, and hospital obstetric volume.
[c]Among all deliveries.
[d]Among vaginal deliveries only.
[e]N=21 nulliparous women and N=27 parous women were missing data on length of infant stay.

CHAPTER 6, EXTENDED ANALYSES

This chapter describes the methods and results for the following extended analyses:

1. Evaluation of the Association between Total GWG and Stillbirth using SCRN Data (**Aim 1** extension)
2. Evaluation of the Association between Net GWG and Stillbirth using SCRN Data (**Aim 1** extension)
3. Assessment of Additive and Multiplicative Interaction between Elective IOL and Obesity Class in Studies of Maternal and Infant Outcomes (**Aims 2 and 3** extension)
4. Use of Generalized Estimating Equations (GEE) in Studies of Elective IOL and Maternal and Infant Outcomes (**Aims 2 and 3** extension)

EXTENDED ANALYSES 1 AND 2. EVALUATING THE ASSOCIATIONS BETWEEN TOTAL GWG AND STILLBIRTH AND NET GWG AND STILLBIRTH USING SCRN DATA

BACKGROUND AND METHODOLOGY

As previously discussed in **Chapter 1** (Introduction), it is challenging to evaluate the association between GWG and stillbirth because both variables are strongly correlated with GA. The GWG z-score has been proposed as one method of accounting for this correlation. Other proposed methods exist. For instance, Hinkle et al. demonstrated that adjusting for GA as a covariate is appropriate in analyses of total GWG, as long as confounders of the association between GA and the outcome are accounted for.[174] In an exploratory analysis, we employed Hinkle et al.'s method by evaluating the relation between **total GWG** and stillbirth, while adjusting for GA as a covariate. Subsequently, we considered the limitations to the use of this method in studies of

stillbirth.

Another challenge to evaluating the relation between GWG and stillbirth is that stillbirths may be growth restricted for reasons unrelated to maternal weight.[176] In a second exploratory analysis, we assessed the relation between **net GWG** and stillbirth, while adjusting for GA as a covariate.

Similarly to main analyses, total GWG (in lb) was defined as maternal weight at delivery—pre-pregnancy weight. Net GWG (in lb) was defined as GWG—infant birthweight.

Modeling strategies were similar to main analyses (see **Chapter 2 [**Research Questions and Methods] and **Chapter 3** [The Association between Gestational Weight Gain Z-Score and Stillbirth: A Case-Control Study]). We used SAS-callable SUDAAN (Research Triangle Park, NC) to conduct multivariable logistic regression, and analyses were weighted to account for SCRN's sampling design and individuals' probabilities of participating and completing all parts of the data collection process.[243] Likewise, we assessed multiplicative interaction between pre-pregnancy BMI category and GWG and adjusted for maternal sociodemographic and pregnancy characteristics. In contrast to main analyses, adjusted models of total and net GWG included adjustment for autoimmune disorder (which was removed from GWG z-score models due to collinearity issues) and GA at delivery.[174]

We modeled total GWG and net GWG with quadratic terms due to their hypothesized u-shaped associations with stillbirth.[67] Similarly to main analyses, we calculated odds ratio contrasts of interest by comparing the 10th, 15th, 25th, 35th, 45th,

55th, 65th, 75th, 85th, and 90th percentiles of each exposure variable to the 50th percentile referent (percentiles were calculated among live birth controls only).

We conducted numerous sensitivity analyses, which were similar to those in **Chapter 3** (The Association between Gestational Weight Gain Z-Score and Stillbirth: A Case-Control Study). First, we utilized stillbirths' estimated GA at death, rather than GA at delivery. In subsequent models using stillbirths' estimated GA at death, we: 1) excluded stillbirths that had an estimated GA at fetal death <20 weeks; 2) fit separate models for antepartum and intrapartum stillbirths; 3) excluded stillbirths with causes of death related to fetal genetic, structural, or karyotypic abnormalities or maternal/fetal hematologic conditions; 4) used weight at last prenatal visit as an estimate of weight at delivery for women missing delivery weight; 5) controlled for weight and height squared as separate variables; 6) excluded mummified stillbirths; and 7) in a new sensitivity analysis restricted to observations with a placental examination, adjusted for chorioamnionitis (controlling for potential confounders of the GA—stillbirth association, such as chorioamnionitis,[163,269] is important in models with regression-based control of GA[174]). Information on chorioamnionitis was obtained from placental pathology reports and chart abstraction.

RESULTS

Generally, women with stillbirths had lower values of total GWG and net GWG than women with live births (**Table 6-1**). Total and net GWG were inversely associated with pre-pregnancy BMI category.

Results from unadjusted and adjusted models are presented in **Figure 6-1, Table 6-2,** and **Table 6-3**. We did not observe multiplicative interaction between pre-pregnancy BMI and either total or net GWG (data not shown), so interaction terms were removed.

In unadjusted analyses, total GWG was strongly inversely related with stillbirth (**Table 6-2**). Associations were attenuated upon adjusting for GA at delivery; subsequent adjustment for additional covariates made no further difference. There was some evidence that very low total GWG (≤10th percentile) was harmful (e.g., aOR [95% CI] for the 10th versus 50th percentile= 1.21 [0.96, 1.52]; **Figure 6-1a**). As total GWG increased from the 10th to the 50th percentile, adjusted odds ratios declined and plateaued at the null.

Net GWG was also inversely associated with stillbirth in unadjusted analyses (**Table 6-3**), and associations were attenuated after adjusting for GA at delivery. Adjusted odds ratios for low levels of net GWG were only modestly elevated (e.g., aOR [95% CI] for the 10th versus 50th percentile= 1.12 [0.88, 1.42]; **Figure 6-1b**).

SENSITIVITY ANALYSES

In models with GA at death (rather than GA at delivery), aORs for low total and net GWG (≤45th percentile) moved slightly down and toward the null (**Tables 6-2 and 6-3**). In models restricted to intrapartum stillbirths, aORs for total and net GWG moved slightly up and away from the null, although precision was poor due to small sample sizes (data not shown). Results were not meaningfully impacted in remaining sensitivity analyses.

COMMENTS

Supplemental analyses suggested that low total GWG (≤10th percentile) may be associated with an increased risk of stillbirth. The odds of stillbirth were elevated by 21% for GWG ≤10th percentile (≤12 pounds, versus the median of 31 pounds). These findings have parallels to our main analyses, in which low GWG z-score was associated with an increased risk of stillbirth (see **Chapter 3**). However, compared to low total GWG, low GWG z-score was more strongly associated with stillbirth; furthermore, the odds of stillbirth were elevated for GWG z-scores up to the 35th percentile. High total GWG was not associated with the risk of stillbirth, similarly to main analyses of GWG z-score (see **Chapter 3**).

In models of net GWG, in which infant birthweight was removed from the exposure definition, point estimates dropped and approached the null. The difference in point estimates between the total and net GWG models suggests that the association between low GWG and stillbirth is driven by fetal/infant weight. Furthermore, the results for net GWG suggest that maternal (net) weight gain is not causally related to stillbirth.

Beginning in the second trimester, low total GWG may be an indicator of low fetal weight gain. However, we cannot determine whether poor fetal growth caused stillbirth or, alternatively, whether fetuses at higher risk of stillbirth simply stopped growing as a result of congenital or intrauterine complications. It is unlikely that the associations between low GWG z-score and stillbirth in this dissertation were driven by stillbirths with congenital anomalies or hematologic conditions specifically: for all exposure variables, sensitivity analyses excluding stillbirths with these conditions produced similar results to main analyses.

As described in **Chapter 1**, Hinkle et al. used a simulation of GWG and neonatal mortality to justify regression-based adjustment for GA.[174] As noted previously, GWG and GA at delivery temporally precede neonatal mortality. However, Hinkle et al.'s approach does not perfectly correspond to our study of GWG and stillbirth, an outcome that occurs at or before delivery. To use regression-based adjustment for gestational duration in studies of stillbirth, GWG should preferably be measured before fetal death occurs. Under this hypothetical scenario, adjusting for GA at the time of measurement would be appropriate. However, in our study, we used GA (and GWG) at delivery due to limitations in what data was available.

In addition, Hinkle et al.'s approach was designed to adjust for confounding by gestational duration.[174] In Hinkle et al.'s analysis, it can be argued that GA at delivery confounds the association between GWG and neonatal death. However, it is an oversimplification to argue that GA at delivery confounds the association between GWG and stillbirth. Although the risk of stillbirth varies over GA and may be influenced by time in utero, antepartum fetal death may also influence GA at delivery (typically cutting it short). Regression-based adjustment for GA may be more appropriate for outcomes that occur *after* delivery (in contrast to stillbirth, which occurs *at or before* delivery).

Our analysis of net GWG also contains specific limitations. We did not have information on amniotic fluid weight, placental weight, or fetal weight at the time of death, which should ideally be used in calculations of net GWG. However, we excluded macerated stillbirths, who may have notable discrepancies between fetal weight at death and delivery, in sensitivity analyses, and conclusions were not meaningfully impacted. The placenta and amniotic fluid are typically only 2-3 pounds combined,[101] but their

weights may differ between cases and controls. As noted in **Chapter 3**, we were unable to calculate a "net GWG z-score" (analogous to the total GWG z-score), which would allow a more thorough evaluation of the impact of fetal, versus maternal, weight.

All methods of assessing the relation between GWG and stillbirth have limitations. However, in our study of stillbirth, the GWG z-score approach has fewer limitations, and a stronger justification, than regression-based adjustment for GA. Hence, we have more confidence in the findings from our main analyses using the GWG z-score (see **Chapter 3**) than in analyses of total GWG (this chapter). Notably, despite differences in methodology between total GWG and the GWG z-score, the odds of stillbirth were elevated for total GWG $\leq 10^{th}$ percentile as well as GWG z-score $\leq 10^{th}$ percentile.

Table 6-1. Distributions of Total GWG and Net GWG by Case-Control Status[a,b]

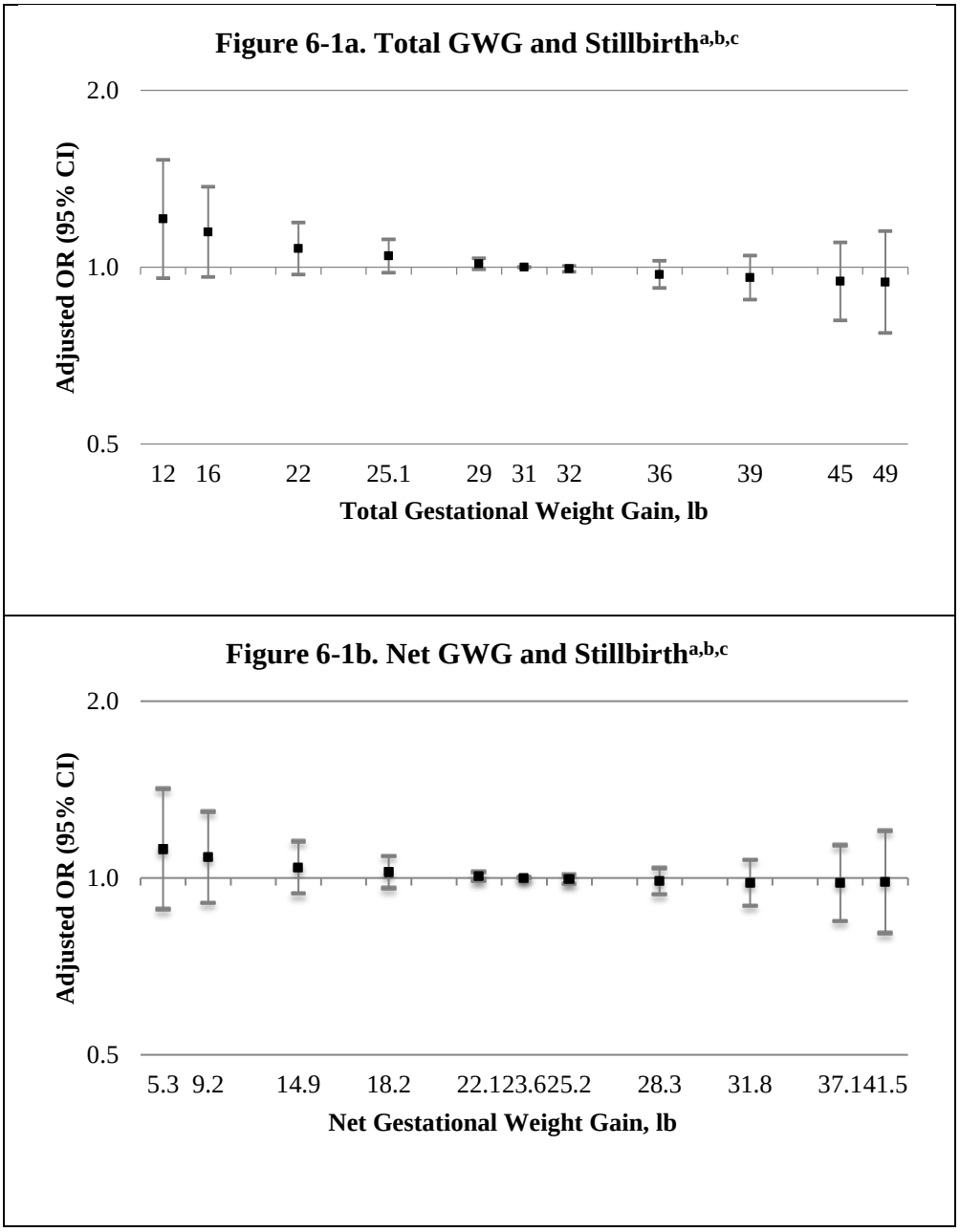
	Stillbirths (N=426)		Live births (N=1,459)		
Total GWG, lb	**Mean**	**SE**	**Mean**	**SE**	**P-value[c]**
Total sample (All BMI Categories)	18.59	0.87	30.89	0.45	<.0001
Normal weight (BMI 18.5 - <25.0 kg/m^2)	21.73	1.19	33.77	0.54	<.0001
Overweight (BMI 25.0 - <30.0 kg/m^2)	21.85	1.89	30.89	0.87	<.0001
Class 1 Obese (BMI 30.0 - <35.0 kg/m^2)	15.02	2.05	26.22	1.36	<.0001
Morbidly Obese (BMI ≥35.0 kg/m^2)	8.65	1.90	22.19	1.90	<.0001
Net GWG, lb	**Mean**	**SE**	**Mean**	**SE**	**P-value[c]**
Total sample (All BMI Categories)	15.63	0.83	23.64	0.44	<.0001
Normal weight (BMI 18.5 - < 25.0 kg/m^2)	18.54	1.11	26.62	0.53	<.0001
Overweight (BMI 25.0 - < 30.0 kg/m^2)	19.09	1.86	23.61	0.86	0.0278
Class 1 Obese (BMI 30.0 - <35.0 kg/m^2)	12.00	1.91	18.76	1.33	0.0037
Morbidly Obese (BMI ≥35 kg/m^2)	6.10	1.88	14.73	1.76	0.0008

[a]Frequencies, means, and standard errors are weighted, but sample sizes are unweighted.

[b]N=17 additional observations (5 stillbirths and 12 live births) were excluded in the analysis of Net GWG due to missing data on infant birthweight.

[c]2-sample t-test.

Figure 6-1. Adjusted Associations of Total GWG and Net GWG with Stillbirth[a,b]



Description: This figure displays adjusted odds ratios for the associations between total GWG and stillbirth (**Figure 6-1a**) and net GWG and stillbirth (**Figure 6-1b**).
[a]In **Figure 6-1a**, the 10th, 15th, 25th, 35th, 45th, 55th, 65th, 75th, 85th, and 90th percentiles of total GWG were compared to the 50th percentile (31 lb, referent). In **Figure 6-1b**, the 10th, 15th, 25th, 35th, 45th, 55th, 65th, 75th, 85th, and 90th percentiles of net GWG were compared to the 50th percentile (23.6 lb, referent).
[b]Adjusted for maternal age at delivery, maternal race/ethnicity, mother born in the United States, maternal education, marital status/cohabitating, health insurance type, trimester

prenatal care began, family income in the last 12 months, WIC enrollment, average cigarettes/day during the 3 months prior to pregnancy, alcohol consumption in the 3 months prior to pregnancy, lifetime drug use, pregnancy history, pre-pregnancy BMI category, history of hypertension, history of thyroid disorder, and history of autoimmune disorder.

Table 6-2. Unadjusted and Adjusted Odds Ratios for Total GWG and Stillbirth

Percentile Contrast[a]	Total GWG Contrast[a]	Unadjusted OR [95% CI][b]	OR [95% CI] adjusted for GA at delivery only	OR [95% CI]adjusted for all covariates[c,d]	Adjusted OR [95% CI] using GA at death for stillbirths[c,e]
10th vs. 50th	**12.0 vs. 31.0 lb**	2.95 (2.46, 3.53)	1.18 (0.95, 1.46)	1.21 (0.96, 1.52)	1.11 (0.87, 1.41)
15th vs. 50th	**16.0 vs. 31.0 lb**	2.26 (1.97, 2.59)	1.13 (0.95, 1.33)	1.15 (0.96, 1.37)	1.07 (0.89, 1.29)
25th vs. 50th	**22.0 vs. 31.0 lb**	1.58 (1.46, 1.71)	1.06 (0.97, 1.17)	1.08 (0.97, 1.19)	1.04 (0.93, 1.15)
35th vs. 50th	**25.1 vs. 31.0 lb**	1.33 (1.27, 1.40)	1.04 (0.98, 1.10)	1.05 (0.98, 1.12)	1.02 (0.95, 1.09)
45th vs. 50th	**29.0 vs. 31.0 lb**	1.10 (1.08, 1.12)	1.01 (0.99, 1.03)	1.01 (0.99, 1.04)	1.01 (0.98, 1.03)
50th vs. 50th	**31.0 vs. 31.0 lb**	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
55th vs. 50th	**32.0 vs. 31.0 lb**	0.96 (0.95, 0.96)	1.00 (0.99, 1.01)	0.99 (0.98, 1.00)	1.00 (0.99, 1.01)
65th vs. 50th	**36.0 vs. 31.0 lb**	0.81 (0.78, 0.85)	0.98 (0.93, 1.03)	0.97 (0.92, 1.03)	0.99 (0.94, 1.05)
75th vs. 50th	**39.0 vs. 31.0 lb**	0.73 (0.67, 0.78)	0.98 (0.90, 1.05)	0.96 (0.88, 1.05)	0.99 (0.90, 1.08)
85th vs. 50th	**45.0 vs. 31.0 lb**	0.60 (0.52, 0.69)	0.97 (0.85, 1.12)	0.95 (0.81, 1.10)	0.99 (0.84, 1.16)
90th vs. 50th	**49.0 vs. 31.0 lb**	0.54 (0.45, 0.65)	0.98 (0.82, 1.17)	0.94 (0.77, 1.15)	0.99 (0.81, 1.22)

[a]Percentiles of total GWG. 31.0 lb is the median (50th percentile) GWG. Selected percentiles were compared to the 50th percentile referent.

[b]OR, Odds Ratio; CI, Confidence Interval.

[c]Adjusted for pre-pregnancy BMI index, maternal age at delivery, maternal race/ethnicity, mother born in the United States, maternal education, marital status/cohabitating, health insurance type, trimester prenatal care began, family income in the last 12 months, WIC enrollment, average cigarettes/day during the 3 months prior to pregnancy, alcohol consumption in the 3 months prior to pregnancy, lifetime drug use, pregnancy history, obesity class, history of hypertension, history of thyroid disorder, and history of autoimmune disorder.

[d]Also adjusted for GA at delivery.

[e]Also adjusted for GA at death.

Table 6-3. Unadjusted and Adjusted Odds Ratios for Net GWG and Stillbirth

Percentile Contrast[a]	Net GWG Contrast[a]	Unadjusted OR (95% CI)[b]	OR [95% CI] adjusted for GA at delivery only	OR [95% CI] adjusted for all covariates[c,d]	Adjusted OR [95% CI] using GA at death for stillbirths[c,e]
10th vs. 50th	**5.3 vs. 23.6 lb**	2.08 (1.76, 2.46)	1.11 (0.89, 1.38)	1.12 (0.88, 1.42)	1.06 (0.83, 1.36)
15th vs. 50th	**9.2 vs. 23.6 lb**	1.74 (1.53, 1.98)	1.07 (0.91, 1.27)	1.08 (0.91, 1.30)	1.04 (0.86, 1.26)
25th vs. 50th	**14.9 vs. 23.6 lb**	1.37 (1.27, 1.47)	1.03 (0.94, 1.14)	1.04 (0.94, 1.16)	1.02 (0.91, 1.13)
35th vs. 50th	**18.2 vs. 23.6 lb**	1.21 (1.16, 1.26)	1.02 (0.96, 1.08)	1.02 (0.96, 1.09)	1.01 (0.95, 1.08)
45th vs. 50th	**22.1 vs. 23.6 lb**	1.05 (1.04, 1.07)	1.00 (0.99, 1.02)	1.01 (0.99, 1.02)	1.00 (0.98, 1.02)
50th vs. 50th	**23.6 vs. 23.6 lb**	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
55th vs. 50th	**25.2 vs. 23.6 lb**	0.95 (0.94, 0.96)	1.00 (0.98, 1.01)	0.99 (0.98, 1.01)	1.00 (0.98, 1.02)
65th vs. 50th	**28.3 vs. 23.6 lb**	0.86 (0.83, 0.90)	0.99 (0.95, 1.04)	0.99 (0.94, 1.04)	1.00 (0.95, 1.05)
75th vs. 50th	**31.8 vs. 23.6 lb**	0.78 (0.73, 0.84)	0.99 (0.92, 1.08)	0.98 (0.90, 1.07)	1.00 (0.91, 1.10)
85th vs. 50th	**37.1 vs. 23.6 lb**	0.69 (0.61, 0.78)	1.00 (0.88, 1.15)	0.98 (0.84, 1.14)	1.01 (0.86, 1.18)
90th vs. 50th	**41.5 vs. 23.6 lb**	0.63 (0.53, 0.74)	1.02 (0.85, 1.22)	0.98 (0.81, 1.20)	1.02 (0.83, 1.25)

[a]Percentiles of net GWG. 23.6 lb is the median (50th percentile) net GWG. Selected percentiles were compared to the 50th percentile referent.
[b]OR, Odds Ratio; CI, Confidence Interval.
[c]Adjusted for pre-pregnancy BMI index, maternal age at delivery, maternal race/ethnicity, mother born in the United States, maternal education, marital status/cohabitating, health insurance type, trimester prenatal care began, family income in the last 12 months, WIC enrollment, average cigarettes/day during the 3 months prior to pregnancy, alcohol consumption in the 3 months prior to pregnancy, lifetime drug use, pregnancy history, obesity class, history of hypertension, history of thyroid disorder, and history of autoimmune disorder.
[d]Also adjusted for GA at delivery.
[e]Also adjusted for GA at death.

EXTENDED ANALYSIS 3. ASSESSMENT OF ADDITIVE INTERACTION BETWEEN ELECTIVE IOL AND OBESITY CLASS IN STUDIES OF MATERNAL AND INFANT OUTCOMES (AIMS 2 AND 3 EXTENSION)

BACKGROUND AND METHODOLOGY

This section displays output from additive and multiplicative interaction models assessed in Aims 2-3. As described previously, for all dichotomous outcomes, we assessed multiplicative interaction between eIOL and obesity class using likelihood ratio tests ($p<0.20$).

For dichotomous outcomes, we assessed additive interaction between eIOL and obesity class using the Relative Excess Risk of Interaction (RERI).[263] Cesarean delivery and operative vaginal delivery were modeled separately in the assessment of additive interaction, as SAS code was not available for multinomial outcomes.[263] Assessing additive interaction between a dichotomous exposure variable and a 3-category covariate involves the estimation of 3 separate RERIs[263]: 1) RERI comparing obesity classes 2 and 1 (obesity class 1 is the referent); 2) RERI comparing obesity classes 3 and 2 (obesity class 2 is the referent); and 3) RERI comparing obesity classes 3 and 1 (obesity class 1 is the referent). For each outcome, we calculated a total of 30 RERIs: 5 gestational age-specific comparisons *x* 3 RERIs per model *x* 2 parity categories. For maternal postpartum hospital stay, we assessed additive interaction between eIOL and obesity class using Type 3 likelihood ratio tests of the interaction terms ($p<0.20$).

RESULTS

Results from the assessment of multiplicative and additive interaction can be seen in **Tables 6-4 and 6-5** (maternal outcomes) and **6-6** (infant outcomes) on the following pages. For protective associations (aOR <1), a negative RERI value indicates that the

association is more strongly protective for higher obesity classes (assuming that women in the lowest BMI category were coded as the referent category). For harmful associations (aOR >1), a positive RERI indicates that the exposure is more harmful in more severely obese women.

Overall, we did not observe evidence of additive interaction between eIOL and obesity class for most outcomes. Few RERIs reached statistical significance, and patterns were sporadic and difficult to interpret for most outcomes. However, we noted two exceptions among nulliparas: cesarean delivery and macrosomia. With respect to cesarean delivery, additive interaction models suggested that the benefits of eIOL may increase with obesity severity among nulliparas (evidenced by the negative RERIs for this outcome; **Table 6-4**). Similarly, additive interaction models suggested that protective associations between eIOL and macrosomia may be stronger in classes 2 and 3 (versus class 1) obese nulliparas (**Table 6-6**). Notably, for CD and macrosomia, 95% CIs around several of the RERI values overlapped the null. **Table 6-7** displays crude frequencies of CD and macrosomia by obesity class and exposure status. The crude frequency of CD and macrosomia increased with obesity severity. In addition, for most weeks, the crude risk differences for cesarean delivery (risk of CD$_{\mathbf{eIOL}}$ - risk of CD$_{\mathbf{EM}}$) and macrosomia (risk of macrosomia$_{\mathbf{eIOL}}$ - risk of macrosomia$_{\mathbf{EM}}$), grew in absolute magnitude as obesity severity increased. (That is, risk differences were negative, but they tended to grow in absolute magnitude as obesity severity increased.) These unadjusted results are consistent with our adjusted results, which suggests that the benefit of eIOL, with respect to CD and macrosomia, may be greater with increasing obesity severity.

Ln(maternal postpartum stay) was the only continuous outcome evaluated in this

study. Most coefficients for the interaction terms were negative, which would suggest that the benefits of eIOL increase with obesity severity for this outcome (**Table 6-5**). However, we detected statistically significant additive interaction in only one out of ten models of maternal postpartum stay.

COMMENTS

Among nulliparas, our results suggest that protective associations between eIOL and CD, as well as protective associations between eIOL and macrosomia, may be stronger among severely obese women. For other outcomes, we observed limited evidence of interaction between elective labor induction and obesity class. Our study may lack the power to detect interaction between eIOL and obesity severity for rare outcomes. Additional research using larger sample sizes of morbidly obese women is warranted.

There are limitations of using the RERI to evaluate additive interaction. Although the RERI measure provides information on the direction of interaction (i.e., whether eIOL is more or less beneficial among certain obesity classes), it does not provide information on how much more beneficial (or risky) eIOL is for women in each BMI category.[263] Likewise, we cannot calculate numbers needed to treat using the RERI.[263] These limitations are due to the inherent challenges of evaluating additive interaction in logistic regression models.[263]

Table 6-4. Assessment of Multiplicative and Additive Interaction between Elective IOL and Obesity Class for Maternal Outcomes[a]

	P-value, multiplicative Interaction[b]	Additive Interaction								
		Obesity class 2 vs. 1			Obesity class 3 vs. 2			Obesity class 3 vs. 1		
		RERI[c]	Lower 95% CL	Upper 95% CL	RERI[c]	Lower 95% CL	Upper 95% CL	RERI[c]	Lower 95% CL	Upper 95% CL
Cesarean section[d]										
Nulliparas										
Week 37	0.00	-0.7	-0.9	-0.4	-0.1	-0.5	0.3	-0.8	-1.3	-0.3
Week 38	0.22	-0.1	-0.3	0.1	-0.3	-0.6	0.0	-0.5	-0.8	-0.1
Week 39	0.27	-0.2	-0.4	0.0	0.0	-0.3	0.2	-0.2	-0.5	0.0
Week 40	0.55	-0.1	-0.2	0.1	0.0	-0.3	0.2	-0.1	-0.4	0.1
Week 41	0.97	0.0	-0.4	0.4	-0.1	-0.6	0.5	-0.2	-0.8	0.5
Parous women										
Week 37	0.32	-0.2	-0.6	0.2	0.2	-0.5	0.9	0.1	-0.7	0.9
Week 38	0.52	-0.2	-0.5	0.1	-0.2	-0.6	0.2	-0.4	-0.8	0.0
Week 39	0.73	-0.2	-0.3	0.0	0.0	-0.3	0.2	-0.2	-0.5	0.1
Week 40	0.47	-0.2	-0.4	0.1	-0.2	-0.5	0.2	-0.3	-0.7	0.0
Week 41	0.64	-0.4	-1.1	0.3	0.4	0.0	0.9	0.3	-0.4	1.0
Operative vaginal delivery[d]										
Nulliparas										
Week 37	0.00	0.8	-0.1	1.6	-1.0	-2.2	0.2	-0.1	-0.9	0.8
Week 38	0.22	-0.3	-0.7	0.2	-0.3	-0.9	0.3	-0.6	-1.1	-0.1
Week 39	0.27	-0.2	-0.5	0.1	0.0	-0.4	0.5	-0.2	-0.5	0.2
Week 40	0.55	0.2	0.0	0.5	-0.2	-0.7	0.3	0.1	-0.2	0.5
Week 41	0.97	0.0	-0.7	0.7	-0.3	-1.4	0.9	-0.4	-1.3	0.5
Parous women										
Week 37	0.32	-0.6	-1.1	0.0	0.9	-0.3	2.1	0.3	-0.8	1.4
Week 38	0.52	-0.1	-0.5	0.3	0.3	-0.4	0.9	0.1	-0.4	0.6
Week 39	0.73	0.0	-0.3	0.2	-0.1	-0.5	0.3	-0.1	-0.4	0.2
Week 40	0.47	0.0	-0.4	0.3	-0.2	-0.6	0.3	-0.2	-0.6	0.2
Week 41	0.64	-0.2	-1.2	0.9	-0.1	-1.3	1.2	-0.2	-1.4	1.1

Postpartum hemorrhage										
Nulliparas										
Week 37	0.31	-0.8	-1.5	-0.1	-0.1	-0.6	0.3	-1.0	-1.6	-0.3
Week 38	0.85	0.1	-0.5	0.7	0.1	-0.8	1.1	0.2	-0.6	1.0
Week 39	0.97	0.0	-0.3	0.4	-0.1	-0.6	0.4	0.0	-0.5	0.4
Week 40	0.37	0.0	-0.3	0.2	0.3	-0.1	0.7	0.3	-0.1	0.7
Week 41	0.23	0.4	-0.2	0.9	-0.9	-2.4	0.6	-0.3	-1.2	0.6
Parous women										
Week 37	0.42	0.6	-0.4	1.7	-0.6	-1.9	0.8	0.0	-1.1	1.2
Week 38	0.55	0.2	-0.3	0.6	0.0	-0.6	0.6	0.2	-0.4	0.8
Week 39	0.16	-0.3	-0.5	0.0	0.0	-0.4	0.4	-0.3	-0.6	0.1
Week 40	0.72	0.1	-0.2	0.4	0.0	-0.4	0.4	0.1	-0.3	0.5
Week 41	0.15	0.7	0.2	1.2	-1.9	-5.3	1.5	0.0	-0.9	0.9
Severe perineal lacerations										
Nulliparas					0.6	-2.7	4.0	1.2	-1.0	3.5
Week 37	0.15	0.8	-0.5	2.2	-0.4	-1.3	0.6	-0.3	-0.9	0.4
Week 38	0.78	0.0	-0.6	0.6	0.4	-0.4	1.1	0.4	-0.1	0.9
Week 39	0.21	0.2	-0.2	0.5	-0.1	-0.8	0.5	-0.1	-0.5	0.4
Week 40	0.90	0.0	-0.3	0.4	0.3	-0.7	1.2	-0.4	-1.6	0.9
Week 41	0.44									
Parous women					-0.8	-2.1	0.6	-0.6	-1.4	0.1
Week 37	1.00	0.0	-1.3	1.4	-0.5	-1.6	0.7	-0.2	-0.9	0.6
Week 38	0.72	0.2	-0.5	1.0	0.7	-0.2	1.6	0.5	-0.2	1.1
Week 39	0.20	0.0	-0.5	0.4	0.5	-0.4	1.3	-0.3	-1.0	0.5
Week 40	0.19	-0.7	-1.3	0.0	-12525.9	-1876678.1	1851626.4	0.2	-1.2	1.7
Week 41	0.10	1.2	0.6	1.8	0.6	-2.7	4.0	1.2	-1.0	3.5
Severe Maternal Morbidity										
Nulliparas										
Week 37	0.93	0.1	-0.6	0.9	0.0	-1.3	1.3	0.1	-0.9	1.2

Week 38	0.97	0.1	-0.4	0.5	0.0	-0.7	0.7	0.0	-0.5	0.6
Week 39	0.64	0.1	-0.2	0.3	0.1	-0.3	0.5	0.2	-0.1	0.5
Week 40	0.71	0.0	-0.2	0.2	0.1	-0.2	0.5	0.1	-0.1	0.4
Week 41	0.29	0.2	-0.3	0.7	-0.7	-1.8	0.4	-0.4	-1.1	0.4
Parous women										
Week 37	0.34	0.5	-0.4	1.4	-0.7	-1.8	0.3	-0.2	-1.1	0.6
Week 38	0.80	0.1	-0.3	0.5	-0.1	-0.7	0.4	0.0	-0.5	0.4
Week 39	0.28	-0.2	-0.4	0.0	0.2	-0.2	0.5	0.0	-0.3	0.3
Week 40	0.68	-0.1	-0.4	0.2	0.1	-0.2	0.5	0.0	-0.3	0.3
Week 41	0.04	0.8	0.4	1.2	-2.4	-6.1	1.4	0.1	-0.6	0.9

[a]Every model was run among the sample of all deliveries (not vaginal deliveries only).
[b]Likelihood ratio test of the interaction terms (2 degrees of freedom).
[c]RERI, Relative Excess Risk of Interaction.
[d]Mode of delivery was a 3-category outcome (cesarean delivery, operative vaginal delivery, non-operative vaginal delivery). A multinomial logistic regression model was used for mode of delivery in main analyses and to assess multiplicative interaction. To assess additive interaction, cesarean delivery and operative vaginal delivery were modeled separately using logistic regression.

Table 6-5. Assessment of Additive Interaction between Elective IOL and Obesity Class for Ln(Maternal Postpartum Stay)

Nulliparas	**P-value**[a]	**Parameter estimate (95% CI) of eIOL *x* obesity class$_{2versus1}$ interaction term**	**Parameter estimate (95% CI) of eIOL *x* obesity class$_{3versus1}$ interaction term**
Week 37	0.001	-0.09 (-0.15, -0.04)	-0.10 (-0.18, -0.02)
Week 38	0.27	0.02 (-0.01, 0.06)	-0.01 (-0.05, 0.03)
Week 39	0.45	0.001 (-0.02, 0.02)	-0.02 (-0.05, 0.01)
Week 40	0.58	-0.01 (-0.03, 0.01)	-0.01 (-0.04, 0.02)
Week 41	0.67	-0.01 (-0.06, 0.03)	-0.02 (-0.08, 0.03)
Parous women			
Week 37	0.38	-0.02 (-0.06, 0.01)	-0.02 (-0.07, 0.03)
Week 38	0.82	-0.01 (-0.02, 0.01)	-0.01 (-0.03, 0.02)
Week 39	0.27	-0.01 (-0.02, 0.01)	-0.01 (-0.03, 0.01)
Week 40	0.27	-0.01 (-0.03, 0.01)	-0.01 (-0.03, 0.01)
Week 41	0.11	-0.04 (-0.08, 0.004)	0.02 (-0.03, 0.07)

[a]Type 3 likelihood ratio tests of the interaction terms (2 degrees of freedom test). Ln (maternal postpartum hospital stay) was modeled as a continuous outcome.

Table 6-6. Assessment of Multiplicative and Additive Interaction between Elective IOL and Obesity Class for Infant Outcomes[a]

	P-value, multiplicative interaction[b]	Additive interaction								
		Obesity class 2 vs. 1			Obesity class 3 vs. 2			Obesity class 3 vs. 1		
		RERI[c]	Lower 95% CL	Upper 95% CL	RERI[c]	Lower 95% CL	Upper 95% CL	RERI[c]	Lower 95% CL	Upper 95% CL
Infant death										
Nulliparas										
Week 37	1.00	-0.6	-1.4	0.2	-0.2	-0.9	0.6	-1.0	-2.2	0.2
Week 38	0.31	1.2	-5.4	7.8	5.8	-5.7	17.3	10.8	-7.8	29.4
Week 39	0.12	-1.1	-2.3	0.2	1.7	-1.0	4.4	2.4	-3.2	8.0
Week 40	0.09	1.8	-0.6	4.2	-0.2	-3.1	2.7	1.4	-1.1	3.9
Week 41	Did not converge	Questionable convergence; extremely imprecise estimate			Questionable convergence; extremely imprecise estimate			Questionable convergence; extremely imprecise estimate		
Parous women										
Week 37	0.91	2.2	-7.2	11.6	-5.7	-13.6	2.1	-4.2	-8.5	0.1
Week 38	0.95	0.5	-2.8	3.8	-2.5	-5.9	0.9	-1.9	-3.7	-0.1
Week 39	0.95	-0.1	-1.2	1.0	0.1	-1.7	2.0	0.1	-1.7	1.8
Week 40	0.77	-0.2	-1.6	1.2	1.5	-1.9	4.8	0.8	-1.6	3.2
Week 41	Did not converge	1.2	0.7	1.8	-153.3	-32203.8	31897.1	1.2	0.4	2.0
Infant length of stay >5 days										
Nulliparas										
Week 37	0.58	0.8	-0.8	2.5	-2.4	-3.8	-1.0	-1.7	-2.4	-1.0
Week 38	0.54	-0.1	-0.6	0.4	0.4	-0.5	1.4	0.3	-0.6	1.3
Week 39	0.00	0.7	0.3	1.1	-0.6	-1.3	0.0	0.1	-0.4	0.6
Week 40	0.79	0.0	-0.3	0.3	0.1	-0.4	0.7	0.1	-0.4	0.5
Week 41	0.49	0.2	-0.4	0.7	-0.9	-2.8	1.1	-0.6	-1.8	0.6
Parous women										
Week 37	0.16	-0.8	-2.1	0.4	-0.9	-2.1	0.4	-1.7	-2.9	-0.5
Week 38	0.38	0.5	-0.3	1.2	-0.2	-1.3	0.8	0.2	-0.7	1.2
Week 39	0.82	0.0	-0.4	0.3	-0.2	-0.7	0.4	-0.2	-0.7	0.3
Week 40	0.61	-0.2	-0.7	0.3	0.0	-0.7	0.8	-0.2	-0.9	0.5

Week 41	0.50	-0.9	-3.3	1.4	0.9	-0.3	2.1	0.6	-1.4	2.7
Macrosomia (≥4000 g)										
Nulliparas										
Week 37	0.48	-0.3	-0.5	-0.1	-0.2	-0.3	-0.1	-0.5	-0.7	-0.3
Week 38	0.81	-0.2	-0.4	0.1	0.0	-0.3	0.3	-0.1	-0.5	0.2
Week 39	0.30	-0.2	-0.3	0.0	0.1	-0.1	0.3	0.0	-0.3	0.2
Week 40	0.03	-0.2	-0.4	0.0	0.2	0.0	0.4	0.1	-0.1	0.3
Week 41	0.24	-0.4	-0.9	0.1	0.1	-0.3	0.5	-0.2	-0.8	0.3
Parous women										
Week 37	0.25	0.0	-0.2	0.3	-0.3	-0.6	0.0	-0.3	-0.6	0.0
Week 38	0.24	-0.1	-0.3	0.0	0.1	-0.1	0.3	0.0	-0.2	0.2
Week 39	0.78	-0.1	-0.2	0.0	-0.1	-0.2	0.1	-0.2	-0.3	0.0
Week 40	0.86	0.0	-0.1	0.1	-0.1	-0.2	0.1	-0.1	-0.2	0.1
Week 41	0.42	0.1	-0.2	0.5	-0.4	-1.0	0.3	-0.3	-0.9	0.3
Chorioamnionitis										
Nulliparas										
Week 37	0.18	0.0	-0.8	0.7	1.2	-0.6	3.0	1.1	-0.6	2.9
Week 38	0.05	-0.3	-0.7	0.0	0.7	0.1	1.3	0.3	-0.2	0.9
Week 39	0.85	0.1	-0.2	0.3	0.0	-0.4	0.3	0.0	-0.2	0.3
Week 40	0.80	-0.1	-0.3	0.1	0.1	-0.2	0.4	0.0	-0.2	0.3
Week 41	0.23	0.4	0.0	0.8	-0.6	-1.9	0.6	0.0	-0.6	0.7
Parous women										
Week 37	0.52	-0.8	-2.1	0.4	0.1	-1.9	2.2	-0.8	-2.7	1.1
Week 38	0.72	-0.3	-1.0	0.4	-1.0	-1.7	-0.3	-1.3	-1.8	-0.8
Week 39	0.17	-0.4	-0.8	0.0	0.0	-0.6	0.6	-0.4	-1.0	0.3
Week 40	0.32	-0.1	-0.7	0.4	-0.5	-1.2	0.3	-0.7	-1.5	0.0
Week 41	0.74	-0.2	-2.5	2.0	1.2	-0.5	2.9	1.4	-1.5	4.3
Respiratory distress syndrome										
Nulliparas										
Week 37	0.70	-0.7	-2.2	0.9	1.0	-1.8	3.8	0.3	-2.6	3.3
Week 38	0.29	0.2	-0.9	1.3	-1.1	-2.2	0.0	-1.0	-1.9	-0.1
Week 39	0.96	0.1	-0.5	0.6	0.0	-0.9	0.8	0.0	-0.8	0.8
Week 40	0.03	-0.4	-0.9	0.0	0.8	0.2	1.4	0.5	-0.1	1.1

Week 41	0.34	-0.2	-1.4	0.9	0.6	0.0	1.2	0.6	0.0	1.3
Parous women										
Week 37	0.72	-0.3	-1.7	1.1	0.8	-1.4	3.1	0.7	-1.8	3.1
Week 38	0.12	1.0	0.0	2.1	-0.8	-2.1	0.5	0.1	-0.9	1.2
Week 39	0.41	-0.3	-0.9	0.2	0.4	-0.3	1.0	0.2	-0.6	0.9
Week 40	0.95	0.1	-0.5	0.6	-0.1	-0.8	0.6	0.0	-0.7	0.7
Week 41	0.49	0.4	-0.7	1.5	0.4	-1.1	2.0	0.8	-0.3	2.0
Meconium aspiration syndrome										
Nulliparas										
Week 37	1.00	1.1	-1.1	3.2	-1.3	-3.4	0.9	-0.2	-0.5	0.1
Week 38	1.00	-0.5	-1.0	0.1	-0.3	-0.6	0.1	-0.7	-1.3	-0.1
Week 39	0.95	0.1	-0.6	0.8	-0.3	-1.4	0.8	-0.2	-1.2	0.7
Week 40	0.68	0.2	-0.2	0.6	0.0	-0.7	0.8	0.2	-0.4	0.8
Week 41	0.51	0.6	0.0	1.2	-1.0	-5.0	3.1	0.2	-1.1	1.4
Parous women										
Week 37	0.83	0.7	-2.0	3.4	-1.4	-3.8	1.1	-0.8	-1.8	0.2
Week 38	0.35	0.1	-0.7	0.9	0.8	-1.2	2.7	0.8	-1.0	2.6
Week 39	0.65	-0.2	-0.7	0.3	-0.1	-1.0	0.8	-0.4	-1.2	0.5
Week 40	0.20	0.4	-0.3	1.1	-1.0	-2.5	0.4	-0.6	-1.6	0.4
Week 41	0.90	0.3	-1.0	1.6	-0.3	-3.6	3.0	-0.5	-3.2	2.3
Shoulder dystocia										
Nulliparas										
Week 37	0.50	1.3	-1.2	3.8	-2.4	-4.8	-0.1	-1.1	-2.1	-0.1
Week 38	0.54	0.1	-0.9	1.1	0.7	-1.1	2.6	0.8	-0.9	2.4
Week 39	0.15	0.5	-0.2	1.2	0.4	-1.0	1.8	0.8	-0.3	1.9
Week 40	0.22	0.3	-0.2	0.8	0.2	-1.2	1.5	0.4	-0.3	1.2
Week 41	0.63	-0.5	-2.0	1.0	-1.3	-7.6	5.1	-1.2	-3.6	1.3
Parous women										
Week 37	0.64	0.3	-0.6	1.2	0.2	-1.2	1.5	0.5	-0.8	1.7
Week 38	0.29	-0.1	-0.5	0.3	0.5	-0.1	1.1	0.4	-0.2	1.0
Week 39	0.92	0.0	-0.2	0.3	0.0	-0.4	0.3	0.0	-0.3	0.3
Week 40	0.84	0.1	-0.2	0.4	-0.1	-0.6	0.3	0.0	-0.4	0.3
Week 41	0.59	0.3	-0.5	1.0	-0.7	-2.6	1.1	-0.4	-1.8	0.9

Brachial Plexus Injury										
Nulliparas										
Week 37	1.00	-0.4	-0.9	0.2	-0.2	-0.8	0.5	-0.5	-1.3	0.2
Week 38	0.91	1.3	-1.7	4.4	1.4	-4.8	7.6	2.7	-3.2	8.5
Week 39	0.98	0.1	-1.3	1.4	-0.4	-1.8	1.0	-0.3	-1.3	0.6
Week 40	0.96	-0.2	-1.6	1.2	0.2	-1.8	2.2	0.1	-1.8	1.9
Week 41	Did not converge	Questionable convergence; extremely imprecise estimate			Questionable convergence; extremely imprecise estimate			Questionable convergence; extremely imprecise estimate		
Parous women										
Week 37	0.93	-2.0	-4.4	0.4	3.4	-4.0	10.7	2.2	-7.2	11.7
Week 38	0.77	0.5	-1.4	2.4	-0.5	-2.8	1.8	-0.2	-2.5	2.2
Week 39	0.62	-0.5	-1.7	0.7	0.7	-0.9	2.3	0.6	-1.6	2.7
Week 40	0.06	0.8	0.0	1.5	-0.2	-2.0	1.6	0.7	-0.2	1.7
Week 41	0.47	0.5	-0.9	1.9	-1.8	-9.1	5.5	-1.2	-5.0	2.7

[a]Every model was run among the sample of all deliveries (not vaginal deliveries only).
[b]Likelihood ratio test of the interaction terms (2 degrees of freedom).
[c]RERI, Relative Excess Risk of Interaction.

Table 6-7. Frequencies of Cesarean Delivery and Macrosomia by Obesity Class and Exposure Status

	EIOL, 37 weeks	EM, 37 weeks	Difference	EIOL, 38 weeks	EM, 38 weeks	Difference	EIOL, 39 weeks	EM, 39 weeks	Difference	EIOL, 40 weeks	EM, 40 weeks	Difference	EIOL, 41 weeks	EM, 41 weeks	Difference
Cesarean (%)	31.0	34.7	-3.7	29.5	35.7	-6.2	34.2	37.9	-3.7	38.9	42.8	-3.9	42.1	45.9	-3.8
Macrosomia (%)	2.2	11.2	-9	6.7	12.5	-5.8	9.1	15.2	-6.1	14.3	19.6	-5.3	20.6	23.0	-2.4
Cesarean (%)	20.0	41.0	-21	35.2	42.0	-6.8	36.6	44.1	-7.5	44.5	49.4	-4.9	48.7	51.9	-3.2
Macrosomia (%)	0.8	13.0	-12.2	6.9	14.4	-7.5	8.6	16.8	-8.2	13.7	22.0	-8.3	21.3	30.0	-8.7
Cesarean (%)	30.0	49.1	-19.1	37.9	50.0	-12.1	44.3	51.1	-6.8	51.8	56.3	-4.5	55.6	59.9	-4.3
Macrosomia (%)	0.0	14.5	-14.5	8.9	15.8	-6.9	11.4	17.7	-6.3	17.1	21.0	-3.9	20.2	26.1	-5.9

EXTENDED ANALYSIS 4. USE OF GENERALIZED ESTIMATING EQUATIONS (GEE) IN STUDIES OF ELECTIVE IOL AND MATERNAL AND INFANT OUTCOMES (AIMS 2 AND 3 EXTENSION)

BACKGROUND AND METHODOLOGY

Obstetric management decisions (e.g., the decision to electively induce) may be correlated for deliveries occurring in the same facility. The risks of maternal and infant morbidity are likely correlated for these deliveries, as well. In extended analyses of Aims 2-3, we used generalized estimating equations (GEE) with an exchangeable correlation structure to account for the correlation of deliveries occurring within the same hospital. Darney et al. used a similar approach in a study of eIOL versus expectant management among women of all BMIs.[145] We did not use GEE models in main analyses for 2 reasons: 1) we could not assess additive interaction between eIOL and obesity class using GEE logistic models, and 2) we could not use GEE models for our 3-category mode of delivery outcome, as SAS does not support GEE for non-ordinal multinomial outcomes. Fewer models also converged using the GEE approach.

Our research questions, data source, exclusion criteria, exposure definition, and study outcomes were identical to main analyses (see **Chapters 2, 4 and 5**). Our modeling approach was also equivalent, with three exceptions: 1) we could not assess mode of delivery for reasons listed above, 2) this extended analysis was modeled using GEE, and 3) interaction between eIOL and obesity class was not evaluated, similarly to other sensitivity analyses.

RESULTS

When we accounted for clustering of births by delivery hospital, some maternal morbidity associations appeared more protective (severe perineal lacerations, postpartum

hospital stay), while others appeared less protective (postpartum hemorrhage, SMM; **Table 6-8,** next page). Most associations did not change direction from protective to harmful or vice versa.

For most infant outcomes, GEE models yielded similar aORs and conclusions to those in main analyses (**Table 6-9**). In models of chorioamnionitis, point estimates moved up and toward the null; however, most associations did not change direction. Similarly, although some associations lost statistical significance, most stayed in the same direction (i.e., either protective or harmful). In GEE models, aORs for RDS were no longer elevated at 37 weeks (either parity) or 38 weeks (parous women), and a protective association between eIOL at 39 weeks and RDS emerged (both parity categories).

COMMENTS

Our findings that accounted for correlation within delivery hospital are reassuring because most point estimates changed only in magnitude, not direction. However, we were unable to utilize GEE models for our 3-category mode of delivery outcome. In addition, several GEE models for brachial plexus injury and infant death did not converge.

Table 6-8. Adjusted Odds Ratios for Elective Labor Induction versus Expectant Management and Obstetric Outcomes, Accounting for Clustering by Delivery Hospital[a]

Nulliparous women (N=83,534)					
	eIOL, 37 weeks (N=496)	**eIOL, 38 weeks (N=1,616)**	**eIOL, 39 weeks (N=3,942)**	**eIOL, 40 weeks (N=7,061)**	**eIOL, 41 weeks (N=4,961)**
Outcome	**vs. EM (N=77,984)**	**vs. EM (N=65,333)**	**vs. EM (N=40,667)**	**vs. EM (N=12,453)**	**vs. EM (N=967)**
Postpartum hemorrhage	0.83 (0.53, 1.31)	1.05 (0.84, 1.32)	0.89 (0.76, 1.05)	0.95 (0.82, 1.10)	0.76 (0.55, 1.05)
Severe perineal lacerations[b]	1.35 (0.83, 2.18)	1.09 (0.81, 1.47)	0.90 (0.73, 1.10)	1.05 (0.88, 1.25)	1.15 (0.74, 1.78)
Severe perineal lacerations[c]	1.16 (0.72, 1.89)	0.90 (0.64, 1.25)	0.77 (0.62, 0.96)	0.92 (0.76, 1.12)	1.04 (0.67, 1.60)
Severe maternal morbidity[d]	1.01 (0.72, 1.42)	1.10 (0.92, 1.31)	0.87 (0.78, 0.99)	0.98 (0.87, 1.09)	0.93 (0.70, 1.23)
Ln(postpartum hospital stay)	-0.02 (-0.05, -0.001)	-0.03 (-0.05, -0.02)	-0.03 (-0.04, -0.02)	-0.03 (-0.04, -0.02)	-0.01 (-0.03, -0.011)
Parous women (N=135,826)					
	eIOL, 37 weeks (N=1,130)	**eIOL, 38 weeks (N=3,862)**	**eIOL, 39 weeks (N=9,626)**	**eIOL, 40 weeks (N=10,748)**	**eIOL, 41 weeks (N=4,948)**
Outcome	**vs. EM (N=125,849)**	**vs. EM (N=100,642)**	**vs. EM (N=54,427)**	**vs. EM (N=12,826)**	**vs. EM (N=961)**
Postpartum hemorrhage	1.09 (0.80, 1.48)	0.84 (0.69, 1.01)	0.99 (0.88, 1.12)	0.84 (0.71, 0.99)	0.89 (0.62, 1.29)
Severe perineal lacerations[b]	0.72 (0.30, 1.69)	0.78 (0.46, 1.33)	0.77 (0.57, 1.04)	1.05 (0.71, 1.56)	Did not converge
Severe perineal lacerations[c]	0.69 (0.29, 1.66)	0.76 (0.45, 1.30)	0.75 (0.55, 1.01)	1.00 (0.66, 1.50)	Did not converge
Severe maternal morbidity[d]	1.01 (0.78, 1.32)	0.84 (0.71, 1.00)	0.94 (0.84, 1.05)	0.87 (0.75, 1.01)	0.93 (0.64, 1.34)
Ln(postpartum hospital Stay)	0.01 (-0.003, -0.031)	-0.0003 (-0.01, 0.01)	-0.01 (-0.01, -0.001)	-0.01 (-0.02, -0.001)	-0.01 (-0.03, -0.011)

[a]eIOL, elective induction of labor. EM, Expectant Management. Table data are adjusted odds ratios (95% confidence intervals). Ln(maternal hospital stay) was modeled using multivariable linear regression. Remaining outcomes were modeled using multivariable logistic regression. Models were adjusted for maternal age, maternal education, maternal race/ethnicity, initiation of prenatal care in the first trimester, principal source of payment for delivery, birth year, obesity class, and weekday delivery. We used generalized estimating equations with an exchangeable correlation structure to account for clustering of deliveries by maternal hospital.
[b]Among all deliveries.
[c]Among vaginal deliveries only.
[d]Composite outcome including postpartum hemorrhage, severe perineal laceration, unplanned surgical procedure, uterine rupture, maternal intensive care unit admission, maternal sepsis, and endometritis.

Table 6-9. Adjusted Odds Ratios for Elective Labor Induction versus Expectant Management and Infant Outcomes, Accounting for Clustering by Delivery Hospital[a]

Nulliparous women (N=83,534)

Outcome	**eIOL, 37 weeks (N=496) vs. EM (N=77,984)**	**eIOL, 38 weeks (N=1,616) vs. EM (N=65,333)**	**eIOL, 39 weeks (N=3,942) vs. EM (N=40,667)**	**eIOL, 40 weeks (N=7,061) vs. EM (N=12,453)**	**eIOL, 41 weeks (N=4,961) vs. EM (N=967)**
Infant Death	Did not converge	2.33 (0.87, 6.25)	0.22 (0.03, 1.56)	Did not converge	Did not converge
Infant stay >5 days[e]	1.53 (1.04, 2.27)	0.81 (0.58, 1.15)	0.78 (0.63, 0.97)	0.76 (0.63, 0.92)	0.71 (0.52, 0.98)
Macrosomia (≥4000 g)	0.12 (0.06, 0.24)	0.51 (0.42, 0.62)	0.56 (0.50, 0.63)	0.71 (0.64, 0.78)	0.78 (0.66, 0.92)
Chorioamnionitis	0.96 (0.62, 1.49)	0.77 (0.62, 0.96)	0.79 (0.68, 0.91)	0.91 (0.79, 1.05)	0.92 (0.66, 1.30)
Meconium aspiration syndrome	0.31 (0.05, 1.73)	0.36 (0.15, 0.83)	0.59 (0.39, 0.89)	0.30 (0.20, 0.45)	Did not converge
Respiratory distress	0.94 (0.61, 1.45)	1.10 (0.82, 1.48)	0.70 (0.54, 0.91)	0.85 (0.69, 1.05)	Did not converge
Shoulder dystocia[c]	1.20 (0.63, 2.31)	1.01 (0.68, 1.51)	1.16 (0.90, 1.50)	1.24 (0.96, 1.58)	1.75 (0.92, 3.32)
Shoulder dystocia[d]	1.09 (0.57, 2.11)	0.90 (0.60, 1.35)	1.06 (0.81, 1.37)	1.14 (0.88, 1.46)	1.52 (0.78, 2.94)
Brachial plexus injury[c]	Did not converge	0.75 (0.19, 2.86)	0.40 (0.13, 1.29)	Did not converge	Did not converge
Brachial plexus injury[d]	Did not converge	0.68 (0.17, 2.63)	0.39 (0.12, 1.25)	Did not converge	Did not converge

Parous women (N=135,826)

Outcome	**eIOL, 37 weeks (N=1,130) vs. EM (N=125,849)**	**eIOL, 38 weeks (N=3,862) vs. EM (N=100,642)**	**eIOL, 39 weeks (N=9,626) vs. EM (N=54,427)**	**eIOL, 40 weeks (N=10,748) vs. EM (N=12,826)**	**eIOL, 41 weeks (N=4,948) vs. EM (N=961)**
Infant Death	3.48 (1.46, 8.29)	1.48 (0.69, 3.17)	0.46 (0.19, 1.12)	1.08 (0.51, 2.29)	Did not converge
Infant stay >5 days[e]	1.46 (0.94, 2.27)	1.00 (0.76, 1.32)	0.67 (0.54, 0.83)	0.77 (0.62, 0.96)	1.15 (0.67, 1.97)
Macrosomia (≥4000 g)	0.34 (0.27, 0.44)	0.54 (0.49, 0.60)	0.62 (0.58, 0.66)	0.74 (0.69, 0.79)	0.91 (0.78, 1.07)
Chorioamnionitis	1.06 (0.55, 2.04)	0.94 (0.65, 1.37)	0.80 (0.63, 1.01)	0.74 (0.56, 0.98)	Did not converge
Meconium aspiration syndrome	0.55 (0.13, 2.29)	0.39 (0.17, 0.89)	0.40 (0.25, 0.65)	0.46 (0.30, 0.71)	0.42 (0.20, 0.89)
Respiratory distress	0.84 (0.40, 1.76)	0.97 (0.72, 1.32)	0.74 (0.62, 0.89)	0.85 (0.63, 1.13)	0.87 (0.44, 1.73)
Shoulder dystocia[c]	0.82 (0.56, 1.21)	0.68 (0.54, 0.85)	0.76 (0.66, 0.88)	0.80 (0.67, 0.95)	0.91 (0.63, 1.31)
Shoulder dystocia[d]	0.81 (0.55, 1.20)	0.67 (0.54, 0.84)	0.75 (0.65, 0.86)	0.79 (0.66, 0.94)	0.89 (0.62, 1.28)
Brachial plexus injury[c]	1.38 (0.48, 3.92)	0.65 (0.28, 1.52)	Did not converge	Did not converge	Did not converge

Brachial plexus injury[d]	1.35 (0.48, 3.84)	0.64 (0.27, 1.49)	Did not converge	Did not converge	Did not converge

[a]eIOL, elective induction of labor. EM, Expectant Management.
[b]Table data are adjusted odds ratios (95% confidence intervals) from multivariable logistic regression models. Models were adjusted for maternal age, maternal education, maternal race/ethnicity, initiation of prenatal care in the first trimester, principal source of payment for delivery, birth year, obesity class, and weekday delivery. We used generalized estimating equations with an exchangeable correlation structure to account for clustering of deliveries by maternal hospital.
[c]Among all deliveries.
[d]Among vaginal deliveries only.
[e]N=21 nulliparas and N=27 parous women were missing data on length of infant stay.

CHAPTER 7, IMPLICATIONS AND CONCLUSIONS

AIM 1

AIM 1 **IMPLICATIONS**

This dissertation highlights possible ways to reduce the risk of adverse pregnancy outcomes associated with maternal weight. In **Aim 1**, we found that gaining below the 35th percentile of GWG z-score was associated with a small increase in the risk of stillbirth among women irrespective of pre-pregnancy BMI. Despite differences in study design and methodology, our findings showing increased risk of stillbirth at low levels of GWG z-score are consistent with trends from three of four previous investigations.[51,140,155] In our main analyses, which were not stratified by BMI category, we found no association between high GWG z-score and stillbirth; these results are in concordance with three of four previous studies.[51,140,154] Our **Aim 1** findings may not be generalizable to women with multiple gestations or preexisting diabetes.

In concordance with our hypotheses, low GWG z-score (≤35th percentile, versus the 50th percentile) was associated with an increased risk of stillbirth in normal weight and overweight women (z-score ≤-0.51, versus -0.17). Among normal weight women, this GWG z-score comparison translated to an increased risk of stillbirth for women with GWG ≤30 lb, compared to women with GWG of 34 lb (at term [40 weeks]). Among overweight women, the risk of stillbirth was increased for women with a GWG ≤26.8 lb (at term), compared to those who gained 32 lb. Previous research has shown that low GWG increases the risk of intrauterine growth restriction[3] and preterm labor,[118] both of which are risk factors for stillbirth,[163,164] among normal weight and overweight gravidas.

We did not find an association between high GWG z-score and stillbirth among normal weight women. The risks of gestational hypertension, gestational diabetes, and

LGA are lower in normal weight women than in women of higher BMI categories;[9,10,16,17,52] in addition, the mean GWG among normal weight control mothers in the SCRN (33.8 lb) was within current IOM guidelines. Overall, our findings suggest that normal weight women may minimize their risk of stillbirth by gaining 30 lb or more during pregnancy (GWG above 30 lb was not associated with increased or decreased odds of stillbirth among normal weight women in our sample). These recommendations are in line with current IOM guidelines for normal weight women (25-35 lb).[101]

As hypothesized, excess GWG z-score (≥75th percentile, versus the 50th percentile) was positively associated with the risk of stillbirth among overweight women. This corresponds to an elevated risk of stillbirth for overweight women with GWG z-score ≥0.50 (total GWG ≥41.2 lb at term), compared to overweight women with a median z-score of -0.17 (total GWG of 32 lb). Notably, our findings for high GWG z-score were imprecise, suggesting that more research is needed among overweight women. Excess GWG may increase the risk of gestational diabetes, gestational hypertension, and macrosomia,[3,104-106] which are already more common among overweight women than among normal weight women.[9,10,16,17,52] These medical conditions are risk factors for stillbirth.[163,164] Considering both low and high GWG together, our findings suggest that overweight women may minimize their risk of stillbirth by gaining between the 35th and 75th percentiles of GWG z-score (26.8-41.2 lb). These upper and lower bounds closely correspond to current IOM recommendations for overweight women (25-35 lb).[101] However, our findings do not support ACOG's recent (2013) conclusion that overweight women may safely gain below IOM recommendations without increasing the risk of adverse pregnancy outcomes.[103] GWG

counseling for overweight women should emphasize the importance of avoiding excess GWG. In our dataset, the mean GWG among overweight mothers (30.9 lb) exceeded the IOM's recommended upper limit of 25 lb.[101] Other researchers have found that overweight women are the most likely to exceed IOM GWG recommendations, compared to women in other BMI categories.[110,112,115,122]

Contrary to our hypotheses, the odds of stillbirth were increased among obese women who gained ≤35th percentile of GWG z-score; we expected that low GWG would reduce the odds of stillbirth. Among class 1 obese women (who were evaluated separately from morbidly obese women in sensitivity analyses), this corresponds to an increased risk of stillbirth for women with a GWG z-score ≤-0.43 (total GWG ≤21.0 lb), versus women with a median GWG z-score of -0.09 (total GWG of 26.8 lb). The risk of stillbirth was highest at GWG z-scores at or below the 15th percentile (z-score= -1.11, corresponding to a total GWG of 10.9 lb).

Among morbidly obese women (BMI ≥35 kg/m^2), the odds of stillbirth were elevated for women with a GWG z-score ≤35th percentile (-0.14, versus the median of 0.26). As described in **Chapters 2-3**, GWG z-scores were calculated separately for classes 2 and 3 obese women (i.e., the values used in GWG z-score calculations [where GWG z-score= , $\frac{\ln(GWG+c)-mean\,(\ln(GWG))}{standard\ deviation(\ln(GWG))}$[156,157]] differed by obesity class). Consequently, GWG z-scores of ≤-0.14 and 0.26 correspond to slightly different values of <u>total GWG</u> for classes 2 versus 3 obese women. Accounting for these differences, our findings suggest that the risk of stillbirth may be increased among class 2 obese women who gain ≤19.0 lb [versus 27.6 lb] and among class 3 obese women who gain ≤11.8 lb [versus 21.9 lb]. Our findings for class 3 obese women, which show a reduced risk of

stillbirth for GWG >11.8 lb, agree with the IOM's recommended lower limit of GWG for obese women (the recommended range is 11-20 lb).[101] However, for classes 1 and 2 obese women, our results suggest that gaining above IOM guidelines (i.e., >21.0 lb and >19.0 lb, respectively) may be associated with reduced risk of stillbirth. Classes 2 and 3 obese women should ideally be evaluated in separate models; however, we did not have adequate sample size to further separate morbidly obese women into classes 2 and 3 obese gravidas. Future research should assess how the association of GWG with stillbirth may differ between classes 2 and 3 obese women.

We hypothesized that low GWG z-score would reduce the risk of stillbirth among obese women, as previous research showed that low GWG reduces the risk of LGA and gestational hypertension[3,105,120-126] (which are risk factors for stillbirth[163,164]) among obese gravidas. However, inadequate GWG is also a risk factor for SGA. SGA is more strongly associated with stillbirth than is LGA.[164] SGA may have driven the overall association between low GWG z-score and *increased* odds of stillbirth among obese women in our study. Our findings correspond to a recent study of GWG and infant mortality by Bodnar et al., who found that the risk of infant mortality was increased among obese women with GWG z-scores <0 (however, findings among class 3 obese women were imprecise).[67]

In contrast to our hypotheses, high GWG z-score did not increase the risk of stillbirth among obese women. Rather, GWG z-score and stillbirth were not associated among class 1 obese women. Furthermore, among morbidly obese women, the odds of stillbirth were lower in women with GWG z-scores ≥75th percentile (z-score of 1.12 vs. 0.26). As described above, GWG z-scores of 1.12 and 0.26 correspond to slightly

different values of total GWG for classes 2 and 3 obese women. Our results indicate that the risk of stillbirth may be higher in class 2 obese women who gain ≥51.0 lb (versus 27.6 lb) and for class 3 obese women who gain ≥50.6 lb (versus 21.9 lb). These findings for high GWG z-score were imprecise; they are also preliminary, given that classes 2 and 3 obese women were not assessed in separate, stratified models. Our findings suggesting that classes 2 and 3 obese women should avoid gaining >51 lb during pregnancy concur with IOM recommendations, which advise obese gravidas not to gain above 20 pounds.[101] Notably, the IOM's GWG recommendations were based on many different (and sometimes competing) pregnancy outcomes, such as SGA, LGA, and postpartum weight retention.[101] Clinical GWG recommendations must balance the seriousness as well as the likelihood of these adverse outcomes. Stillbirth is one of the most *serious* potential effects of inadequate or excess GWG. However, it is also rare, and most associations between GWG and stillbirth appear modest. Decisions about which pregnancy outcomes to prioritize during GWG counseling are subjective and may depend upon a patient's individual risk factors and pregnancy history.

In summary, our findings for class 3 obese women agree with current IOM recommendations. For classes 1 and 2 obese women, our results suggest that gaining above IOM recommendations may slightly reduce the risk of stillbirth, although extremely high GWG (>51 lb) appeared harmful in class 2 obese women. Although the IOM recommends the same range of GWG for all obese women, our study suggests that associations between GWG and stillbirth may differ by obesity severity. As described in **Chapter 1**, associations between GWG and many other adverse pregnancy outcomes vary by obesity class.

Our findings suggest that low GWG z-score—and for some women, high GWG z-score—may be an indicator of poor fetal health. Investigators have proposed that the GWG z-score be employed in perinatal epidemiologic research studies, with the hope that the GWG z-score will eventually be applied in clinical settings. Given the modest effect sizes in our study, as well as stillbirth's complex etiology, it is unlikely that the GWG z-score will have high discriminatory power for stillbirth. However, in combination with other clinical measurements (e.g., estimated fetal size), GWG z-score may be useful in the clinical setting as a way to identify women whose fetuses are at risk of stillbirth. More research is needed to assess whether the GWG z-score can accurately identify women and fetuses who are at risk of other adverse pregnancy outcomes.

AIM 1 LIMITATIONS, STRENGTHS, AND INNOVATION

Aim 1 of this dissertation has several limitations, which were discussed in detail in **Chapter 3**. For instance, our study lacked data on GWG trajectories over time.[174] Hence, we could not assess 1) whether women maintained the same GWG z-score throughout all of pregnancy, and, if not, 2) whether GWG z-scores at certain time points were more important than at other time points.

We lacked information on GWG at the time of fetal death. This is important because fetal weight may change between fetal death and delivery. However, we addressed this limitation by excluding macerated stillbirths in a sensitivity analysis.

As discussed previously, the GWG z-scores in our study may not be fully independent of GA (i.e., using Hutcheon et al.'s formulas, low GWG z-scores in our study could still reflect a short gestational duration, rather than a low GWG that is

standardized for [i.e., independent of] gestational duration).[174] This could result in an association between low GWG z-score and stillbirth that is biased away from the null.[174]

We were not able to assess the relation between GWG and stillbirth among underweight women due to an inadequate sample size for stratified analysis. Pre-pregnancy underweight is rare and declining in the U.S. However, it is biologically plausible that low GWG could increase the risk of stillbirth among underweight gravidas.

Women tend to understate their pre-pregnancy weight.[270-272] This could result in underestimation of pre-pregnancy BMI and overestimation of GWG. If control mothers more frequently underreport their pre-pregnancy weight (which would result in an overestimated GWG for control mothers), then associations between low GWG z-score and stillbirth could be biased away from the null. In addition, women with higher pre-pregnancy BMIs more frequently underreport their weight.[120,271,272] Consequently, the associations between low GWG z-score and stillbirth are potentially more strongly biased among more severely obese women. However, many researchers have shown that the amount of bias using self-reported BMI is minimal.[105,270-272]

We cannot exclude the possibility of residual confounding by other maternal or fetal risk factors. For example, there could be confounding by exercise/physical activity during pregnancy,[264] which were not measured in SCRN. Selection bias could arise if participation varies by both case status and GWG. We could not use sampling weights to directly adjust for participation by GWG level, as GWG was not measured in nonparticipants. However, sampling weights accounted for differential likelihood of participation by case status and other factors (e.g., maternal age and GA[243]) that are related to GWG. Consequently, the use of these analysis weights would correct for some

of this potential selection bias.[273] Furthermore, SCRN's sampling method—selecting controls randomly (within strata) from the population of live births—should limit the amount of selection bias that occurs from specifying the sample.

Despite the limitations of our research study, this project has numerous strengths. First, this study addresses a large research gap—the association between GWG and stillbirth. Previous research on the association between GWG and stillbirth[51,140,154,155] is limited and inconclusive.[49] The single previous U.S. study on GWG and stillbirth was published in 1986.[155] Second, this project improves upon many methodological problems present in other studies. Our study is the first to examine stillbirths at 20-27 weeks, which constitute half of stillbirths in the U.S.[147] Another study strength is that our exposure variable, the GWG z-score, standardizes for GA. Two of four previous studies did not account for GA in their measure of exposure,[154,155] which is a major limitation since GA is so strongly associated with both GWG and stillbirth. Our analysis also includes intrapartum stillbirths, unlike two previous investigations.[51,140] Furthermore, we did not exclude women with conditions that could be influenced by GWG,[101] such as gestational diabetes or hypertensive disorders (in contrast to a previous analysis[51]). To the best of our knowledge, ours was the first study of GWG and stillbirth to assess differences between class 1 obese and morbidly obese women. We also tested our assumptions in nine different sensitivity analyses. For instance, we excluded stillbirths with congenital malformations in one sensitivity analysis and excluded macerated stillbirths in another. In addition, we conducted sensitivity analyses using two different GWG z-score referent populations.

Data quality in the SCRN case-control study is high. The SCRN collected comprehensive information on maternal sociodemographic characteristics and maternal and fetal medical conditions using fetal autopsy, placental pathology, medical records, and maternal interviews.[243] SCRN also conducted a thorough assessment of the timing and cause of fetal death.[163,243] We adjusted for a large number of potential confounding variables in our study.

Compared to previous studies, our results may be more generalizable to the rest of the U.S. SCRN hospitals included both academic teaching hospitals and nonacademic hospitals of different levels of care. Many studies are currently only conducted in academic settings, which may not be applicable to the rest of the population,[183] or in tertiary care hospitals, which represent higher-risk deliveries.[243]

AIM 1 CONCLUSIONS

Gaining sufficient weight during pregnancy may reduce the risk of stillbirth among normal weight, overweight, and obese women. In addition, high GWG may increase the risk of stillbirth among overweight women. Our findings for normal weight, overweight, and class 1 obese women closely corresponded to the Institute of Medicine's GWG recommendations.[101] Among morbidly obese women, there was a trend toward reduced risk of stillbirth with increasing GWG, and our results suggested that GWG above IOM recommendations may slightly reduce the risk of stillbirth among morbidly obese gravidas. Our findings among morbidly obese women were preliminary, and additional research with larger sample sizes of classes 2 and 3 obese women is needed.

AIMS 2 AND 3

AIMS 2-3 IMPLICATIONS

In **Aim 2** of this dissertation, we found that elective induction of labor between 37 and 41 weeks' gestation was associated with reduced odds of cesarean delivery in obese women. Furthermore, additive interaction models suggested that the benefits of eIOL, with respect to cesarean delivery, may increase with obesity severity among nulliparous women. Additionally, eIOL between 38-40 weeks' gestation was associated with reduced odds of postpartum hemorrhage and severe maternal morbidity. Likewise, eIOL was associated with a modestly reduced postpartum hospital stay (≤-0.1 days) among obese nulliparas. Findings for cesarean delivery, postpartum hemorrhage, severe maternal morbidity, and maternal postpartum stay were consistent with our hypotheses. Elective IOL to prompt earlier delivery may prevent risk factors for CD and maternal morbidity that increase throughout pregnancy, such as macrosomia[145,187] and preeclampsia.[183] In contrast to our hypotheses, eIOL was associated with slightly increased risk of operative vaginal delivery. The positive association between eIOL and operative vaginal delivery may be due to side effects of IOL (greater need for epidural,[37] fetal distress,[211] prolonged labor) that increase the need for forceps or vacuum delivery. These side effects may be exacerbated among obese women, who have longer durations of labor, and who more frequently use analgesics, than non-obese women. We did not observe an association between eIOL and third-or-fourth-degree perineal lacerations. Because eIOL is associated with reduced risk of macrosomia,[145,187] we hypothesized that eIOL would be associated with reduced risk of perineal lacerations. However, any protective association between eIOL and perineal lacerations due to the prevention of macrosomia may have been

counteracted by the positive association between eIOL and operative vaginal delivery.

The **true** association between eIOL and all maternal and infant outcomes likely falls somewhere in between the findings from our main analyses and our sensitivity analyses. Our first sensitivity analysis addressed the fact that certain intrapartum complications could either be causes or consequences of induction, depending on their timing. The list of IOL indications in our main analysis represents the circumstances that we hypothesized to be most likely (based on plausible biological mechanisms). We revised our list of IOL indications in a sensitivity analysis, which allowed us to evaluate potential alternative scenarios. Associations between eIOL and cesarean delivery appeared more strongly protective in this sensitivity analysis; conclusions for most other outcomes were unchanged.

Our second sensitivity analysis explored an alternative expectant management classification. This second sensitivity analysis was necessary because our dataset only contained an obstetric estimate of gestational age in weeks, rather than days. As a result, we did not know whether deliveries occurred on the first or the last day of a given week, and it was not possible to determine whether electively induced deliveries <u>preceded</u> spontaneous deliveries during a particular week. (In order for spontaneous deliveries to be considered *expectantly managed,* they would need to follow, rather than precede, electively induced deliveries.) To ensure that the unexposed group truly depicted delayed delivery, relative to the exposed group, we defined expectant management as *'all deliveries in later weeks'* in main analyses. This can be considered one 'extreme,' as all spontaneous deliveries during the index week were excluded from the given analysis. Point estimates in main analyses could be biased downward—which would make eIOL

look artificially preferable—because the risk of many outcomes (e.g., cesarean, macrosomia) increases with gestational age.

In sensitivity analyses, all spontaneous deliveries during the given week were included in the expectant management group. This can be considered the other 'extreme.' The true association between eIOL and pregnancy outcomes is likely in between these two 'extremes' and is influenced by the average gestational age distribution of elective inductions and spontaneous deliveries during a given week. This GA distribution likely varies by year, hospital, and provider (hospital and year were included as covariates in our model; we lacked data on individual providers). Due to hard-stop policies prohibiting elective delivery <39 weeks, [230] elective induction at 39 weeks 0 days may be particularly likely. This would support the use of our alternative (sensitivity analysis) expectant management definition for 39 weeks' gestation. A randomized, controlled trial would ultimately be needed to better understand the true associations between eIOL and pregnancy outcomes. We chose the main expectant management definition (all deliveries in later weeks) over that of the sensitivity analysis definition for reasons described in Chapter 2: namely, we were not convinced that labor onset/type were accurately recorded for all cesarean deliveries. Notably, most conclusions were unchanged from main analyses using this revised expectant management definition. However, results for eIOL ≥39 weeks and cesarean delivery were strikingly different from main analyses. Using the new expectant management classification, eIOL ≥39 weeks became associated with up to a 2.52 times **higher** odds of cesarean delivery. This is in stark contrast to the protective associations between eIOL and CD observed in main analyses. We hypothesize that these sensitivity analysis results may be biased up and away from the null for 2 reasons. First,

the risk of CD in a given week is lower in spontaneous than in induced deliveries (all spontaneous deliveries were considered expectantly managed in this sensitivity analysis). Second, some women with both spontaneous labor onset and cesarean delivery during the index week may not have been detected in our dataset. Regardless, it is reassuring that our findings for most maternal and infant clinical endpoints (e.g., severe maternal morbidity) were relatively unaffected in this sensitivity analysis.

Conclusions from our study were similar to those of other investigators. For example, our findings agree with a recent modeling study, which found that routine IOL at 39 weeks would reduce CD risk and health care costs among obese women.[238] Likewise, a clinical protocol involving routine IOL by 40 weeks' gestation was recently found to reduce the rate of CD among obese women in a Pennsylvania health system, as compared to the rate of CD prior to protocol initiation.[239] Similarly to our study, eIOL was associated with reduced odds of CD, macrosomia, and postpartum hemorrhage (although postpartum hemorrhage results were imprecise), in Lee et al.'s analysis of obese women in the 2007 California Linked dataset.[187] Notably, eIOL was also associated with reduced odds of CD in a study among women of all BMI categories, which used the 2006 California Linked dataset.[145] Our findings of no association between eIOL and severe perineal lacerations agree with those of Lee et al.[187]

Although eIOL was associated with slightly increased odds of operative vaginal delivery in our study, Lee et al. detected no association.[187] Lee et al. analyzed operative vaginal delivery as a dichotomous outcome,[187] rather than assessing it as part of a multinomial mode of delivery outcome, as we did. Our findings for operative vaginal delivery and severe perineal lacerations differ from a recent study of eIOL among women

of all BMI categories.[145] Among Darney et al.'s sample of all BMI categories, term eIOL was associated with reduced odds of operative vaginal delivery and severe perineal lacerations among parous women. It is expected that these findings would differ between obese women and the general population. As previously mentioned, obese women are at higher risk of epidural use and prolonged labor, which are possible side effects of IOL.[37] These factors may increase the need for operative vaginal delivery, and therefore, the likelihood of severe perineal lacerations.

In **Aim 3** of this dissertation, we found that eIOL at <39 weeks was associated with increased risk of infant mortality among offspring of obese women. Elective IOL at 37 weeks increased the odds of infant hospital stay >5 days, while eIOL between 39 and 40 weeks was associated with reduced odds of extended infant hospital stay. The adjusted odds of RDS were mildly elevated among electively induced obese women prior to 39 weeks, but 95% CIs overlapped the null. Term eIOL was associated with reduced odds of macrosomia (37-40 weeks), meconium aspiration syndrome (≥38 weeks), and chorioamnionitis (≥38 and 39-40 weeks among nulliparas and multiparas, respectively). Among infants born to obese parous women, eIOL was associated with reduced odds of shoulder dystocia (38-40 weeks) and brachial plexus injury (40-41 weeks). Additive interaction models suggested that eIOL may be more strongly associated with reduced risk of macrosomia in classes 2 and 3 (versus class 1) obese nulliparas. Our Aim 3 findings were in concordance with our original hypotheses.

Early delivery via eIOL may prevent neonatal complications that increase throughout gestation. For instance, eIOL may prevent macrosomia;[145,187] in turn, this may reduce the risks of shoulder dystocia and brachial plexus injury.[6] Early delivery via

elective IOL may also prevent meconium aspiration syndrome, which is more frequent at later GAs.[188] Elective IOL may prevent premature rupture of membranes, which is a risk factor for chorioamnionitis.[208] However, delivering before 39 weeks' gestation may compromise fetal lung maturity,[193] which could increase the risk of RDS and infant mortality. In **Aim 2** of our study, we observed a reduced risk of cesarean delivery among electively induced obese women (as did Lee et al.[187]). A reduction in cesarean delivery among electively induced women may also benefit their offspring by reducing neonatal morbidity.[207]

Our findings corroborated those of other investigators. For instance, a hospital-based study of obese nulliparas reported lower birthweight among electively induced women at 39-40 weeks' gestation.[240] Likewise, a retrospective study among women of all BMI categories found that eIOL was associated with reduced risk of macrosomia.[145] These results parallel our findings for macrosomia. In addition, other investigators found that a clinical protocol to induce obese women by their estimated due date slightly reduced NICU length of stay.[239] In a study of all BMI categories, eIOL between 38-40 weeks was associated with reduced odds of extended infant stay/NICU admission.[145] These findings are similar to our results for extended infant hospital stay. Similarly to our study, Lee et al. found that term eIOL was associated with reduced risks of macrosomia, shoulder dystocia, and chorioamnionitis among offspring of obese women in the 2007 California linked dataset.[187] However, precision was limited in their analyses, and many 95% CIs for chorioamnionitis and shoulder dystocia overlapped the null.

Our findings reinforce ACOG's recommendation against elective delivery <39 weeks' gestation,[193] as well as current health system-wide policies which discourage or

prohibit elective delivery <39 weeks.[222,223,230-232] However, between 39 and 41 weeks, eIOL, as compared to expectant management, may optimize the health of both obese women and their offspring. Future studies may wish to assess the tradeoffs of eIOL versus expectant management using BMI at delivery, as one study has done.[240] Delivery BMI may be more immediately relevant to obstetric decision-making *at delivery* than pre-pregnancy BMI. However, BMI at delivery may not be as valid of a measure of *maternal adiposity* as is pre-pregnancy BMI, as maternal delivery weight includes fetal weight, amniotic fluid weight, and placental weight, as well as blood volume. Thus, using observational data, it could be challenging to determine whether women with equal delivery BMIs were comparable with respect to maternal adiposity.

We recommend that future research should: 1) explore the association between eIOL and adverse pregnancy outcomes in populations other than California; 2) evaluate differences by obesity severity (using larger sample sizes of obese women); 3) evaluate whether term eIOL affects some obese subgroups (e.g., those with a favorable cervix) differently than others;[89] 4) examine stillbirth, which is a potential consequence of expectant management (the risk of stillbirth increases with gestational age[89,163,166,199-201]); and 5) assess cost-effectiveness outcomes (beyond length of maternal and infant postpartum hospital stay, which were evaluated in this study).

Depending on future observational study findings, a randomized, controlled study may ultimately be warranted in order to reduce residual confounding, eliminate exposure misclassification, and further refine the estimated effects of eIOL among obese gravidas. Obstetric management of obese gravidas will likely continue to be an important topic in

coming years due to the high and increasing prevalence of pre-pregnancy obesity in U.S. women.[2]

AIMS 2-3 LIMITATIONS, STRENGTHS, AND INNOVATION

Dissertation **Aims 2 and 3** have limitations. Gestational age may be misclassified in our study. We used the best obstetric estimate of GA; however, this is less accurate than a first-trimester ultrasound.[274] Furthermore, LMP dating, which may be used to calculate the best obstetric estimate of GA, is less accurate among obese than non-obese women.[56] Obese women are more likely to have irregular menses.[56] As a result, they more frequently overestimate and underestimate their GA.[275] Moreover, it is particularly challenging for clinicians to read ultrasounds in obese women due to their excess adiposity.[276] GA misclassification affects both electively induced and expectantly managed women in our study and could obscure important gestational age-specific differences between these treatment options. We would expect GA misclassification to be non-differential with respect to study outcomes.

The obstetric estimate overestimates GA compared to early ultrasound.[274] Barradas et al. found that the sensitivity of the obstetric estimate (versus the gold standard of an early ultrasound) was lowest at 42 weeks' gestation (21.5%). Under this scenario, the accuracy of our study analyses may decrease with GA. Week-specific sensitivities of GA may be low on the birth certificate due to the fact that the best obstetric estimate of GA is rounded down to the nearest week (rather than being recorded in days).[274] This "flooring" produces other problems, as well; for instance, it can obscure differences within weeks, as the risk of complications is likely not uniform over a particular week of GA.[166] Gestational age flooring also makes it challenging to compare

eIOL during a given week to spontaneous deliveries in that same week. That is, our dataset does not contain information on whether the GA distribution of spontaneous deliveries during the index week differed from the GA distribution of elective inductions that week. We used two different expectant management classifications in **Aims 2 and 3** to address alternative scenarios.

We calculated pre-pregnancy BMI using height and weight on vital records. Information on pre-pregnancy weight may come from self-report *at the time of delivery,* or it may have been abstracted from prenatal records, labor and delivery records, or other hospital medical records.[270] Women typically underreport their weight/BMI,[270-272] and the frequency of underreporting increases with BMI category.[270-272] In Aims 2-3, this could result in women who were truly obese being erroneously excluded from our sample. In addition, obesity class (1-3) may be underestimated for some women. This may have impacted our assessments of additive and multiplicative interaction by obscuring potentially important differences between classes 1, 2, and 3 obese women.

It is possible that misclassification of pre-pregnancy BMI could differ by exposure status, particularly if pre-pregnancy BMI is *reported at delivery*. Women who deliver at earlier gestational ages may more accurately recall their pre-pregnancy BMI (i.e., because less time has passed between conception and delivery, compared to later gestational ages). Similarly, because electively induced women deliver earlier than expectantly managed women, pre-pregnancy BMI may be more accurately reported among the exposed group. (However, the accuracy of pre-pregnancy BMI may decrease with GA among both exposed and unexposed groups.) These differences may be most exacerbated when eIOL at early gestational ages is evaluated (e.g., 37 weeks versus all

deliveries at 38 weeks or later). It is also possible that misclassification of pre-pregnancy BMI *reported at delivery* may differ by outcome status. Immediately after a difficult delivery, women may be overwhelmed and unable to accurately recall answers to questions about their pre-pregnancy BMI. On the other hand, if women with adverse outcomes women can accurately recall their pre-pregnancy BMI, they may be more likely to respond truthfully regarding their pre-pregnancy height and weight.

If expectantly managed women are more likely to underreport their pre-pregnancy BMI (i.e., due to poorer recall with a longer gestation), then they may also be more likely to be wrongly excluded from our dataset (due to apparent pre-pregnancy BMI <30 kg/m^2). If women *without* the outcome of interest are <u>also</u> more likely to underreport their BMI, then they may also be more likely to be wrongly excluded from our study sample. Under this scenario, the association between eIOL and adverse pregnancy outcomes could appear artificially protective due to the disproportionate exclusion of expectantly managed women with optimal pregnancy outcomes from our study. However, alternative scenarios are also possible (e.g., disproportionate exclusion of expectantly managed women with adverse outcomes, which would make eIOL look artificially harmful).

On the whole, we find it unlikely that misclassification of pre-pregnancy BMI would differ meaningfully by exposure status. Accurate recall of pre-pregnancy BMI is likely similar between electively induced and expectantly managed women, as all women in our study delivered within a several weeks of each other. Furthermore, it seems improbable that the likelihood of *truthfully* reporting pre-pregnancy BMI would differ by exposure status. We lack information on the proportion of women in our dataset who self-reported pre-pregnancy BMI *at delivery*.

Many researchers have found a relatively high validity and reliability of pre-pregnancy weight and height on the birth certificate.[270] For instance, a 2011 Florida study found a sensitivity of 76% and a positive predictive value of 92.7% for obesity calculated from the birth certificate, as compared to height and weight measured during a first trimester prenatal care visit (gold standard). Furthermore, BMI underreporting does not impact overall BMI category for most women.[105]

Another limitation to our study is that our results may not be generalizable to deliveries outside of California. Demographics in California are slightly different than in rest of the U.S. For instance, in 2012, 49.2% of births in California were to Hispanic mothers, compared to 23.7% in the U.S. as a whole.[277] California also has a higher fertility rate than the rest of the U.S.[277] In addition, maternal and child health are slightly better in California than in the rest of the U.S. In 2007, the risks of neonatal mortality, infant mortality, low birth weight, and preterm birth were approximately 15-20% lower in California than in the U.S. as a whole, although the risks of stillbirth were similar.[277]

Our studies may not be generalizable to women with preexisting conditions, such as diabetes. However, we do not think of this as a weakness. Women with chronic conditions are known to be managed differently than women without chronic conditions. We aimed to evaluate whether, in the absence of preexisting maternal conditions, obesity itself should be considered an indication for earlier delivery.

Our dataset does not include information on whether an IOL was considered medically indicated or elective by the attending physician. In addition, there is no single accepted definition of elective or medically indicated IOL. Similarly to other investigators,[145,187] we utilized Joint Commission guidelines[218] to rule out medically

indicated IOL, as these standards are regularly used in clinical settings. We lacked information on whether fetal distress, placental abruption, and other intrapartum complications preceded or followed IOL. However, we evaluated both possible scenarios in sensitivity analyses.

Maternal, infant, and pregnancy complications may be underreported in our dataset compared to patient medical records; however, the accuracy of many maternal diagnoses is high in linked datasets,[258-260] particularly compared to vital records data alone.[278] Still, the possibility of differential misclassification cannot be ruled out; for instance, coders may spend more time abstracting exposure information if they come across a case versus if they come across a control.[279] Under this scenario, induced women with poor pregnancy outcomes might be more often classified as having medically indicated, rather than elective, IOL (due to the increased detection of medical complications among this group). This could result in associations between eIOL and pregnancy outcomes that appear artificially protective.

We lacked information on method of IOL, and associations between eIOL and pregnancy outcomes may differ by this factor.[267] Although we accounted for a large number of potential confounders that were associated with the exposure and the outcome variables,[145,187] unmeasured confounding by cervical status,[241] patient or provider preferences,[193] or "soft indications" for IOL (e.g., maternal discomfort[193] or distance from hospital[193]) may be present.

If electively induced women are healthier than expectantly managed women, protective associations may be biased down and away from the null.[145] However, we

adjusted for socioeconomic status, obesity severity, and first-trimester prenatal care initiation,[145] which may partially eliminate this confounding.

On the other hand, our results for CD may be conservative if physicians do not provide induced women with sufficient time to labor. In a recent study, half of induced women who underwent CD because of "failure to progress" had not yet achieved cervical dilation ≥6 cm (i.e., the active phase of labor). Zhang et al. recommend that physicians allow their induced patients to reach the active phase of labor (≥6 cm dilation) before intervening via CD.[268] This may be especially important among obese women, whose labor progression is slower than that of non-obese women, particularly before 7 cm dilation.[91]

Because we did not have information on whether (and when) cesarean deliveries were scheduled, some scheduled CDs may have been included in the expectant management group. This could make expectant management look artificially harmful with respect to CD and perhaps other complications. However, it could also be argued that women who had scheduled CDs (regardless of the outcome) should be included in the expectant management group until they are delivered. For instance, women who deliver via planned CD at 40 weeks are expectantly managed, compared to women who are electively induced at 37, 38, and 39 weeks.

Additional residual confounding by SES or access to healthcare may remain. For instance, women with higher access to care may be more likely to be induced. However, Flanders and Khoury demonstrated that the amount of confounding of an effect estimate may be relatively small, even if the association between the covariate and the disease is quite strong.[280] A randomized controlled trial would help eliminate residual confounding.

However, our observational study may be more generalizable than an RCT of the same topic. Women in RCTs are under heightened observation, and their experience under expectant management may not represent what would occur in a regular hospital-based setting.[202]

We could not evaluate stillbirth, as all fetal deaths were excluded during the sample selection. Out of 642 stillbirths ≥37 weeks' gestation to obese women, a total of 337 were excluded due to study exclusion criteria (19 due to multiple gestations, 23 due to birth defects, and 295 due to preexisting maternal conditions or non-cephalic presentation). This left 305 eligible observations. However, all remaining 305 observations were excluded due to missing data on preexisting conditions or fetal presentation (i.e., without data on preexisting conditions or fetal presentation, we could not tell whether these N=305 stillbirths were eligible for our study). Improving the quality and completeness of U.S. fetal death certificates should be a top priority for clinicians and public health officials, as it would benefit future research on stillbirth risk factors, causes, and prevention.

In addition, we could not account for the non-independence of multiple births to the same woman. However, in sensitivity analyses, we accounted for the correlation between deliveries that occur in the same hospital. Despite our large sample size, our study may have lacked the power to detect additive and multiplicative interaction between eIOL and obesity class.

Aims 2 and 3 of this dissertation have many strengths. To the best of our knowledge, Dissertation Aim 2 is the second and largest study to compare eIOL at each week of term gestation to expectant management among obese women.[187] Similarly, Aim

3 is the second and largest study to compare eIOL versus expectant management among offspring of obese women. Our study is the first to examine the association between term eIOL and severe maternal morbidity, maternal postpartum stay, meconium aspiration syndrome, infant hospital stay, and infant death. It is also the first to examine eIOL at 41 weeks' gestation in obese women and the first to assess interaction between eIOL and obesity class. Only one prior study assessed the relation between eIOL (versus expectant management) and perinatal outcomes among obese women separately for each week of term gestation (37-40).[187] However, this prior study lacked the statistical power to detect differences in several rare outcomes, such as postpartum hemorrhage and RDS. With four additional years of data (2008 through 2011), we newly observed both increased risk of infant death, RDS, and extended infant stay for deliveries <39 weeks, as well as several significant protective associations between eIOL and other major infant complications (e.g., meconium aspiration syndrome and brachial plexus injury). Other studies on IOL among obese women examined different research questions or had other notable limitations, such as combining electively induced women across multiple weeks.

The California Linked Patient Discharge Data/Birth Cohort File is population-based[105] and captures nearly all deliveries and infant deaths in each calendar year.[166] This should limit selection bias in our study. California successfully links more than 95% of vital records with hospital discharge data.[257] The California dataset is also diverse racially/ethnically and socioeconomically,[105,166] which facilitates subgroup analyses and generalizability.[166] Data quality in California is also high; the California Agency of Health and Human Services conducts numerous data quality assessments.[166] We also included a large sample size of almost 220,000 deliveries.

Similarly to Lee et al.,[187] we compared eIOL to expectant management, rather than to spontaneous labor in the index week, which is not part of obstetric decisions.[183,187] In studies of obstetric decision-making, expectant management is a more appropriate comparison group for eIOL than spontaneous labor. At any time point, a physician may decide either to deliver a woman (e.g., by eIOL) or to expectantly manage a woman. Although comparing eIOL to spontaneous labor may yield some interesting observations, this comparison is not directly relevant to clinical decision-making. Furthermore, in epidemiological terms, expectant management represents the true counterfactual to eIOL.

Our exposure definition (elective IOL) limited confounding by indication as compared to observational studies that examine IOL as a whole. Combining both medically indicated and elective inductions—as is done in analyses of total IOL—could make IOL appear artificially harmful. This is because women with medically indicated inductions may be at higher risk of adverse outcomes due to the indication itself, rather than any potential effects of IOL.

We compared elective IOL to expectant management separately for each term gestational week. This approach may more closely represent "real-time" obstetric-decision making than analyses that combine eIOL across multiple weeks.[240] Confounding by contraindication (to IOL) should also be limited because we excluded deliveries complicated by non-cephalic presentation, a prior cesarean delivery, multiple gestations, major fetal anomaly, and preexisting medical conditions.

We excluded many high-risk obese women (e.g., women with gestational diabetes), for whom obstetric management would likely differ significantly from the general obese population.[187] We also accounted for potential confounding by many

maternal sociodemographic and hospital factors. Unlike several previous studies, we did not control for potential intermediates (e.g., preeclampsia) of the association between eIOL/expectant management and adverse outcomes. This allowed us to estimate the total effect of the exposure on perinatal outcomes.

We classified medical diagnoses and procedures as present if they were detected in either vital records or hospital discharge data. This approach improves sensitivity, while only negligibly impacting specificity, compared to using either vital records or hospital discharge data alone.[258-260]

Another strength of our study is our extensive sensitivity analyses. We accounted for the uncertain timing of intrapartum complications (e.g., fetal distress) that may either precede or follow IOL. In addition, we considered multiple definitions of expectant management. Finally, we investigated whether the use of GEE models, which accounted for clustering by delivery hospital, impacted our results.

AIMS 2-3 CONCLUSIONS

Although elective IOL before 39 weeks' gestation may improve outcomes among obese mothers, it should not be recommended owing to increased risk of infant mortality in their offspring. In contrast, elective IOL between 39 and 41 weeks' gestation may reduce the risk of cesarean delivery, maternal morbidity, and infant morbidity, without increasing infant mortality.

SUMMARY

This dissertation highlights possible ways to improve pregnancy outcomes associated with maternal weight. Our **Aim 1** findings indicate that gaining sufficient

weight during pregnancy may reduce the risk of stillbirth among normal weight, overweight, and obese women. Avoiding excess GWG may also reduce the risk of stillbirth among overweight women; however, these findings were imprecise. Our findings for normal weight, overweight, and class 1 obese women were consistent with clinical guidelines. In contrast, our findings among morbidly obese women (BMI ≥35 kg/m^2) suggest that gaining above IOM guidelines may reduce the risk of stillbirth. However, our findings for morbidly obese gravidas should be considered preliminary given lack of precision (95% CIs overlapped the null among this group) and given our inability to separate morbidly obese women into classes 2 and 3 obese gravidas. In addition, the limitations of our analytic approach must be considered: most importantly, we lacked information on GWG at the time of fetal death, and the GWG z-scores in our study may not be independent of GA. Future research should evaluate the association between GWG and stillbirth among women of each obesity class. Forthcoming studies should also apply the FGLS[175] and Hutcheon et al.'s[156,157] GWG z-score standards in different populations.

Our **Aims 2 and 3** findings suggest that obesity should be considered as an indication for delivery at 39 weeks' gestation and beyond. Although we found protective associations between eIOL and cesarean delivery, postpartum hemorrhage, and severe maternal morbidity before 39 weeks' gestation, the risks of infant mortality and extended infant hospital stay were elevated at early term gestations. Hence, elective IOL is not recommended before 39 weeks. In contrast, elective IOL between 39 and 41 weeks' gestation was associated with reduced risks of cesarean delivery, maternal morbidity, and neonatal morbidity, and no added risk of infant mortality. Our findings agree with several

previous studies of eIOL among obese women. However, more research on stillbirth, which we were unable to evaluate, is necessary. Likewise, more cost-effectiveness research is warranted.[213] Finally, because our studies were retrospective and observational in nature, issues such as residual confounding and exposure misclassification may remain. Randomized, controlled trials evaluating term eIOL ≥39 weeks versus expectant management would help reduce these biases.

In summary, this dissertation suggests that normal weight, overweight, and obese women should gain sufficient weight during pregnancy in order to minimize their risk of stillbirth. In addition, clinicians should consider electively inducing obese women between 39-41 weeks' gestation to reduce their risks of cesarean delivery, maternal complications, and neonatal morbidity.

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